

NIH GUIDE

for GRANTS and CONTRACTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

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

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NOTICE

SMALL BUSINESS INNOVATIVE RESEARCH (SBIR) PROGRAM

SMALL BUSINESS INNOVATION DEVELOPMENT ACT OF 1982 (P.L. 97-219)

PUBLIC HEALTH SERVICE

P.L. 97-219, an amendment to the Small Business Act, requires agencies of the Public Health Service (PHS) and certain other federal agencies to set aside a specified amount of their research and development (R&D) budgets for a Small Business Innovative Research (SBIR) Program. This legislation is intended to:

- o stimulate technological innovation;
- o use small business to meet federal research and development needs;
- o increase private sector commercialization of innovations derived from federal research and development; and
- o foster and encourage participation by minority and disadvantaged persons in technological innovation.

PHS agencies/offices participating in the SBIR Program include the National Institutes of Health (NIH), the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), the National Center for Health Services Research (NCHSR), and the Office of Adolescent Pregnancy Programs (OAPP). NIH accounts, however, for approximately 94% of the SBIR set-aside funds in PHS.

For purposes of the SBIR Program, a "small business" is any organization that is independently owned and operated for profit, not dominant in the field in which it is operating and meets the size standard of 500 or fewer employees.

"Research" or "research and development," when used in reference to the missions of the PHS agencies, refers to (a) a systematic study directed toward greater knowledge or understanding relevant to improving human health and well-being; (b) a systematic study directed specifically toward applying new knowledge to meet a recognized health need; or (c) a systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development and improvement of prototypes and new processes to meet specific requirements in the health area.

IMPLEMENTATION OF THE SBIR PROGRAM

The SBIR Program of the PHS will consist of the following three phases:

Phase I: establishing the technical merit and feasibility of R&D ideas which may ultimately lead to commercial products or services in the health area. This phase must precede the submission of Phase II requests for funding.

Phase II: in-depth development of proposed R&D ideas that are likely to result in commercial products or services, with special consideration given to proposals demonstrating prospective private capital commitments for commercial applications.

Phase III: only where appropriate, the involvement of private capital for commercializing the results of R&D funded by a federal agency, or the involvement of non-SBIR funded contracts with a federal agency for products or processes intended for use by the U.S. government.

The Public Health Service (PHS) wishes to identify small businesses that may have the expertise to contribute to the R&D mission of these agencies. Small business firms which believe that they have such capabilities should contact the office indicated below. A solicitation for grant applications will be available shortly which will provide detailed information on implementation of the SBIR Program, grant application and review procedures, and the R&D needs of the agencies which lend themselves to performance by small businesses. SBIR solicitation for R&D contract proposals relevant to specific agency requirements will be announced at a later date.

Small businesses interested in contracts for R&D support services, as distinct from R&D per se, should pursue opportunities through the regular small and small disadvantaged business set-aside programs. PHS agencies will continue to entertain responses to competitive contract solicitations from the small business sector in program areas not covered by SBIR Program Solicitations.

Small Business Conference

The PHS invites the participation of small-business R&D firms in a conference to be held at NIH in early February 1983. The purpose of the conference will be to discuss agency implementation of the SBIR Program and to offer an opportunity for small-business scientists to discuss R&D needs with PHS program staff.

If you are interested in receiving a copy of the Program Solicitation of a given PHS agency and/or attending the Small Business Conference, please contact:

Office of Grants Inquiries
Division of Research Grants
National Institutes of Health
Westwood Building - Room 449
Bethesda, Maryland 20205

NOTICE

SMALL GRANT APPLICATIONS

ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

The Alcohol, Drug Abuse, and Mental Health Administration urges prospective small grant applicants to give careful attention to the following:

1. Obtain special information and instructions for preparation of the application from the appropriate institute, e.g., National Institute of Mental Health (NIMH), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and National Institute on Drug Abuse (NIDA).
2. Clearly identify the mailing envelope as containing an ADAMHA SMALL GRANT APPLICATION
3. Do not package with other types of applications.
4. Submit the application to the Division of Research Grants (DRG) as early as possible.

Adherence to the above should facilitate prompt processing of the applications.

ERRATUM

NIGMS SHARED INSTRUMENTATION GRANTS

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

An Announcement in the November 5, 1982, NIH Guide for Grants and Contracts (Vol. 11, No. 12) printed on page 13, from the National Institute of General Medical Sciences, had an error in the Institute's name. The correct name for the Institute is the **NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES**.

NOTICE

INDIVIDUAL NRSA APPLICATION FORMS PHS 416-1 AND PHS 416-9

DIVISION OF RESEARCH GRANTS

The new competing Individual National Research Service Award (NRSA) Application Form (PHS 416-1, revised 12/81 and announced in the NIH Guide for Grants and Contracts, Vol. 11, No. 11, October 8, 1982, is now available. Copies of this form may be obtained by writing to:

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

Individual copies may be obtained by writing to:

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

Because of the proximity of the February 1, 1983 deadline, the National Institutes of Health (NIH) will accept the 11/79 revision of Form PHS 416-1 for that deadline. The 12/81 revision should be used exclusively for deadlines after February 1, 1983.

Competing applications mailed out by NIH will include updated information statements describing the Postdoctoral Fellowship (July 1, 1982) or Senior Fellowship (October 1, 1982) as appropriate. Individual copies of these statements are available from the Office of Grants Inquiries at the address identified above.

The noncompeting Individual NRSA Continuation Application Form PHS 416-9, revised 12/81, was put into use in late November. NIH will continue to mail fellowship continuation forms directly to individual fellows at the appropriate time. This form will not be distributed through institutional control offices.

NOTICE

RESEARCH LACKING PLANS FOR INVOLVEMENT OF HUMAN SUBJECTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

On January 26, 1981, the Department of Health and Human Services (DHHS) revised its regulations for the protection of human subjects. 45 CFR 46.118 addresses applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to the Department with the knowledge that subjects may be involved within the period of funding, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants (including bloc grants) where selection of specific projects is the institution's responsibility; research training grants where the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research described in 46.101(b) (exempted research) no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in these regulations, and certification submitted to the Department.

In activities such as the above, even though an IRB review need not take place at the time of submission of the application, DHHS requires the attachment to the application of the Form HHS-596, "Protection of Human Subjects Assurance/Certification/Declaration." This form may serve either as a certification that IRB review and approval has taken place for the research proposed in the application, or as a pledge that review and approval and submission of a certification will occur before human subjects are involved in the research.

In many instances trainees supported by institutional training grants will be participating in research supported by research project grants, for which the IRB review of human subjects is already complete. This review is sufficient providing that the research would not be substantially modified by the participation of a trainee.

For proposed projects in which the research has received IRB review and approval, block 5 of the Form HHS-596, "Certification of IRB Review and Declaration of Exemption," should indicate the date of review. For research in which definite plans are not set forth in the application, instead of checking a box in block 5 of the Form HHS-596, the applicant should write "See Note," and on the reverse of the form indicate the following: "This is an institutional research training grant (for example) for which plans are not definite. A certification of IRB review and approval of research involving human subjects will be provided before the activity begins if certification has not already been filed. This is in accord with 45 CFR 46.118."

NOTICEALCOHOL RESEARCH GRANTS AND NEW INVESTIGATOR RESEARCH AWARDPROGRAM ANNOUNCEMENTS NOW AVAILABLE**NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM**

Updated program announcements providing current information about areas in which support is available from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) are now available. In addition to the Institute's interest in supporting research on the etiology of alcoholism and the adverse consequences of alcohol abuse, it should be noted that there are several high priority areas in the Alcohol Research Grants program announcement; namely, treatment research, prevention research, and research on alcohol-related accidents, injuries, and violence. Of special interest are treatment and prevention research studies that are focused on high priority groups such as teenagers and women.

Potential applicants for Alcohol Research Grants and for New Investigator Research Awards may obtain these updated program announcements from:

Division of Extramural Research
National Institute on Alcohol Abuse
and Alcoholism
Parklawn Building - Room 14C-17
5600 Fishers Lane
Rockville, Maryland 20857

Applications must be received by March 1, 1983, to be eligible for funding in FY 1983.

NOTICE

PUBLIC BRIEFING MEETINGS BY THE
NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The National Heart, Lung, and Blood Advisory Council will hold four public briefing meetings for the purpose of informing biomedical scientists, administrators, volunteer health organizations, and the public about the status of the National Heart, Lung, and Blood Institute (NHLBI) and about possible strategies for achieving and maintaining a balance of program mechanisms and for protecting the number of research grants awarded by the Institute. The briefing meetings are designed as an educational effort that will also provide the opportunity for the Council and the NHLBI to hear directly from those interested in and concerned about the future of the Institute's extramural programs.

The public meetings will be held at the following times and locations:

February 24-25, 1983

WASHINGTON, D.C.

9:00 a.m.

Lister Hill Auditorium, Building 38A
National Institutes of Health

March 3-4, 1983

SAN FRANCISCO, CALIFORNIA

9:00 a.m.

San Francisco Hilton and Tower
333 O'Farrell Street

March 24-25, 1983

NEW ORLEANS, LOUISIANA

9:00 a.m.

International Hotel
300 Canal Street

April 14-15, 1983

CHICAGO, ILLINOIS

9:00 a.m.

Radisson Chicago Hotel
505 North Michigan Avenue

Send requests for a complete statement of the purpose of these meetings to:

Public Briefing Meetings
National Heart, Lung, and Blood
Advisory Council
National Heart, Lung, and Blood Institute
National Institutes of Health
Building 31 - Room 5A-03
Bethesda, Maryland 20205

Those who wish to speak at a briefing meeting must submit a written request to the National Heart, Lung, and Blood Advisory Council no later than January 21, 1983. The request to speak must include the following:

1. The name of the person who wishes to address the Council;
2. The professional affiliation of the requesting speaker, if appropriate;
3. A brief summary of the statement that would be presented; and
4. The address and telephone number where the requesting speaker can be reached during business hours.

Speakers will be selected from the constituencies who look to the Institute to advance knowledge about heart, lung, and blood diseases and from others whose interests correspond to the extramural programs of the NHLBI.

Each speaker will be allowed about ten minutes. A list of speakers for a meeting will be sent in advance to the region in which that particular meeting will be held. Additional written comments of any length may be submitted, at any time, for distribution to the Council. The results of these briefing meetings, including the texts of the speakers and all other materials submitted, will be available in the summer of 1983. For further information, please call (301) 496-6331.

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS:

RFA-NIH-NCI-DRCCA-82-17

PATTERNS OF CARE FOR ELDERLY CANCER PATIENTS:

IMPLICATIONS FOR CANCER CONTROL

NATIONAL CANCER INSTITUTE

Application Receipt Dates: April 19, 1983 and December 6, 1983

I. PURPOSE

The National Cancer Institute (NCI) invites qualified researchers to submit grant applications for research projects to investigate problems and needs unique to the elderly in the diagnosis and management of cancer. NCI, in consultation with the National Institute on Aging (NIA), is directing a specific focus on the older adult who has cancer. Although the majority of cancers affect older persons disproportionately and the probability of developing cancer increases as one grows older, relatively little is known about how the problems of old age affect cancer patient work-up, treatment and care. The dearth of data makes it impossible to provide definitive answers to the many questions which arise about the impact of old age on cancer patient management.

As a cancer control effort for the elderly, NCI is encouraging studies directed toward the interface of cancer and aging. The major objective of cancer control is to reduce cancer incidence, morbidity, and mortality through an orderly sequence from conducting research on interventions and their impact in defined populations to their broad, systematic application to the general population. Research support will be provided under the auspices of NCI's Division of Resources, Centers, and Community Activities (DRCCA). DRCCA's cancer control mandate, authorized by Congress, includes the responsibility to study and bring into medical practice proven research which will improve prevention, detection, diagnosis, and treatment of cancer.

Old people in poor health frequently present a chronic disease complex which is long-term and severely debilitating. When cancer is linked with the chronic disabling conditions which persons acquire over the course of their lives, medical decision-making and differences in management must often be uniquely applied to

This program is described in the Catalog of Federal Domestic Assistance No. 13.399, Cancer Control. Awards will be made under the authority of the Public Health Service Act, Title IV, Section 403 (Public Law 78-410, as amended; 42 USC 284) and administered under PHS grant policies and Federal regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

the older-aged patients. Decisions are influenced not only by the cancer signs and symptoms with which patients present, but also by their frailty; other health difficulties and chronic disabilities; and social, psychological, and economic handicaps. Advancing age with its concomitant changes in physical ability, physiological function, and social relationships complicate providing care to elderly cancer patients. Physicians must consider these various factors when planning cancer treatment and care recommendations for the elderly. Thus, the assessment of the patterns of care (i.e., the diagnosis, work-up, staging, and treatment) for evaluation of elderly cancer patients requires an adequate data base.

The purpose of this Request for Applications (RFA) is to solicit high quality research grant applications that address the mutual interests and concerns about cancer and old age as they interact and relate to clinical research and medical practice so as to contribute to our understanding of the management of cancer in the elderly. This initiative, by stimulating the fields of oncology, geriatrics, gerontology, and other relevant disciplines and professions to conduct multidisciplinary research, is intended to reduce the knowledge gap about cancer treatment and care in the older-aged population. Information is being sought on the natural history of cancer in the elderly, treatment patterns, the interaction of the normal and/or pathophysiological processes of aging and cancer, the overlap of intercurrent disease with cancer, and the extent to which interdisciplinary approaches may foster coordinated application of special skills for optimal cancer care for the elderly.

II. STATEMENT OF THE PROBLEM

Cancer is primarily a disease which occurs in the older-aged segment of the population. Approximately 50 percent of all cancers occur in persons 65 years and older; close to 60 percent of all cancer deaths occur after 65 years of age. The risk of developing cancer increases rapidly with each decade of life. Incidence data from the Surveillance, Epidemiology, and End Results (SEER) Program of the Biometry Branch, NCI, reveal that the average annual age-specific incidence rate for ages 65-69 years is 1360.6 per 100,000 persons. This is almost double the rate of 748.8 observed for those aged 55-59 years. The 75-79 years of age group reflects a continuing increase to 2028.9 per 100,000 persons with the rise peaking at 2308.0 for those 85 years and older.

Not only does cancer affect the older age group in our society disproportionately, but the nation's number of older persons is gradually increasing and will constitute a larger percentage of the population in the future. In 1900, the over 65 years of age group numbered 3.1 million persons and represented only 4.1% of the entire population. By 1975, this same age group had 22.4 million persons and represented 10% of the population; estimates for the year 2000 predict a rise to 33.2 million persons making up almost 12% of the U.S. population. By 2030, possibly the peak year for the overall growth of the population, there will be approximately 55 million persons 65 years or older in the U.S. Coupled with these increases is the expansion of the 75 and older population segments of the age categories. There are and will be more persons 85 years of age and older. Clearly, within the context of the U.S. health care system, there will be more old people who require cancer care.

In the area of early detection, when the older person enters the medical care system could be significant for the course of potentially malignant lesions. Early detection efforts for older persons have been minimal. There is no information on

what older persons do when they become aware of themselves as ill with signs and symptoms of cancer and the factors affecting promptness in their decisions to seek care.

When considering surgical, radiotherapeutic, chemotherapeutic or a combination of these therapies, age-imposed compromises are particularly true for the very young and the elderly. Anatomic development and degeneration as well as physiologic factors must always be considerations in these situations.

The selection of surgical procedures which are conservative or aggressive in approach and palliative or curative in intent will be influenced by age, as will the incidence of complications during the postoperative recovery period. There are limited data relative to the choice of surgical treatment in the elderly.

Administering radiotherapy to the aged cancer patient is a common practice, yet again little information is available related to the incidence and type of complications associated with advancing age. Tolerance to irradiation varies with the radiation fields, dosage, and type of cancer under treatment.

Age-dependent differences in drug absorption, distribution, metabolism, and excretion are all appreciated. Drug-drug interactions receive less attention but represent a significant hazard in the multiple medicated elderly. Adverse drug reactions (e.g., the stomatitis from adriamycin or 5-fluorouracil) in the elderly may represent life-threatening situations. Changes in physiology (e.g., decreased renal function), anatomy (e.g., intracavitary fluid retention acting as a drug reservoir), and rapid weight changes altering drug-to-weight ratios all represent potentially hazardous changes for these patients.

Health professionals should also be able to distinguish between the changes that occur as a result of aging and those which may be attributed to cancer and other disease processes. In addition to having a sound clinical information base and a variety of skills in cancer care and treatment, oncology professionals must be able to carry on surveillance and monitoring for the concomitant effects of aging. In the normal process of aging, significant changes occur in body structure, composition, and function. The skin and mucosa grow thinner, stature decreases as the skeletal frame settles, functional capacities of organs decline, bone mass decreases, muscle size and strength are diminished, sensory loss occurs over time, the systems (e.g., pulmonary, digestive, cardiovascular, renal, nervous, and endocrine) undergo multiple changes which result in a diminution of many important functions. These changes occur over time and most persons accommodate to the changes. But the altered levels of functioning and decreased sensitivities when accompanied by an illness such as cancer create a multitude of treatment and care problems for health care providers.

Health professionals who work in oncology settings are often required to apply different skills and techniques to manage various adverse social, economic, and environmental influences which may dominate management decisions for the aged cancer patient. The elderly, perhaps to a greater degree than younger patients, have certain social needs that impact on their health. Together with the stresses of daily living, such age-related life crises as reduced income, loss of loved ones and family support, and changing living arrangements are all interconnected with the older person's physical condition. A thorough understanding of the elderly

cancer patient's life situation in conjunction with his or her medical symptoms and course of illness may provide for a more successful treatment regimen. Quality of life issues are relevant to cancer care for the elderly.

III. PROGRAM PLANNING AND RELEVANCE

In September 1981, responding to the paucity of data available and major deficiencies apparent in our knowledge about cancer and its relationship to old age, NCI and NIA co-sponsored a conference which invited professionals working in both fields of cancer and aging to identify and examine a variety of issues in prevention and treatment of cancer in the elderly to ascertain research needs and make recommendations for programmatic direction. Questions arose as to what intervention techniques are available to offset the unusual or specific problems of elderly cancer patients. Since many unsubstantiated or unsupported assertions exist about cancer in old age, conference discussions centered on laying the groundwork for needed research in cancer and aging at the clinical interface of the two fields.

Building upon the conference recommendations for research, this RFA represents an important step toward fulfillment of the congressional intent of the National Cancer Act and Amendments of 1978. Developing information and resources for health professionals in the use of cancer control interventions are major objectives of the cancer control mission.

This RFA is a cancer control project which comes under the program areas of Treatment, Continuing Care, and Rehabilitation (TCCR) in DRCCA. TCCR programs emphasize (1) cancer control research which develops or tests actions or interventions aimed at specific high risk population groups; (2) participation of community physicians in applying advanced treatment research to cancer patients; (3) improved approaches to pain control; (4) development of effective methods to improve the care of advanced cancer patients and support of their families; (5) rehabilitation; (6) expansion of the cancer care knowledge base of physicians, nurses, and other health professionals; and (7) developing information for reducing the social, economic, and emotional burdens which cancer creates for patients and families.

IV. RESEARCH SCOPE

To be responsive to this RFA, investigations which use descriptive and analytic (e.g., longitudinal, cohort, case-control, and cross-sectional) designs are acceptable. The study population in which the research would be conducted should be well defined within a community or the general population. Use of objective, reliable, and valid measures is essential. Study settings may include nursing homes, hospitals, other health care institutions, the community, and the occupational context.

A single or combination of activities from the broad spectrum of early detection, early diagnosis, pre-treatment evaluation, treatment, rehabilitation, and continuing care cancer control efforts may be addressed. Topics of major interest to DRCCA are listed below. However, grant applications are not limited to these areas. The list is neither all-inclusive nor exclusive, nor is it an order of priority of interest. Related issues designated by the applicant will be considered as well.

o Patterns of care for the elderly cancer patient.

Not much is known about how physicians care for older-aged cancer patients at the community level. Neither has there been a distinct focus on the behavior of neoplasms and tumor characteristics as they present in the elderly. It is known, however, that multiple clinical problems of the aged frequently require physicians to look for subtle or masked features of adverse conditions in addition to the presenting complaint. These special features of aging and symptoms of illness in old age influence the treatment and care of the elderly cancer patient and tend to complicate carrying out prescribed regimens. Studies are needed on the assessment of the effectiveness of different treatments relative to cancer, the stage of the disease, and significant features and characteristics of old age (e.g., poor repair mechanisms, functional loss, greater susceptibility to toxicity of treatment). In these types of studies, a special effort should be made to minimize biases, for example, through the use of defined populations.

o Variations in response factors to signs and symptoms of cancer by older aged persons.

To a large extent, improved cancer cures depend on early recognition and appreciation of signs and symptoms of the disease and prompt referral to treatment. The actions taken by older persons in response to the signs and symptoms of cancer will affect the cure, number of complications, and sequelae. Elderly persons are often directly or indirectly excluded from most early cancer detection efforts. Though they represent one of the groups at highest risk, older aged persons have not been singled out as a target group. Research strategies to ascertain what factors influence decisions made by older persons in response to signs and symptoms of cancer and the individual variations which may result in delay are needed.

o Analysis of existing data bases which are relevant to addressing cancer patient management for older aged persons.

Secondary analyses of surveys or studies which have been designed to address other issues in treatment of cancer or other chronic illnesses, the processes of normal aging, long-term care, and related health issues may be appropriate. This choice would require a thorough and detailed explanation of the data elements in the data base identified as a candidate for this research to determine the utility of addressing the problems at the interface of cancer and aging raised in this RFA. Special attention must be given to ascertaining biases in the data base.

o Evaluation of tolerance of and response to standard or experimental chemotherapy regimens.

Studies should involve entry of patients across the entire age spectrum (with efforts to minimize selection bias) into predetermined chemotherapy protocols with doses based either on surface area or adjusted for physiologic parameters such as creatinine clearance. Data should be collected on other factors known to affect toxicity or response to therapy so that the independent effect of age can be

evaluated in a multivariate model. Tumors selected for study should be those of intermediate sensitivity to chemotherapy such as breast cancer, small cell lung cancer, head and neck cancer and ovarian cancer so that one has a reasonable statistical probability of observing either increases or decreases in response rate as an effect of age. A similar approach might be considered for surgery, radiation therapy, or multimodality treatment interventions.

- o Socio-emotional and economic consequences of cancer for the older person and family members.

Cancer is an isolating illness, and old age is an isolating phenomenon. As a person grows older, various forms of social support diminish. There is a decline in social network involvement. Geographic distance may preclude kinship network involvement. The older individual may experience loss of friends, family, and spouse. Sickness may also be demoralizing and alienating. Often the cancer patient must be cared for in the home by a family member, friend, or spouse who is also in relatively poor health. Then, too, since cancer affects both the patient and family as a unit, family stress, health, and the organization of health behavior are high priorities which may be addressed.

- o Epidemiologic Studies.

Specific questions which address the problems concomitant with old age (e.g., effects of previous illnesses and concurrent illnesses; stages of disease at detection; second primaries; recurrence) in combination with the general epidemiologic concerns about the patterns of disease occurrence and the influential factors are of interest. Much useful information can be derived from epidemiologic studies on incidence and mortality in old age. Experimental epidemiologic approaches (i.e., clinical trials or community trials) to examine treatment, intervention, or preventive efficacy are appropriate.

V. DEFINITION OF "OLD AGE" OR "ELDERLY"

Frequently, old age or elderly is defined using the chronological age of 65 as a point of demarcation. However, this arbitrary age cutoff, while perhaps useful for dealing with age limitations for entitlements or eligibilities for various programs, may not be useful for the research encouraged by this RFA. Applicants should address critically the issue that physiological and chronological ages do not necessarily coincide. With advancing chronological age, there are greater variations in physiological age.

Methods should be proposed by the applicant which express physiological age of the study subjects. For the most part, persons in their middle to late seventies, that is, the older elderly, present the most profound medical problems. Parameters to be considered in describing the elderly patient could include level of physical activity, response to graded levels of physical activity, response to graded levels of exercise, or, in the case of clinical research, measurement of organ function such as creatinine clearance or hepatic clearance of a marker substance.

Thus, the definition of "old age" or "elderly" is flexible for the RFA and is dependent on investigator-defined parameters. Applicants are expected to identify what is meant by "old" in the context of the research and be able to evaluate the correlation of outcome variables and chronological and physiological age.

VI. MECHANISM OF SUPPORT

Applicants funded under this RFA will be supported through the customary National Institutes of Health (NIH) grant assistance award in accordance with Public Health Service (PHS) policies applicable to research project grants including cost sharing. Assistance awards are provided to non-profit organizations and institutions, governments and their agencies, for-profit organizations, and occasionally to individuals when deemed by the PHS to be consistent with legislative intent and program purposes. NCI plans to support up to six awards within the limits of the funds for both review cycles under this RFA if sufficient high quality applications are received. Awards will be for three year projects. Receipt dates for applications are April 19, 1983 and December 6, 1983.

VII. REVIEW PROCEDURES AND CRITERIA

A. Review Panel

Applications responsive to this RFA will be reviewed by an appropriate peer review panel set up by the Division of Extramural Activities (DEA), NCI, NIH. Final review is provided by the National Cancer Advisory Board.

B. Review Criteria

Peer review will consider the following criteria:

1. Relevance and significance of the issues to the overall objectives of the RFA;
2. Scientific merit of the research project design and feasibility of the procedures that are to be used;
3. Potential for evaluating success of the project;
4. Experience, commitment, and leadership ability of the staffing for the research project which must include medical professionals in oncology and/or geriatrics at the leadership level; the qualifications and experience of other members of the study team to do the proposed research;
5. Availability of multidisciplinary expertise from related fields of gerontology, epidemiology, behavioral and social sciences, and health care as required;
6. Adequacy of existing and proposed facilities and resources;
7. Reasonableness of the budget in relation to the research and/or demonstration effort.
8. Adequacy of the proposed means for protecting against hazardous or unethical research procedures.

VIII. METHOD OF APPLYING

Applications should be submitted on 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 (DRG), NIH.

A. Letter of Intent

1. Applicants are encouraged to submit a letter of intent addressing the following topics:
 - a. A brief description of the intended project.
 - b. A description of available research facilities.
 - c. Positions and research interests of the principal investigator(s) and staff who will be involved in the study.
 - d. Plans for oncology and geriatric medical collaboration, delineation of staff roles, manner of anticipated participation of principal investigator(s) and multidisciplinary approach.
 - e. Projections for patient involvement in the study.

B. Timetable

<u>Letters of Intent</u>	<u>Receipt of Applications</u>	<u>NCAB Review</u>	<u>Earliest Possible Award Date</u>
Feb. 15, 1983	Apr. 19, 1983	Oct. 3-5, 1983	Dec. 1, 1983
Sept. 15, 1983	Dec. 6, 1983	May 16-18, 1984	July 1, 1984

C. 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. Grant applications that are not responsive to the RFA or are not received on or before April 19, 1983, will not be accepted for review in the first cycle. They will be deferred to the second review cycle. Applications not received on or before the second receipt date of December 6, 1983, will be returned to the applicant.

D. Format for Applications

The conventional presentation for grant applications should be utilized. The points identified under the Review Criteria must be considered. The words "RFA: PATTERNS OF CARE FOR ELDERLY CANCER PATIENTS: IMPLICATIONS FOR CANCER CONTROL" must be typed in bold letters in line number 2 of the face page of the application.

Please enclose a cover letter indicating that the application is in response to this RFA. A copy of the cover letter should also be sent to Dr. Rosemary Yancik, NCI, DRCCA, at the address provided.

E. Application Procedure

Applications must be received on or before the application receipt dates stipulated above. The original and six copies of the application should be sent or delivered to:

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

Two additional copies should be sent to:

Referral Officer, Grants Review Branch
Division of Extramural Affairs
National Cancer Institute
National Institutes of Health
Westwood Building - Room 826
5333 Westbard Avenue
Bethesda, Maryland 20205

F. Inquiries and Correspondence

All correspondence related directly to application development, letters of intent, and the copies of the cover letter which accompany the applications should be directed to:

Rosemary Yancik, Ph.D.
Division of Resources, Centers, and
Community Activities
National Cancer Institute
Blair Building - Room 729
Bethesda, Maryland 20205

Telephone: (301) 427-8636

Questions pertaining to business matters should be addressed to:

Mr. William G. Wells
Grants Management Specialist
Grants Administration Branch, OD
National Cancer Institute
National Institutes of Health
Westwood Building - Room 852
Bethesda, Maryland 20205

Telephone: (301) 496-7444

ANNOUNCEMENTSMOKELESS TOBACCO AND NON-TOBACCO SMOKING PRODUCT USE:*IDENTIFICATION OF INITIATION MECHANISMS IN CHILDREN AND ADOLESCENTS

DIVISION OF RESOURCES, CENTERS AND COMMUNITY ACTIVITIES

NATIONAL CANCER INSTITUTE

The Division of Resources, Centers, and Community Activities (DRCCA) of the National Cancer Institute (NCI) has the principal Federal responsibility for assuring the rapid and effective application of cancer research findings in the fields of prevention, detection, diagnosis, treatment, rehabilitation, and continuing care. DRCCA's goal is to develop the means for reducing cancer morbidity and mortality.

As part of its responsibilities in the area of cancer prevention, DRCCA is expanding its program initiatives under the NCI's Smoking, Cancer and Health Program ** which has been designed to facilitate the development of effective approaches to smoking prevention and cessation. The purpose of this Announcement is to encourage research activities which will: (1) identify factors that lead to the use of smokeless tobacco and/or non-tobacco smoking products (NTSP) by children and adolescents; (2) identify those conditions which may lead to shifts in tobacco usage patterns; and (3) develop prevention and cessation strategies which can be integrated into school based health and/or anti-smoking programs.

I. RATIONALE

Shifts in tobacco usage patterns and initiation of non-tobacco smoking behaviors have been reported by the research community. Data published by the USDA indicate that 11 million Americans use smokeless tobacco annually.¹ This figure represents a 12% annual increase in smokeless tobacco use since 1974.¹ In

* For purposes of this Announcement smokeless tobacco is defined as chewing, dipping, or snuffing commercial tobacco products; non-tobacco smoking products are defined as commercially sold "smokes."

** NIH Guide for Grants and Contracts Vo. 9, No. 1, January 3, 1980.

¹ Smoking & Health, A Report of the Surgeon General DHEW Publication No. (PHS) 79-50066.

This program is described in the Catalog of Federal Domestic Assistance No. 13.393, Cancer Cause and Prevention. Awards will be made under the authority of the Public Health Service Act Section 301(c) and Section 402, PL 78-410, as amended; (42 USC 241 and 282) and administered under PHS Grant Policies and Federal regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

addition, the recent introduction of NTSP increases the potential for recruitment to smoker behavior by offering alternate smoking products.

Epidemiological evidence suggests that use of smokeless tobacco increases the risk of oral cancer.² While little scientific evidence is available on NTSP, preliminary reports suggest that constituents in the gas phase of the smoke are suspected contributors to impairment of lung functioning, as well as acting as potential promoters of neoplastic disease.³ In addition, multiple tobacco use, (e.g., dipping and smoking) is a likely contributor to an increased cancer risk.

II. RESEARCH GOALS AND SCOPE

These projects should focus on the development of research strategies to identify, within well-defined population group(s)--e.g., junior high school students--the antecedents and correlates associated with initiation of smokeless tobacco and/or non-tobacco smoking product use and identification of those concurrent or interacting conditions which may lead to shifts from these products to regular tobacco cigarette smoking. Evaluation of possible changes in knowledge, attitudes, beliefs, and behavior concerning the use of non-traditional smoking and smokeless tobacco products and/or the decision to shift from these products to regular tobacco cigarette smoking will be considered a major component of the research design. Due to the generally similar behavior correlates between use of these products and cigarette smoking, demonstrated knowledge of the relevance and significance of current smoking prevention and cessation strategies aimed at children and adolescents is to be included in the research design. Knowledge of the psychological and social mechanisms potentially inherent in recruitment to these products is a general requirement. In addition, the investigators must demonstrate as in depth knowledge of state-of-the art research in the areas of smokeless tobacco and NTSP as well as regular tobacco cigarette smoking as it relates to the research population. In addition to self-report, the study design should include biochemical measurements to increase the validity of self-reports, as well as to provide independent estimates of levels of tobacco use.

Description of the research populations, rationale for the method of sampling, definition of the variables and size of the group, as well as proven access and cooperation from intended research population, school authorities, parents will be required.

This program is, therefore, seeking grant applications concerned with basic and applied studies in prevention of disease with emphasis on behavioral, cognitive, attitudinal and motivational factors, as well as other appropriate research areas.

III. GENERAL INFORMATION

It should be emphasized that this statement of interest in developing new grant applications is neither a Request for Applications (RFA-Grants) nor a Request for Proposals (RFP-Contracts), but rather an announcement of the NCI's intent to stimulate investigator-initiated research in the stated area. As such, proposals are reviewed by the usual National Institutes of Health (NIH) peer review groups for technical merit and recommendation to the National Cancer Advisory Board.

² Christen, A.G., Armstrong, W.R., McDaniel, R.K., "Intraoral Leukoplakia, Abrasion, Periodontal Breakdown and Tooth loss in a Snuff Dipper," JADA, Vol. 98, April 1979.

³ Personal Communication from Oak Ridge National Laboratories to NCI, 10-23-80.

Additional needs for specific, in-depth activity in any or all of the Programs may be met in the future with issuance of RFAs and/or RFPs.

The announcement leaves the choice of specific research objective, identification of specific aims, development of appropriate protocols and methodology, and the procedures of analysis and interpretation of data to the investigators' initiative. However, once the award is made under the program, any substantial modification of the research originally proposed must be mutually agreed upon by the investigator and the respective NCI division.

For purposes of tracing responses to this program announcement, investigators should indicate its title on line 2, page 1 of the PHS 398 grant application.

IV. APPLICATION AND REVIEW PROCEDURES

A letter of intent and requests for additional information should be sent to:

Catherine S. Bell, M.S.
Program Director for Behavioral Smoking Projects
National Cancer Institute (DRCCA) (BMB)
Blair Building - Room 629
8300 Colesville Road
Bethesda, Maryland 20205

Telephone: (301) 427-8656

Application kits may be obtained from an organization's application control office or from the:

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

The application receipt dates for grants submitted under this program announcement are those indicated in PHS form 398.

Completed applications are to be sent to:

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

ANNOUNCEMENT

TOBACCO AND THE BLUE COLLAR WORKER

DIVISION OF RESOURCES, CENTERS AND COMMUNITY ACTIVITIES

NATIONAL CANCER INSTITUTE

The Division of Resources, Centers, and Community Activities (DRCCA) of the National Cancer Institute (NCI) has the principal Federal responsibility for assuring the rapid and effective application of cancer research findings in the fields of prevention, detection, diagnosis, treatment, rehabilitation, and continuing care. DRCCA's goal is to develop the means for reducing cancer morbidity and mortality.

As part of its responsibilities in the area of cancer prevention, DRCCA is expanding its program initiatives under the NCI's Smoking, Cancer and Health Program* which has been designed to facilitate the development of effective approaches to smoking prevention and cessation. The purpose of this announcement is to encourage research activities which will: (1) identify those factors that lead to recruitment, maintenance, cessation, and recidivism as related to tobacco use in the blue collar population; (2) identify concurrent and interacting conditions which may lead to shifts in tobacco usage patterns; and (3) develop prevention and cessation strategies which can be integrated into planned or on-going workplace based health/and or anti-smoking programs.

I. RATIONALE

This program announcement was developed in response to survey research data which indicate that 51% of the blue collar workers are smokers as contrasted with 37% of the total smokers in the U.S. population. In addition, research data suggest that blue collar workers have a potentially greater risk of exposure to known and suspected carcinogenic substances in the workplace. This occupational exposure may act in synergy with smoking behavior thus exacerbating the risk of cancer for this population.¹

*NIH Guide for Grants and Contracts Vol. 9, No. 1, January 3, 1980.

This program is described in the Catalog of Federal Domestic Assistance No. 13.393, Cancer Cause and Prevention. Awards will be made under the authority of the PHS Act Section 301(c) and Section 402, PL 78-410, as amended; (42 USC 241 and 242) and administered under PHS Grant Policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

¹ Surgeon General's Report on Health Consequences of Smoking 1979.

II. RESEARCH GOALS AND SCOPE

These projects will focus on the development of research strategies to identify, within a well-defined population group(s)--e.g., asbestos workers, who are tobacco users--the antecedents, correlates and consequences that are related to recruitment, maintenance, recidivism, and cessation of tobacco use in blue collar workers. The study design should include identification of those concurrent and interacting conditions which may lead to shifts in tobacco usage patterns--e.g., from non-user to user, occasional user to regular user, regular user to non-user, cigarette smoker to smokeless tobacco user, etc. The project should focus on the individual, social, and environmental factors that determine the influences affecting tobacco use in the blue collar worker, e.g., occupational related stress, social support and interaction effects, need for stimulation, maintenance of status, etc. Knowledge of the adverse health effects that result from the interaction between tobacco use and exposure to known and suspected carcinogens in the workplace will be a general requirement. The study design should include a reliable definition of the status of tobacco usage among blue collar workers and should consider multiple forms of tobacco use, e.g., regular tobacco cigarettes, cigars and pipes, non-tobacco smoking products, chewing, and dipping. In addition to self-report, the study design should include biochemical measurements to validate self-reporting, as well as to provide independent estimates of levels of tobacco use. The investigator should address application of research results to future prevention and cessation strategies.

Description of the research population, rationale for the method of sampling, definition of the variables and size of the sample, as well as proven access and cooperation from the intended research sample and appropriate labor and management representatives will be required.

The program is, therefore, seeking grant applications concerned with basic and applied studies in disease prevention with an emphasis on behavioral, attitudinal, and motivational factors, as well as other appropriate research areas.

III. GENERAL INFORMATION

It should be emphasized that this statement of interest in developing new grant applications is neither a Request for Applications (RFA - Grants) nor a Request for Proposals (RFP - Contracts), but rather an announcement of the National Cancer Institute's intent to stimulate investigator initiated research in the stated area. As such, proposals are reviewed by the usual NIH peer review groups for technical merit and recommendation to the National Cancer Advisory Board. Additional needs for specific, in-depth activity in any or all of the Programs may be met in the future with the issuance of RFAs and/or RFPs.

The announcement leaves the choice of specific research objective, identification of specific aims, development of appropriate protocols and methodology, and the procedures for analysis and interpretation of data to the investigators' initiative. However, once the award is made under the program, any substantial modification of the research originally proposed must be mutually agreed upon by the investigator and the respective NCI division.

For purposes of tracing responses to this program announcement, investigators should indicate its title on line 2, page 1 of the PHS 398 grant application.

IV. APPLICATION AND REVIEW PROCEDURES

A letter of intent is encouraged and requests for additional information should be sent to:

Catherine S. Bell, M.S.
Program Director for Behavioral Smoking Projects
National Cancer Institute, DRCCA, BMB
Blair Building - Room 629
8300 Colesville Road
Bethesda, Maryland 20205

Telephone: (301) 427-8656

Application kits may be obtained from an organization's application control office or from the:

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

The application receipt dates for grants submitted under this program announcement are included in PHS form 398.

Completed applications are to be sent to:

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

ANNOUNCEMENT

NEW NIH BIOTECHNOLOGY HIGH VOLTAGE ELECTRON MICROSCOPE (HVEM)

RESOURCE AVAILABLE TO BIOLOGICAL AND MEDICAL RESEARCHERS

DIVISION OF RESEARCH RESOURCES

The Biotechnology Resources Program (BRP), Division of Research Resources (DRR), National Institutes of Health (NIH), is supporting part of the operation of the 1.2 million volt electron microscope at the Albany, New York State Department of Health installation, under the direction of Dr. Donald Parsons, to provide access to national users.

This installation is operated as a State facility in the Northeast Region, and is now available on a national basis to users, who are qualified scientists with appropriate biomedical projects, irrespective of institutional affiliation or geographical location.

In applying, the need for, or appropriateness of the Albany installation should be stated. Interested scientists should submit a brief proposal (one to four pages) which includes the following information:

1. Title, name, address and phone number.
2. Curriculum vitae of the investigator.
3. Description of the proposed project, of which the HVEM study will be a part.
4. Statement of the biomedical value of the project.
5. Justification for the use of the HVEM; explanation of its appropriateness to the project proposed.
6. Results already obtained by light or conventional electron microscopy at 100 KV, 200 KV or lower voltages. Selected micrographs should be enclosed.
7. Nature of the specimens, specific methods used in specimen preparation and suitability for HVEM should be documented.
8. A concise bibliography directed relevant to the proposed project should be given.
9. An initial visit for a pilot study will be allowed in relation to your plan for microscope time, which must be estimated in your application. Further visits will be subject to review by the Advisory Committee.

Potential users are encouraged to consult members of the Resource Group, and the Advisory Committee, for technical advice on specimen preparation and advance study advisable before a visit. Instructions on HVEM technique and the various modes of operation and the accessories of the HVEM are available from the Resource and should be obtained early. Periodic workshops on the theory and practice of HVEM and associated image processing will be arranged.

Mail your outline to:

Dr. Donald F. Parsons, Director
HVEM Laboratory
Center for Laboratories and Research
New York State Department of Health
Empire State Plaza
Albany, New York 12201

Telephone: (518) 474-7047 or 474-7049

Advisory Committee:

Dr. Lee D. Peachey (Chairman), 217 Leidy Laboratories of Biology G7,
University of Pennsylvania, Philadelphia, PA 19104 - Tel: (215) 243-5788.
Dr. Caroline Damsky, Wistar Institute, Philadelphia, PA.
Dr. Barry S. Eckert, State University of New York at Buffalo, Buffalo, NY.
Dr. Robert M. Fisher, US Steel Research Lab., Monroeville, PA.
Dr. Stephen Hui, Roswell Park Memorial Hospital, Buffalo, NY.
Dr. Gordon Kaye, Albany Medical College, Albany, NY.
Dr. William Masover, New Jersey Medical School, Newark, NJ.
Dr. Jean-Paul Revel, California Institute of Technology, Pasadena, CA.
Dr. Sam McGee-Russell, State University of New York, Albany, NY.
Dr. John Wolosewick, University of Illinois Medical Center, Chicago, IL 60612.

ANNOUNCEMENT

AVAILABILITY OF SENIOR INTERNATIONAL FELLOWSHIPS FOR 1984-85

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

The John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) announces the availability of senior postdoctoral research fellowships to U.S. health scientists who wish to conduct collaborative research abroad. The purpose of these fellowships is to enhance the exchange of ideas and information in the biomedical, behavioral and health sciences. The types of activity that are supported by this program include collaboration in health sciences, basic or clinical research, and the familiarization with or utilization of special techniques and equipment not otherwise available to the applicant. This program does not provide support for brief observational visits, attendance at scientific meetings, attendance in formal training courses, independent research projects, or full-time clinical, technical or teaching services.

I. ELIGIBILITY REQUIREMENTS

Applicants must meet the following requirements:

1. Be a U.S. citizen or permanent U.S. resident;
2. Hold a doctoral degree in one of the biomedical, behavioral or health sciences;
3. Have five years or more postdoctoral experience;
4. Have professional experience in one of the health, biomedical or behavioral sciences for at least two of the last four years;
5. Hold a full-time appointment on the staff of the U.S. nominating institution;
6. Be nominated by the dean or appropriate U.S. institutional official;
7. Be invited by the foreign institution.

II. APPLICATION AND SELECTION

Fellowship applications are reviewed once annually. The receipt date for Senior International Fellowship applications is June 1, 1983. All applications are reviewed for scientific merit by the National Institutes of Health (NIH). Fellowship awards are made for periods of three to twelve months. A fellowship can be activated within one year after receiving the Notice of Award and the starting date of the fellowship is set by mutual agreement between the fellow and the collaborator at the foreign host institution. Prospective applicants for the Senior International

Fellowship Program may obtain information brochures from FIC. Fellowship applications will be available from the FIC between January 15 and May 15, 1983, and may be requested only by the dean or equivalent institutional official. Information on fellowship applications are available from:

Senior International Fellowship Program
International Research and Awards Branch
Fogarty International Center
National Institutes of Health
Bethesda, Maryland 20205

For an expeditious reply, please send a self-addressed label with your request to the above address.

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DHVD 83G-A

CORONARY ARTERY REACTIVITY, INJURY AND THROMBOSIS

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. PURPOSE

The Division of Heart and Vascular Diseases (DHVD), National Heart, Lung, and Blood Institute (NHLBI), invites grant applications for support of research on the interaction of vascular reactivity, injury, and thrombosis in coronary arteries as contributing factors to myocardial ischemia. Applications received in response to this request will participate in a single competition.

II. DISCIPLINES AND EXPERTISE

Among the disciplines and expertise that may be appropriate for this research are biochemistry, coronary physiology, electrophysiology, hematology and coagulation, hemorrheology, pathology, pharmacology and immunology.

III. BACKGROUND

A. Administrative Background

In 1971, the Institute began a research program of investigation of the fundamental physiology and biochemistry of ischemic myocardium. The program was expanded in 1975, to include research involving the application of laboratory findings to the clinical setting. Subsequently, as the concept of salvageable myocardium developed, emphasis shifted to investigations of interventions which might limit the size of an evolving infarction.

In addition to these research programs, the NHLBI is conducting a clinical trial, The Multicenter Investigation of the Limitation of Infarct Size (MLIS), to assess the efficacy of two drugs, propranolol and hyaluronidase, in limiting the size of an infarct when administered within 18 hours of the onset of symptoms of presumed myocardial infarction. The NHLBI has also supported a substantial number of laboratory and clinical investigations concerning the

This program is described in the Catalog of Federal Domestic Assistance No. 13.837, Heart and Vascular Diseases. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

should request travel funds for a two-day meeting each year, most likely to be held in Bethesda, Maryland. Applicants should also include a statement in their applications indicating their willingness to participate in such meetings.

Applicants, who will plan and execute their own research programs, are requested to furnish their own estimates of the time required to achieve the objectives of the proposed research project; however, the award period for this activity will not exceed three years. At the end of the initial award period renewal applications may be submitted for competitive review through the regular grant program of the NIH. It is anticipated that support for this program will begin on September 30, 1983.

The current policies and requirements that govern the research grant programs of the NIH will prevail.

VII. REVIEW PROCEDURES AND CRITERIA

A. Review Method

Applications responding to this RFA will be reviewed for scientific and technical merit by an initial review group, which will be convened by the Division of Extramural Affairs (DEA), NHLBI, solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the 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 have it considered for the regular research grant program of the NIH. If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factors to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research-project grant applications; the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed. An additional criterion will be the importance of the proposed research to the objectives of this RFA.

VIII. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are encouraged to submit to the Review Branch of the Institute a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions. The Institute requests such letters for the the purpose of providing an indication of the number and scope of applications to be received. A letter of intent is not binding, and it will not enter into the review of any application subsequently submitted, nor is it a necessary requirement for application.

formation and/or the metabolic products of the thrombus. Conversely it is not known whether vasospasm could induce thrombus formation in the coronary arteries.

Thus it seems timely to encourage fundamental studies of the problem.

IV. OBJECTIVES AND SCOPE

This special grant program is intended to encourage the development of a comprehensive and integrated understanding of the biology and/or pathophysiology of the coronary arteries, particularly in relation to the interplay of factors affecting vasomotion and thrombus formation. These studies may, but not necessarily should, involve an *in vivo* and an *in vitro* component to allow comparison of findings in the same preparation. The peripheral blood vessels may be studied, but only to the extent that the hypothesis and experimental results are relevant to the native coronary circulation. A variety of animal species may be investigated but the model selected should be clearly justified. Human material obtained at surgery or autopsy may also be suitable for these investigations. Topics of interest include, but are not limited to, changes in rheology, the role of formed elements of the blood in, for example, clotting and the production of arachidonic acid metabolites, the role of the various components of the vessel wall, the effect of atherosclerosis on vasospasm, the effects of vasoactive peptides and more generally other neurohormonal factors, and the distribution and density of receptors affecting vascular tone. Also of interest are changes in the mechanical properties of vessel walls and the concomitant changes in collagen and elastin content, which might result in, or be the cause of vasospasm in the coronary arteries.

V. EXCLUSIONS

Studies of the causes of, or factors leading to, progressive atherosclerosis would not be considered responsive to this RFA, unless related to the phenomenon of coronary vasospasm or coronary thrombosis in terms of special conditions pertaining to the specific properties of coronary arteries. Furthermore, studies of injury to heart muscle are not appropriate for this program. Although the research topic may be multidisciplinary, it is not the intent of this request to solicit proposals for large studies encompassing a variety of essentially independent research projects (program projects).

VI. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual, research-project grant. Although \$800,000, total costs, for this program are included in the financial plans for fiscal year 1983, award of grants pursuant to this RFA is contingent upon receipt of funds for this purpose. It is anticipated that six to eight grants will be awarded under this program. The specific amount to be funded will, however, depend on the merit and scope of the applications received and the availability of funds. Since a variety of approaches would represent valid responses to this announcement, it is anticipated that there will be a range of costs among individual grants awarded.

Upon initiation of the program, the DHVD will sponsor periodic meetings to encourage exchange of information among investigators who participate in this program. In the preparation of the budget for the grant application, applicants

pathophysiology of myocardial ischemia and therapeutics aimed at limiting infarct size through the Ischemic Heart Disease Specialized Centers of Research (SCOR) Program.

However, these programs are not directed specifically toward elucidating the role of coronary vasomotion and thrombosis in the development of ischemia or the possible effects these two phenomena may have upon each other in causing or exacerbating ischemia and coronary occlusion. Furthermore, while considerable research has been directed toward the injury process in cardiac muscle, little attention has been paid to the occurrence and significance of injury in coronary arteries as a cause or effect of vasospasm and/or thrombosis.

B. Scientific Background

There are two important clinical phenomena which require further research in terms of their significance in ischemic heart disease. (1) Increased tone of large coronary arteries sufficient to cause coronary spasm has been implicated in some cases of clinical myocardial infarction and in a substantial number of patients with rest angina. (2) The occurrence of occlusive thrombi in the coronary arteries has been observed by pathological examination in approximately 80 percent of patients dying of acute transmural myocardial infarction. In addition, occlusion of the infarct-related artery has been documented by coronary angiography in approximately 80 percent of the patients studied in the early hours after infarction. Approximately 75 percent of these completely occluded coronary arteries open with intracoronary thrombolytic therapy to reveal a high grade coronary lesion. This indicates that thrombosis is important in the genesis of myocardial infarction.

Clinical investigators are currently assessing the efficacy of calcium antagonists for the treatment of coronary artery spasm and of thrombolytic agents for the restoration of blood flow in coronary arteries with occlusive thrombi. However, it is clear that these therapies are not necessarily definitive and certainly not curative. For example, recurrent ischemia and/or reocclusion occur in a significant number of patients and it is likely that the underlying lesions, or interplay of precipitating factors remain essentially unchanged. Furthermore, the factors which promote the conversion of a functionally impaired artery, or a marginally functional artery, to one which results in critical coronary spasm and/or thrombosis leading to irreversible myocardial damage are poorly understood. Some evidence suggests that occlusion of an artery reoccurs at a specific location and that there may be special physical, biochemical or anatomic conditions pertaining to that location which predispose it to occlusion. There is also the possibility that varying conditions may exist in the affected location resulting in a cyclic or periodic exacerbation of the ischemia.

A number of mechanisms may be postulated to contribute to coronary spasm, but very little information is available about their relative importance. For example, it is not known to what extent the segment of the coronary artery which undergoes spasm is damaged or contains a non-occlusive thrombus. Although considerable information is available about thrombus formation per se, it is unclear to what extent vasospasm can be induced by thrombus

This letter should be received no later than February 15, 1983, and sent to:

Dr. Charles L. Turbyfill
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Application

Submit applications on form PHS 398, the application form for the traditional research-project grant. This form is available in an applicant institution's office of sponsored research or business office or from the Division of Research Grants (DRG). Use the conventional format for research-project grant applications and ensure that the points identified in the Section on "Review Procedures and Criteria" are fulfilled.

To identify the application as a response to this RFA, check "yes" on Item 2 of page 1 of the application and enter the title CORONARY ARTERY REACTIVITY, INJURY AND THOROMBOSIS and the RFA number NIH NHLBI-DHVD-83G-A.

C. Application Procedure

Send or deliver the completed application and six (6) signed, exact photocopies of it to:

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

Send an additional twenty (20) copies of the application to:

Review Branch, DEA
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 5A15
Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible, but after discussion with the applicant, it may be considered as a regular research-project grant application.

D. Timetable

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by the National Heart, Lung, and Blood Advisory Council	September 22-24, 1983
Notification of applicants	September 28, 1983
Anticipated award date	September 30, 1983

E. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

Dr. Constance Weinstein
National Institute of Health
Federal Building - Room: 3C-06
Bethesda, Maryland 20205

Telephone: (301) 496-1081

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DLD-83G-B

DEFENSE FUNCTIONS IN THE DEVELOPING RESPIRATORY SYSTEM

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. BACKGROUND

The goal of this special grant program is to improve our understanding of the functional development of defense functions such as mucociliary clearance, phagocytosis, and local immune responses relative to host defense, in the tracheobronchial tree and at the alveolar level during fetal and postnatal life.

Studies on host-defense mechanisms in the respiratory system that are needed to maintain the lung in an aseptic state have been given considerable attention in adults in recent years. In the immature and developing respiratory system, however, our knowledge of such mechanisms is rather limited and incomplete.

The immature and developing lung is particularly vulnerable to microorganisms and other types of insults, and respiratory infections are among the most important contributors to morbidity of respiratory disorders in the first years of life. Current estimates indicate that the rate of bronchiolitis attacks may exceed 16 per year per hundred infants less than six months of age, and that the risk of hospitalization for these infants is in the order of 10 per 1,000 infants per year.

To further compound this problem it is now recognized that a significant number of very immature survivors of acute respiratory distress often have persistent complications such as secondary infections and recurrent bronchial obstruction. Although conclusive data are still lacking, it is suspected that respiratory illnesses in infancy and childhood may contribute to respiratory disorders and pulmonary function abnormalities later in life.

This program is described in the Catalog of Federal Domestic Assistance, No. 13.838, Lung Diseases. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

It is suspected that loss of ciliary movement and goblet cell function may occur as a result of repeated intubation and suctioning, and that such injuries may promote invasion of microorganisms that are difficult to eradicate. Furthermore, it has been noted that neonates who survive a long period of oxygen and ventilator dependency seem to be particularly at risk for acute pulmonary insufficiency, necessitating hospitalization, or for recurrent bronchiolitis during the first 2-3 years of life. Fundamental knowledge on the status of respiratory defense functions such as mucociliary clearance, alveolar macrophage phagocytosis and local immune responses as they apply to host defense, is currently lacking for the developing respiratory system.

Specifically, the degree of maturation of such defense functions at birth and during development, their responsiveness to challenges, and their vulnerability to insult are in need of investigation. Consequently, management and prevention of some of the most significant respiratory problems during development is mainly empirical. It is anticipated that a systematic approach to elucidating the functional development of such mechanisms may provide a scientific rationale for improved therapy and prevention.

II. OBJECTIVES AND SCOPE

The specific objective of this program is to encourage research on functional development of mucociliary clearance, phagocytosis, and local immune responses relative to host defense against infectious agents, in the tracheobronchial tree and at the alveolar level in fetal and postnatal life. For the purpose of this announcement, fetal life denotes a time not earlier than the third trimester. Investigations may be carried out in vivo or in vitro, on intact lungs, organ cultures or isolated cells, but must be designed so that meaningful extrapolations to the functional development of human lung defense are possible. Although defense functions during normal lung development should be a major theme of the applications, they may also include studies aimed towards understanding alterations in defense functions in response to insults or stimuli that are comparable to those likely to occur particularly in human infants and children receiving respiratory care.

Structural studies are encouraged if aimed towards elucidating structure-function relationships. Studies on the mature respiratory system may be included if the intent is to make relevant comparisons with the developing respiratory system, but major emphasis must be on the latter.

Research topics presented below are intended to provide a perspective of the scope of research that would meet the goals of this program. It is not required that all of these examples be included. Investigators are encouraged to consider other relevant approaches designed to expand our understanding of functional development of defense functions in the lung in fetal and postnatal life.

1) Alveolar macrophages and local immune responses.

Although alveolar macrophages constitute the major phagocytic defense of the lung, and although considerable research has been directed in the past to studies of the morphology, metabolism, and function of these mononuclear cells, little is known about their functional maturation during fetal and neonatal development including their capacity at different stages during development for phagocytosis and transportation

of particles, and the influence of the environment (e.g., O_2 concentration) on their function. It has been reported that the alveolar macrophages in the newborn are unable to respond to bacterial and viral challenges and lungs of infants have been reported to have lower phagocytic activity than those of adults. The reasons for this, however, remain unclear and studies are needed to elucidate ultrastructural and biochemical parameters related to the maturational development of alveolar macrophages and their phagocytic and microbicidal activities.

Development of local immune responses and the extent to which they may influence or modify the response of the immature lung to challenges from infectious agents are not well understood. Thus, although T and B cells are present as early as the first trimester, their appearance in the alveoli and their interaction with alveolar macrophages in relation to immunologic suppressor or stimulator reactions need investigation.

2) Mucociliary transport

The extent to which immaturity or impaired responses of mucociliary transport in the respiratory system contribute to the high rate of virulent respiratory infections in the premature and young infants and render them susceptible to other insults from the environment is poorly understood. Ciliated cells, ciliary motion and submucosal glands are present in utero well before the age of viability, but the effectiveness of the mucociliary transport mechanism in the immature respiratory system and its possible reaction to mechanical stimuli such as endotracheal intubation during lung development need elucidation. In addition, the possible relationship between the presence or absence of surfactant and alveolar-bronchiolar transport during lung development is unclear. It is known that factors from the environment may contribute to the depressed airway defense in adults. Irritants, for example, interacting with an altered airway epithelium may stimulate exposed sensory receptors resulting in increased vagal tone and chronic stimulation of submucosal glands. Altered mucus composition and secretion may compromise the function of the mucociliary transport system and increase the risk of intercurrent respiratory infection. Whether such processes occur during lung maturation and compromise defense functions in neonates and predispose to attacks of bronchiolitis is poorly understood.

III. EXCLUSIONS

Epidemiological studies and clinical trials will not be supported under this announcement; neither will studies on development of systemic or extrapulmonary immune defense functions, or studies on mechanism of pathogenicity of infectious agents.

IV. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual research grant. Although approximately \$500,000 for this program is included in the financial plans for fiscal year 1983, award of grants pursuant to this RFA is contingent upon receipt of funds for this purpose. It is anticipated that four to six

grants will be awarded under this program. The specific amount to be funded will, however, depend on the merit and scope of the applications received and the availability of funds. Since a variety of approaches would represent valid responses to this announcement, it is anticipated that there will be a range of costs among individual grants awarded.

Upon initiation of the program, the Division of Lung Diseases (DLD) will sponsor periodic meetings to encourage exchange of information among investigators who participate in this program. In the preparation of the budget for the grant application, applicants should request travel funds for a one-day meeting each year, most likely to be held in Bethesda, Maryland. Applicants should also include a statement in their applications indicating their willingness to participate.

Applicants (who will plan and executive their own research programs) are requested to furnish their own estimates of the time required to achieve the objectives of the proposed research project; however, the award period for this activity should not exceed three years. At the end of the initial award period, renewal applications may be submitted for further competitive review through the regular grant program of the NIH. It is anticipated that support will begin on September 30, 1983.

The current policies and requirements that govern the research grant programs of the National Institutes of Health (NIH) will prevail, including the requirement for cost sharing.

V. REVIEW PROCEDURES AND CRITERIA

A. Review Method

All applications submitted in response to this RFA will be reviewed for scientific and technical merit by an initial review group, which will be convened by the Division of Extramural Affairs (DEA), National Heart, Lung, and Blood Institute (NHLBI), solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the 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 have it considered for the regular grant program of the NIH.

If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factors to be considered in the evaluation of scientific merit of each applicant will be similar to those used in the review of traditional research project grant applications including the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed.

VI. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are encouraged to submit a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions. Such letters are requested for the purpose of obtaining an indication of the number and scope of applications to be received. A letter of intent is not binding, and it will not enter into the review of any application subsequently submitted, nor is it a necessary requirement for application. This letter should be received no later than February 15, 1983, and sent to:

Charles L. Turbyfill, Ph.D.
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Applications

Submit applications on form PHS 398, the application form for the traditional research project grant. This form is available in an applicant institution's office of sponsored research or from the Division of Research Grants (DRG). Use the conventional format for research project grant applications and ensure that the points identified in the section on "Review Procedures and Criteria" are fulfilled. To identify the application as a response to this RFA, check "yes" on item 2 of page 1 of the application and enter the title "DEFENSE FUNCTIONS IN THE DEVELOPING RESPIRATORY SYSTEM" and the RFA number NIH-NHLBI-DL D-83G-B.

C. Application Procedure

Send or deliver the completed application and six (6) signed, complete photocopies of it to:

Division of Research Grants
National Institutes of Health
Westwood Building - Room 5A15
Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible.

D. Timetable

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by National Advisory Council	September 1983
Anticipated award date	September 30, 1983

E. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

Bitten Stripp, Ph.D.
Chief, Structure and Function Branch
Division of Lung Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 6A03
Bethesda, Maryland 20205

Telephone: (301) 496-7171

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATION: RFA

RFA-NIH-NHLBI-DHVD-83G-C

BIOBEHAVIORAL FACTORS AFFECTING HYPERTENSION IN BLACKS

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. PURPOSE

The Division of Heart and Vascular Diseases (DHVD), National Heart, Lung, and Blood Institute (NHLBI), invites grant applications for a single competition for support of research on the interaction of physiological and behavioral factors related to blood pressure variations and hypertension among Black populations. The major purpose of this special grant program is to gain basic information on blood pressure and other physiological response differences among population subgroups in the presence of controlled psychological stressors.

II. DISCIPLINES AND EXPERTISE

The interdisciplinary nature of this research makes appropriate combined expertise from biobehavioral research disciplines (psychophysiology, psychobiology, experimental psychology) in cooperation with biomedical disciplines (physiology, cardiology, neurobiology, genetics, and nutrition).

III. BACKGROUND

A. Administrative Background

As a component of the Clinical Applications and Prevention Program of the DHVD, the Behavioral Medicine Branch (DMB) encourages and administers programs of biobehavioral research related to cardiovascular health and disease issues. The program fosters maximum collaboration between the biomedical and behavioral science communities on research problems of mutual concern including the use of behavioral techniques to elucidate basic mechanisms of cardiovascular control and identification of biobehavioral correlates of hypertension. Within that program objective, this solicitation is responsive to recommendations of the National Black Health Providers Task

This program is identified in the Catalog of Federal Domestic Assistance No. 13.837, Heart and Vascular Diseases. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

Force on High Blood Pressure Education and Control (convened by NHLBI, October 1980) for research on the role of psychological and social stressors in the Black community.

Investigator-initiated research presently supported through the Behavioral Medicine Branch includes several projects investigating cardiovascular reactivity to controlled stressors in the laboratory, monitoring of blood pressure variations in response to identifiable stressful events in everyday life, and cardiovascular and neural differences in subgroups of subjects under behavioral challenges. A recent (1982) special announcement solicited proposals for biobehavioral research in animals on genetic and developmental factors in the etiology of hypertension. Encouragement of research addressing different subgroup responses relevant to hypertension in biobehavioral studies with human subjects is appropriate and within the scope of program emphasis.

B. Scientific Background

Hypertension prevalence rates differ among population subgroups with a significantly higher prevalence of the disorder reported among Blacks as compared to Whites in this country. Although the etiology of hypertension is not clearly understood, a broad spectrum of potential physiological, psychological and environmental contributors to the development of hypertension has been identified through scientific investigations. Research evidence suggests physiological and behavioral/environmental factors interact to affect differences in disease prevalence among subgroups and that multifactorial studies of differences among subgroups such as Black and White populations have potential for elucidating the etiology of hypertension and its observed higher prevalence among Blacks.

Epidemiological studies have identified psychosocial and environmental stress factors as relevant and, in some case, primary variables in the development of hypertension. Dietary factors, particularly sodium intake in combination with a constitutional predisposition to salt sensitivity, have been investigated as contributing to increased blood pressure levels. Recent research explores the potential role of other nutrients (including potassium, calcium, magnesium) to elevated blood pressure and hypertension. Biobehavioral research on cardiovascular reactivity to laboratory psychological stressors reveals that behavioral and physiological interactions may be significant for explaining blood pressure variations. However, descriptive studies of environmental stressors in the development of hypertension rarely address interactions of psychological and physiological factors and few laboratory studies have conducted research on the effects of controlled stressors on specific population subgroups including Blacks.

Physiological studies suggest subgroup differences, such as increased sympathetic tone indicated by plasma renin or dopamine beta-hydroxylase levels, are linked to blood pressure variations. Sodium excretion and sodium/potassium ratio differences between Black and White populations have been reported. Recent work on "mild" hypertensives suggests that different mechanisms are significant for development of hypertension among subgroups characterized by differing physiological indicators. These scientific findings, however, do not explain blood pressure variations or hypertension prevalence differences. Evidence suggests a complex etiology for hypertension through

which psychological and environmental factors interact with physiological variables resulting in different prevalence rates for subgroups including Black and White populations.

IV. OBJECTIVES

This special grant program is for the support of research on the interrelatedness of physiological mechanisms which in combination with behavioral factors could clarify the conditions for development of hypertension in groups with significant differences in prevalence of hypertension. Investigations directed toward differing responses of Black and White populations or variables significant for Black populations are required by this special program.

V. SCOPE

The proposed research should be dedicated to augmenting existing knowledge of physiological responses of Blacks and Whites relevant to the development of hypertension and to gain basic information of subgroup responses to specific stressors relevant to blood pressure variations. Proposals involving interdisciplinary approaches in the development of interactive models of selected behavioral and physiological factors are encouraged. Models of the interaction of such factors should use defined variables, justify subject selection, and make use of appropriate biomedical and behavioral measurement techniques. While studies are expected to use controlled stressors within experimental designs, proposed research should indicate relevance to situations of naturally occurring stress.

Physiological factors applicable for proposed studies are those significant in the etiology of hypertension, including but not restricted to studies of nervous system activity and catecholamines; the renopressor or renin-angiotension system; the excretory function of the kidney; other hormonal and fluid balance controlling factors; and measures of cardiovascular reactivity. Dietary factors including sodium, sodium sensitivity, potassium and other nutrients are appropriate, as are other indicators used to differentiate among subgroups of hypertensives. Behavioral variables in proposed research designs may include laboratory challenges, controlled stressors or other emotional stimuli. Research supported under this program should include subjects and/or variables which will expand scientific knowledge of blood pressure variations among Black populations as a subgroup of interest.

Examples of appropriate research include, but are not limited to, the following: investigations of individual differences in behaviorally-induced cardiovascular reactivity among Black and White borderline hypertensives differing in autonomic functioning, studies of individuals differing in physiological indicators such as skin pigmentation, salt excretion, other nutrient levels or dietary intake patterns monitored for their responsiveness to laboratory psychological stimuli (including, but not limited to the cold pressor test, competitive stress, mental arithmetic, or task performance under laboratory-administered stressors); similar subgroups observed for physiological and psychological responses to salt loading; individual blood pressure variations and related physiological responses to stressor situations involving differences in coping strategies.

VI. EXCLUSIONS

Clinical trials or population survey research would not be supported through this solicitation. Educational approaches or comparison of treatments will be excluded from support. Proposals must be directed toward differentiating among factors significant to subgroups including Black populations to be considered appropriate. Although the research topic is interdisciplinary, it is not the intent of this request to solicit proposals for large studies encompassing a variety of essentially independent research projects (program projects).

VII. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual, research-project grant. Although this program is included in the financial plan for fiscal year 1984, award of grants pursuant to this RFA is contingent upon receipt of funds for this purpose. It is anticipated that three to four grants will be awarded under this program. The specific amount to be funded will, however, depend on the merit and scope of the applications received and availability of funds. Since a variety of approaches would represent valid responses to this announcement, it is anticipated that there will be a range of costs among individual grants awarded.

Upon initiation of the program, the DHVD will sponsor periodic meetings to encourage exchange of information among investigators who participate in this program. In the preparation of the budget for the grant application, applicants should request travel funds for a two-day meeting each year, most likely to be held in Bethesda, Maryland. Applicants should also include a statement in their applications indicating their willingness to participate in such meetings and share information on their research methodology and progress.

Applicants, who will plan and execute their own research programs, are requested to furnish their own estimates of the time required to achieve the objectives of the proposed research project; however, the award period for this activity must not exceed three years. At the end of the initial award period, renewal applications may be submitted for further competitive review through the regular grant program of the National Institutes of Health (NIH). It is anticipated that support will begin on December 1, 1983. Should funding become available, awards may be authorized to begin at an earlier (September 30, 1983) date.

The current policies and requirements that govern the research grant programs of the NIH will prevail.

VIII. REVIEW PROCEDURES AND CRITERIA

A. Review Method

All applications responding to this RFA will be reviewed for scientific and technical merit by one initial review group, which will be convened by the Division of Extramural Affairs (DEA), NHLBI, solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the objectives of this RFA. If an application is judged unresponsive, the applicant will be contacted and given an opportunity to withdraw the applicant or to have it considered in the regular research grant program of the NIH.

If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factors to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research-project grant applications, including the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed. An assessment of the importance of the proposed research to the objectives of this RFA and relevance to its goals will be important review considerations.

IX. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are encouraged to submit to the Review Branch of the Institute a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions. The Institute requests such letters for the purpose of providing an indication of the number and scope of applications to be expected. A letter of intent is not binding, and it will not enter into the review of any application subsequently submitted, nor is it a necessary requirement of application. This letter should be received no later than February 15, 1983. Letters of intent should be sent to:

Dr. Charles L. Turbyfill
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Applications

Submit applications on form PHS 398, the application form for the traditional research-project grant. This form is available in an applicant institution's office of sponsored research or business office or from the Division of Research Grants (DRG). Use the conventional format for research-project grant applications and ensure that the points identified in the Section on "Review Procedures and Criteria" are fulfilled.

To identify the application as a response to this RFA, check "yes" on Item 2 of page 1 of the application and enter the title "BIOBEHAVIORAL FACTORS AFFECTING HYPERTENSION IN BLACKS" and the RFA number NIH-NHLBI-DHVD-83G-C.

C. Application Procedure

Send or deliver the completed application and six (6) signed, exact photocopies of it it:

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

Send an additional twenty (20) copies of the application to:

Review Branch, DEA
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 5A15
Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible for this program, but after discussion with the applicant, it may be considered as a regular research-project grant application.

Timetable:

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by the National Heart, Lung, and Blood Advisory Council	September 22-24, 1983
Notification of applicants	September 28, 1983
Anticipated award date	December 1, 1983

D. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

Dr. Katrina W. Johnson
National Institutes of Health
Federal Building - Room 604
Bethesda, Maryland 20205

Telephone: (301) 496-9380

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DHVD-83G-D

CARDIAC HYPERTROPHY AND FAILURE IN CHRONIC HYPERTENSION

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. PURPOSE

The Division of Heart and Vascular Diseases (DHVD), National Heart, Lung, and Blood Institute (NHLBI), invites grant applications for support of research on cardiac hypertrophy in chronic hypertension. The purpose of this special grant program is to expand the study of the transition from normal cardiac structure and function to cardiac hypertrophy and cardiac failure in chronic systemic hypertension, with special emphasis on the mechanisms responsible for these changes. Applications received in response to this request will participate in a single competition.

II. DISCIPLINES AND EXPERTISE

Among the disciplines and expertise that may be appropriate for this research program are molecular biology, physiology, protein and collagen chemistry, pathology, ultrastructure, and clinical cardiology.

III. BACKGROUND

The Hypertension and Kidney Diseases Branch, of the DHVD, designs and administers programs of research and development seeking to understand the etiology of essential hypertension and the impact of hypertension on organ systems. The program fosters the development of new knowledge and the translation of results into methods for clinical application.

The Hypertension and Kidney Diseases Branch currently support research linking cardiac structure and function to hypertension, but the amount of research dealing with the effects of long-term, chronic hypertension is limited.

This program is identified in the Catalog of Federal Domestic Assistance No. 13.837, Heart and Vascular Diseases. Awards will be made under the authority of the Federal Health Service Act, Section 301 (42 USC 241) and administered under PHS grant procedures and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

Two recently held NHLBI-sponsored workshops assessed the status of research relating to cardiac hypertrophy and cardiac failure, the Workshop on Advanced Heart Failure in Spring 1981, and the Workshop on Ventricular Hypertrophy in Hypertension in Fall 1981. This RFA is based upon recommendations arising from these workshops. It was identified as a high priority project by the Arteriosclerosis, Hypertension, and Lipid Metabolism Advisory Committee at its May 1982 meeting.

IV. OBJECTIVES AND SCOPE

The objective of this special grant program is to stimulate the development of research to characterize the transition from normal cardiac structure and function to cardiac hypertrophy and cardiac failure in chronic hypertension. There is special interest in clarifying the mechanisms by which these effects are produced, and in identifying stages in the process where changes are "reversible" and where they are "irreversible." A broad range of research interest areas will be responsive to this initiative, including hemodynamic, morphological, physiological, and biochemical changes affecting stromal, muscular and vascular components of the heart.

This special research program will involve predominantly animal models of chronic systemic hypertension. Scientific advances, such as in cardiac physiology, in the biochemistry of connective tissue synthesis, in the ability to assess ventricular function, and in understanding of drugs which improve cardiac contraction, are available to be applied to these models. Experimental models other than those of chronic hypertension will be acceptable only if their relevance to hypertensive-induced cardiac hypertrophy can be shown. Because this initiative seeks to clarify basic mechanisms, it is anticipated that proposals will be based principally on animal experimentation. However, the Branch does not wish to rule out the possibility that a proposal based on human subjects could be responsive to this announcement.

Applications are sought from individuals and from groups of investigators. Interdisciplinary proposals are encouraged, but such proposals must be carefully focused. If collaborative arrangements through subcontracts with other institutions are planned, NHLBI staff should be consulted regarding the appropriate procedures.

V. EXAMPLES OF RESEARCH TOPICS

The following lines of research are presented as examples only, and do not exhaust the many opportunities for productive research. They are not listed in order of importance:

- o The fibrous skeleton of the heart and its influence on the systolic and diastolic functions of the heart require further characterization. This field is of particular importance because the complex network of collagen bundles in the heart that interconnects the myocytes and capillaries and orders the myocytes into groups, is altered in disease states. There is as yet no organized body of information to relate abnormalities of collagen synthesis to altered ventricular function in cardiac hypertrophy. Closely linked to the study of the connective tissue is the evaluation of the "non-muscle space" in the heart, particularly as regards the organization of the microvascular bed, the lymphatics, and connective tissue matrix.

- o The study of myocardial metabolism has been undertaken mostly in non-hypertensive conditions. It is important to ascertain whether substrates and types of proteins (both contractile and noncontractile) are different between genetic and non-genetic forms of hypertension. Evidence has been developed that protease activity is greatly increased in the myocardium during the development of hypertensive hypertrophy. The systems responsible for this increased activity and their involvement in controlling the rate of proteolysis need to be further defined since an imbalance in them can account for changes in cardiac muscle size and protein composition, as well as result in changes in contractile activity and metabolic function.
- o Analysis of catecholamine turnover in the myocardium is important. A highly suggestive body of evidence has been developed recently, to the effect that adrenergic influences play a role in modulating structural responses of the heart and of resistance vessels to hypertension.
- o There is interest both in the transition to hypertrophy and in the reverse process. Through timed interventions at various stages of the transition and by correlation of the morphological, histological, biochemical, and physiological changes that occur, it may be possible to gain new insights into the fundamental properties of the myocardium in heart failure, and to identify the points of irreversibility in the pathophysiological process.

The presently used animal models of long-term, chronic hypertension are limited and new models would be welcome. How long a given animal must remain hypertensive before initiation of anatomical and biochemical changes is not established. Thus, the early stages of the project could be concerned with long-term model development and characterization.

VI. EXCLUSIONS

No support will be provided for research in cardiac hypertrophy or failure resulting from known initiating factors other than systemic hypertension, unless the relevance to systemic hypertension-induced conditions can be shown. It is not the intent of this request to solicit proposals resembling program projects. However, in some instances the need for several skills will be recognized. Such collaborative research should be justified in the proposal accordingly.

VII. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual, research project grant. Although this solicitation is included in the plans for Fiscal Year 1984, support of grants pursuant to this request for applications is contingent upon ultimate receipt of appropriate funds for this purpose. It is anticipated that up to six grants will be awarded, however, the specific number will be influenced by the amount of funds available to the Division, by the overall merit of proposals, and by their critical relevance to the program objectives. A variety of approaches will be responsive to this announcement; accordingly, it is anticipated that there will be a range of costs among individual grants awarded.

Upon initiation of the program, the DHVD will sponsor periodic meetings to encourage exchange of information among participating investigators. In the preparation of the budget for the grant application, applicants should request travel

funds for a two-day meeting each year, most likely to be held in Bethesda, Maryland. Applicants should also include a statement in their applications indicating their willingness to participate in such meetings.

Applicants, who will plan and execute their own research programs, are requested to furnish their own estimates of the time required to achieve the objectives of the proposed research project; however, the award period for this activity will not exceed five years. At the end of the initial award period, renewal applications may be submitted for further competitive review through the regular grant program of the NIH. It is anticipated that support will begin on December 1, 1983. However, if funds are available an earlier start date could be authorized.

The current policies and requirements that govern the research grant programs of the NIH will prevail.

VIII. REVIEW PROCEDURES AND CRITERIA

A. Review Method

All applications responding to this RFA will be reviewed for scientific and technical merit by one initial review group, which will be convened by the Division of Extramural Affairs (DEA), NHLBI, solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the 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 have it considered for the regular research grant program of the NIH. If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factor to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research-project grant applications; the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed. An additional criterion will be the importance of the proposed work to the objectives of this RFA.

IX. METHOD APPLYING

A. Letter of Intent

Prospective applicants are encouraged to submit to the Review Branch of the Institute a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions. The Institute requests such letters for the purpose of providing an indication of the number and scope of applications to be received. A letter of intent is

not binding, and it will not enter into the review of any application subsequently submitted, nor is it a necessary requirement for application. This letter should be received no later than February 15, 1983, and sent to:

Dr. Charles L. Turbyfill
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Applications

Submit applications on form PHS 398, the application form for the traditional research-project grant. This form is available in an applicant institution's office of sponsored research or business office or from the Division of Research Grants (DRG). Use the conventional format for research-project grant applications and ensure that the points identified in the Section on "Review Procedures and Criteria" are fulfilled.

To identify the application as a response to this RFA, check "yes" on Item 2 of page 1 of the application and enter the title "CARDIAC HYPERTROPHY AND FAILURE IN CHRONIC HYPERTENSION" and the RFA number NIH-NHLBI-DHVD-83G-D.

C. Application Procedure

Send or deliver the completed application and six (6) signed, exact photocopies of it to:

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

Send an additional twenty (20) copies of the application to:

Review Branch, DEA
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 5A15A
Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible, but after discussion with the applicant, it may be considered as a regular research-project grant application.

D. Timetable

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by the National Heart, Lung, and Blood Advisory Council	September 22-24, 1983
Notification of applicants	September 28, 1983
Anticipated award date	December 1, 1983

E. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

Dr. John B. Dunbar
National Institutes of Health
Federal Building - Room 4C08
Bethesda, Maryland 20205

Telephone: (301) 496-1857

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DHVD-83G-E

DYSRHYTHMIAS IN THE DEVELOPING AND IMMATURE HEART

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. PURPOSE

The Division of Heart and Vascular Diseases (DHVD), National Heart, Lung, and Blood Institute (NHLBI), invites grant applications for support of research in developmental electrophysiology and control of dysrhythmias in the young. Knowledge gained by studies on the immature and developing conduction system approached from basic cellular and from clinical perspectives should lead to more appropriate care of the pediatric cardiovascular patient. Applications received in response to this request will participate in a single competition.

II. DISCIPLINES AND EXPERTISE

Disciplines and expertise appropriate for this research program include embryology, pharmacology, electrophysiology, pediatric cardiology, biochemistry, physiology, pathology and biophysics.

III. BACKGROUND

There is incomplete knowledge of the etiology, pathophysiology, and rational therapeutic approach to cardiac dysrhythmias in children.

The prevalence and incidence of dysrhythmia and conduction defects in children are not known but one large study found 2 per cent of randomly selected children had some form of dysrhythmia. Ambulatory monitoring has revealed conduction abnormalities and dysrhythmias to be more prevalent than was previously thought. Whereas some pediatric dysrhythmias are benign and transient, others may be serious or even fatal. Although effort has been expended to define normal electrophysiologic parameters for infants and children, pediatric dysrhythmias and conduction disturbances have not been studied systematically. Some forms of congenital or acquired heart disease are especially susceptible to early or late postoperative dysrhythmias. The number of children with congenital heart disease

This program is described in the Catalog of Federal Domestic Assistance No. 13.837, Heart and Vascular Diseases. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

who survive surgery is increasing, and with their longer survival, an increasing incidence of dysrhythmia is seen. More is known about serious conduction abnormalities and dysrhythmia following surgery for d-transposition of the great vessels (d-TGA) and tetralogy of Fallot (TOF) than any other congenital lesions, yet only basic descriptive and natural history questions have been examined. Each year, 1000 children with d-TGA and 5000 with TOF successfully undergo surgical correction. Follow up studies reveal that most of these patients subsequently develop conduction disturbances. The significance of these different disturbances and their relationship to sudden death is not clear. These children are now surviving into adulthood; the incidence and significance of rhythm disturbances in adult survivors of surgical correction of congenital heart disease is unknown. Virtually nothing is known about dysrhythmias in other congenital lesions.

The etiology and mechanisms of acquired or naturally occurring arrhythmias in the developing and maturing heart are unknown. Additionally there is a paucity of information regarding the pharmacokinetics and pharmacodynamics of conventional and investigational antiarrhythmic agents in neonates and children. This information is needed for safe, effective therapy. No prior organized program of research in the area of dysrhythmia in the young has been undertaken.

IV. OBJECTIVES

The objectives of this solicitation are to stimulate research into the etiology, pathophysiology and treatment of rhythm disturbances in the developing and young heart. The topic requires a multifaceted approach encompassing biochemistry, biophysics, physiology and pharmacology to evaluate abnormalities of impulse generation and conduction in basic cellular systems as well as intact animal and clinical studies.

V. SCOPE

Fundamental electrophysiologic studies in adults are well established, but little is known about how development influences impulse generation, conduction or mechanisms of re-entry. There is great need for further information on these issues.

Experiments at the cellular level have demonstrated differences in the action potential configuration in the fetal, neonatal and adult heart. The neonatal cardiac cell appears to be less sensitive to pharmacologic intervention than the mature cell; whether this is due to differences in cellular drug metabolism and distribution, immaturity of receptors, transmembrane permeability or other factors is not known. Greater understanding of the cellular events in the developing cardiac cell, and their differences from those of the mature cell are needed.

The neonatal myocardium differs structurally and biochemically from the adult myocardium; the neonate has a different capacity for conjugating, detoxifying and excreting drugs, and extracellular fluid volume in neonates is proportionately greater than in adults. There appear to be differences between children and adults in the distribution, biological half life, plasma half life and even the metabolites for some of the major anti-arrhythmic agents. There is almost no information about these differences with the newer agents. Therefore studies of these and other variables (such as effects on cardiovascular function and electrophysiologic

variables) at different stages of development from the fetus to the adult are needed. These studies can be done in great detail in experimental animals, and where appropriate, confirmed in patients of various ages. This would permit identification of appropriate pharmacologic regimens for clinical treatment.

VI. EXCLUSION

Clinical trials or clinical drug validation studies would not be supported through this special solicitation. Studies of sudden infant death syndrome (SIDS) are also not appropriate for this solicitation. Although the research topic may be multidisciplinary, it is not the intent of this request to solicit proposals for large studies encompassing a variety of essentially independent research projects (program projects).

VII. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual, research project grant. Although \$600,000 in total costs for this program are included in the fiscal plans for fiscal year 1983, award of grants pursuant to this RFA is contingent upon receipt of funds for this purpose. Depending on the merit of the application, 5 or 6 applications for a three-year period will be funded. Upon initiation of the program, the Cardiac Diseases Branch (CDC), DHVD, will sponsor meeting to encourage exchange of information among investigators who participate in this program. In the preparation of the budget of the grant application, applicants should request travel funds for a two-day meeting on this topic each year, most likely to be held in Bethesda, Maryland. Applicants should also include a statement in their application indicating their willingness to participate in such meetings. At the end of the initial award period, renewal applications may be submitted for competitive renewal through the regular grant program of the NIH. Since a variety of approaches would represent valid responses to this announcement, it is anticipated that there will be a range of costs amongst the individual grants awarded.

All current policies and requirements that govern the research grant programs of the PHS will apply.

VIII. REVIEW PROCEDURES AND CRITERIA

A. Review Method

All applications responding to this RFA will be reviewed for scientific and technical merit by an initial review group, which will be convened by the Division of Extramural Affairs (DEA), NHLBI, solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the 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 have it considered for the regular research grant program of the NIH.

If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factors to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research-project grant applications; the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed. An additional criterion will be the importance of the proposed work to the objectives of this RFA.

IX. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are encouraged to submit to the Review Branch of the Institute a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions. The Institute requests such letters for the purpose of providing an indication of the number and scope of applications to be received. A letter of intent is not binding, and it will not enter into the review of any application subsequently submitted, nor is it a necessary requirement for application. This letter should be received no later than February 15, 1983 and sent to:

Dr. Charles L. Turbyfill
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Applications

Submit applications on form PHS 398, the application form for the traditional research-project grant. This form is available in an applicant institution's office of sponsored research or business office or from the Division of Research Grants (DRG). Use the conventional format for research-project grant applications and ensure that the points identified in the Section on "Review Procedures and Criteria" are fulfilled.

To identify the application as a response to this RFA, check "yes" on Item 2 of page 1 of the application and enter the title "DYSRHYTHMIAS IN THE DEVELOPING AND IMMATURE HEART" and the RFA number NIH-NHLBI-DHVD-83G-E.

C. Application Procedure

Send or deliver the completed application and six (6) signed, exact photocopies of it to:

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

Send an additional twenty (20) copies of the application to:

Review Branch, DEA
 National Heart, Lung, and Blood Institute
 National Institutes of Health
 Westwood Building - Room 5A15
 Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible, but after discussion with the applicant, it may be considered as a regular research-project grant application.

D. Timetable

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by the National Heart, Lung, and Blood Advisory Council	September 22-24, 1983
Notification of applicants	September 28, 1983
Anticipated award date	September 30, 1983

E. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

Zena McCallum
 National Institutes of Health
 Federal Building - Room 3C06
 Bethesda, Maryland 20205

Telephone: (301) 496-1081

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DBDR-83G-F

RHEOLOGICAL STUDIES IN SICKLE CELL DISEASE

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. PURPOSE

The Division of Blood Diseases and Resources (DBDR), National Heart, Lung, and Blood Institute (NHLBI), invites grant applications for a single competition for support of research designed to clarify rheological aspects of sickle cell disease. The submission of applications with new, especially interdisciplinary approaches, by investigator who may not have previously worked in sickle cell disease is specifically encouraged. The section on Program Scope, based on the program objectives presented, is meant to suggest, rather than circumscribe, the range of approaches of interest for this RFA. No one laboratory is expected to cover the entire Program Scope. A variety of approaches could be considered as valid responses to this announcement.

II. DISCIPLINES AND EXPERTISE

Among the disciplines and expertise that may be appropriate for this research program are rheology, engineering, hemoglobin chemistry, molecular and cell biology, membrane biochemistry, and clinical expertise in hematology.

III. ADMINISTRATIVE BACKGROUND

The Sickle Cell Disease Branch of the Division of Blood Diseases and Resources, sponsors fundamental and clinical research grants and contracts related to the pathophysiology of clinical syndromes caused by sickle hemoglobin. In addition, studies are supported which utilize anatomical, biochemical, biophysical, physiological, and clinical approaches to increase our understanding of the nature, cause, diagnosis and treatment of sickle cell disease.

Several projects in this and related areas are supported by investigator-initiated grants. Research topics include nuclear magnetic resonance techniques for investigating the structure-function relationships in normal and sickle cell

This program is described in the Catalog of Federal Domestic Assistance No. 13.839 Blood Diseases and Resources. Awards will be made under the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is no subject to A-95 Clearinghouse or Health Systems Agency review.

hemoglobins; the use of crystallography and electron microscopy techniques in order to determine the molecular structure of sickle cell fibers; biophysical approaches to erythrocyte sickling; and erythrocyte-endothelial interactions in sickle cell disease. In addition, special initiatives sponsored by the Institute have led to the support of investigators attempting to develop an intravascular system for assaying characteristics of sickle erythrocytes in laboratory animal systems. For example, two grants were awarded in 1979 to (1) study ways of increasing our understanding of the pathophysiology of sickle cell anemia through a systematic in vivo study of the behavior of sickle erythrocytes; (2) employ the intravascular system for the evaluation of the in vivo effectiveness of various drugs known to inhibit sickling in vitro; and (3) correlate in vitro and in vivo rheological changes with the behavior of sickle erythrocytes; (2) employ the intravascular system for the evaluation of the in vivo effectiveness of various drugs known to inhibit sickling in vitro; and (3) correlate in vitro and in vivo rheological changes with manifestations of tissue damage as an explanation of the pathophysiology of sickle cell disease. In each of the two grants, emphasis was on the rheologic behavior of sickle erythrocytes.

IV. SCIENTIFIC BACKGROUND

Since the initial work of Ham and Castle in 1940, it has been evident that alterations of the biophysical properties of sickle erythrocytes affect their ability to flow in the microvasculature and are important elements in the pathogenesis of sickle cell disease and its complications. Numerous in vitro studies on blood from sickle cell patients have established that the deoxygenated sickle cell is 10 to 25 times more rigid than the normal hemoglobin AA cell. When measured in bulk-flow viscometric systems, blood from sickle cell disease patients has a higher than normal viscosity even when oxygenated. In Hgb SC, S + thal and SF double heterozygous states, viscosities are intermediate between those of SS and AA cells and correlate with the clinical severity of disease. In Hgb SC disease, the high hematocrit viscosity effect influences the propensity for vascular occlusions in the ocular fundus and aseptic necrosis of bone.

Techniques designed to measure red cell deformability (capacity of blood to traverse micropore filters) have demonstrated a marked decrease in the filterability of sickle cell blood under both ambient and deoxygenated conditions. The principal contributor in the oxygenated state appears to be the irreversible sickled cell (ISC), a membrane-damaged cell which retains its rigid sickle shape even under oxygenation. These irreversibly sickled cells, which number as many as 35 percent of the total erythrocytes of a patient with sickle cell disease, owe a part of their rigidity to the high corpuscular hemoglobin concentration.

Furthermore, the deformability and rheologic characteristics of sickle erythrocytes, both ISC and non-ISC, have been studied in a variety of systems including viscometric, cell filtration, and artificial blood flow devices. Such studies have shown that the critical oxygen tension for altering the rheologic properties of sickle cells occurs in the range of 60 to 80 mm Hg. This critical P_{O_2} range is substantially above that encountered at the venous end of the capillary bed (40 mm Hg to as low as 18 mm Hg in the coronary sinus). Observations in the capillary beds of experimental animal models and the "apparent" frequency of microvascular occlusion in patients would suggest that sickle cells generally escape entrapment within the microvasculature before a critical P_{O_2} is reached. Such considerations have led molecular biologists to propose the "kinetic hypothesis" for sickling vaso-occlusion. This hypothesis simply states that when capillary transit

time is shorter than sickling time, vaso-occlusion does not occur. Conversely, when capillary transit time is delayed so that it exceeds sickling time, the cell will become rigid within the capillary and initiate vaso-occlusion. Conditions which can retard or impede the capillary transit time of individual SS erythrocytes are manifold. Blockage of the capillary microcirculation at bifurcation points by ISC's hinders the flow of non-ISC's across a given capillary bed causing them to undergo intravascular sickling. Capillary edema, inflammation, and the effect of vasoactive substances may influence the capillary flow rate and substrata in such a way as to prolong transit time. An alternative model, which stresses the equilibrium amounts of polymer at oxygen saturation values in the microcirculation, rather than the kinetics of sickling and possible obstruction to flow at the arteriolar side of the circulation, has also been proposed.

Several recent observations concerning the propensity of sickle cells to adhere to endothelial cells have raised the question of whether these adherent sickle cells, both ISC and non-ISC, can retard blood flow, initiating vaso-occlusion and inducing endothelial damage and microvascular pathology. Both physiologic and ultrastructural methods of assessment have shown that microvascular beds and their individual cell components are capable of active responses to both physiologic and pathologic stimuli. Constrictor substances, such as vasoactive amines, and proteins are capable of inducing dramatic alterations in the blood flow to a given capillary bed. The endothelial cell undergoes significant pathologic alteration in response to stimuli such as hypoxia. With both acute and sustained low oxygen tensions, endothelial cells develop vacuolization and a microvillous luminal surface capable of further impeding blood flow. Thus, since impedance of blood flow is the key rheologic determinant of sickle cell disease, and both in vitro and in vivo evidence points to a wide spectrum of abnormalities in the sickle cell, the capillary bed, and the endothelial cells, it would appear that new research initiatives to elucidate rheologic and microvascular mechanisms in sickle cell disease should be pursued.

Recent studies indicate a strong correlation between adhesion of sickle cells to the endothelium and the clinical severity of the disease. However, as yet no in vitro test has been successful in quantitating the physical properties of the adhesion.

V. OBJECTIVES

The fundamental pathophysiology of sickle cell disease involves a disturbance of microvascular flow. The intracellular gelation of sickle hemoglobin appears to be the critical factor in affecting flow through the microcirculation, although other processes may also contribute. Therefore, an important facet of future research in sickle cell disease is the study of the passage of sickle cells through different regions of the microcirculation under a variety of physiologically relevant conditions. The specific objectives of this solicitation are to:

- o develop models to study normal and sickle erythrocyte deformability and flow;
- o develop an understanding of the influence of the physical state of intracellular hemoglobin on the rheologic properties of sickle erythrocytes;

- o increase knowledge of the structure and function of the erythrocyte membrane in relationship to its direct involvement in the rheologic pathology of sickle cell anemia;
- o develop in vitro flow models, with complex geometry, that incorporate such features as branching, bending, bifurcation, and a length and diameter approximating those of the microcirculation;
- o develop experimental systems using ex vivo or in vivo microcirculatory beds of varying order and geometry in which rheologic and physiologic variables such as pressure, flow, oxygen tension, and hematocrit can be controlled and measured;
- o elucidate the mechanisms of control and anatomical sites of microvascular obstruction in sickle cell disease, including neural and hormonal control, and the function of plasma factor, leukocyte and platelets in microvascular occlusion; and
- o develop techniques for studying the microvasculature in normal human subject and sickle cell patients in order to quantitate rheologic and physiologic variables.

VI. SCOPE

The central derangement in sickle cell disease appears to be an abnormality of microcirculatory flow caused by the sickled erythrocyte. To understand events that lead to the chronic anemia and interfere with tissue perfusion, better comprehension of red cell rheology and microcirculatory dynamics in sickle cell anemia is necessary.

The mechanism of intracellular polymerization of sickle hemoglobin and its effects on the properties of the erythrocyte are areas for further investigation. Studies of the internal viscosity of the erythrocyte, change in the structure and function of the erythrocyte membrane, and alterations in the deformability and flow properties of whole erythrocytes under various conditions of hematocrit, oxygen saturation (degree of hemoglobin ligation), temperature, intracellular pH, osmolarity and other relevant variables are necessary in sickle cell disease rheology. These studies should be done under experimental conditions that best simulate physiological conditions.

Information on irreversibly sickled cells and the interaction of sickle erythrocytes with numerous blood components as well as with other cells including leukocyte and platelets is lacking. The significance of cellular interactions with the endothelium and modulating factors of these interactions, as fibrinogen or bigronectin, are relevant subjects for study since there is evidence that adherence to endothelial cells correlates with clinical severity. Interaction of hemoglobin with the red cell membrane, the structure and function of membrane proteins and lipids, and physiological processes related to cellular dehydration and ion fluxes are also of potential relevance. Considerable importance is placed on the evaluation of the pathophysiological role in all such studies.

Recent work in circulatory physiology using noninvasive methods of measuring organ integrity and blood flow, such as NMR imaging, ultrasound and Doppler measurements, laser and photomicroscopy, and new method of measuring

physiology of whole organs, (for example, position emission tomography), suggests new approaches to rheologic studies of experimental animals or, more important, to the evaluation of organ and tissue blood flow in normal individuals and sickle cell patients. It is expected that such methods will eventually provide objective means for evaluating the severity of sickle cell anemia, studying the clinical heterogeneity of the disease and evaluating potential therapeutic agents.

Interdisciplinary approaches are encouraged, but grant applications should be tightly focused. If collaborative arrangements through subcontracts with other institutions are planned, consult NHLBI staff regarding procedures.

VII. EXCLUSIONS

No support will be provided for major instrument research or development. Clinical trials or clinical validation of currently available instruments would not be supported through this special solicitation. Although the research topic may be multidisciplinary, it is not the intent of this request to solicit proposals for large studies encompassing a variety of essentially independent research projects (program projects).

VIII. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual, research project grant. Although \$500,000 for this program is included in the financial plans for fiscal year 1983, award of grants pursuant to this RFA is contingent upon receipt of funds for this purpose. It is anticipated that three to five grants will be awarded under this program. The specific amount to be funded will, however, depend on the merit and scope of the applications received and the availability of funds. Since a variety of approaches would represent valid responses to this announcement, it is anticipated that there will be a range of cost among individual grants awarded.

Upon initiation of the program, the DBDR will sponsor periodic meetings to encourage exchange of information among investigators who participate in this program. In the preparation of the budget for the grant application, applicants should request travel funds for a two-day meeting each year, most likely to be held in Bethesda, Maryland. Applicants should also include a statement in their applications indicating their willingness to participate in such meetings.

Applicants, who will plan and execute their own research programs, are requested to furnish their own estimates of the time required to achieve the objectives of the proposed research project; however, the award period for this activity must not exceed three years. At the end of the initial award period, renewal applications may be submitted for further competitive review through the regular grant program of the NIH. It is anticipated that support will begin on September 30, 1983.

The current policies and requirements that govern the research grant programs of the NIH will prevail.

IX. REVIEW PROCEDURES AND CRITERIA

A. Review Method

All applications responding to this RFA will be reviewed for scientific and technical merit by an initial review group, which will be convened by the Division of Extramural Affairs (DEA), NHLBI, solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the objectives of this RFA. If an application is judged unresponsive, the applicant will be contacted and given opportunity to withdraw the application or to have it considered for the regular research grant program of the NIH.

If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factors to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research project grant applications. These include the novelty, originality and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed. An additional criterion will be the importance of the proposed research to the objectives of this RFA.

X. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are encouraged to submit to the Review Branch of the Institute a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions.

The Institute requests such letters for the purpose of providing an indication of the number and scope of applications to be received. A letter of intent is not binding, and it will not enter into the review of any application subsequently submitted, nor is it a necessary requirement for application. This letter should be received no later than February 15, 1983, and sent to:

Dr. Charles L. Turbyfill
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Applications

Submit applications on form PHS 398, the application form for the traditional research project grant. This form is available in an applicant institution's office of sponsored research or business office or from the Division of Research Grants (DRG). Use the conventional format for research project grant applications and ensure that the points identified in the Section on "Review Procedures and Criteria" are fulfilled.

To identify the application as a response to this RFA, check "yes" on Item 2 of page 1 of the application and enter the title RHEOLOGICAL STUDIES IN SICKLE CELL DISEASE and the RFA number NIH-NHLBI-DBDR-83G-F.

C. Application Procedure

Send or deliver the completed application and six (6) signed, exact photocopies of it to:

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

Send an additional twenty (20) copies of the application to:

Review Branch, DEA
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 5A15
Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible but, after discussion with the applicant, it may be considered as a regular research project grant application.

D. Timetable

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by the National Heart, Lung, and Blood Advisory Council	September 22-24, 1983
Anticipated award date	September 30, 1983

E. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

John I. Hercules, Ph.D.
National Institutes of Health
Federal Building - Room 508A
Bethesda, Maryland 20205

Telephone: (301) 496-6931

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DBDR-83G-G

MEGAKARYOCYTOPOIESIS AND THROMBOCYTOPOIESIS

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. PURPOSE

The Division of Blood Diseases and Resources (DBDR) invites grant applications for a single competition for support of research on normal and pathological megakaryocytopoiesis and thrombocytopoiesis. The major purposes of this special grant program are to stimulate the investigation of the differentiation and maturation of the precursor cell to the megakaryocyte and subsequently to the platelet, to determine the characteristics of the regulatory mechanism, and to elucidate the function of the megakaryocyte in various bleeding disorders and in thrombosis. These areas may be approached by studying the differentiation, maturation, morphology, physiology, biochemistry, immunology, and pharmacology of the megakaryocyte.

II. DISCIPLINES AND EXPERTISE

Among the disciplines and expertise that may be appropriate for this research program are biochemistry, immunology, physiology, hematology, and pharmacology.

III. ADMINISTRATIVE BACKGROUND

The Blood Diseases Branch Branch (BDB) of the DBDR supports research on the diagnosis, treatment, and prevention of thrombosis and hemorrhage. One component of the program is platelet disorders, in which the emphasis is on platelet function, metabolism, and development in human and in animal systems. Because there are few projects directed towards studies of megakaryocytopoiesis and thrombocytopoiesis, the Branch is attempting to promote the program and accelerate progress through this RFA.

This program is described in the Catalog of Federal Domestic Assistance No. 13.839, Blood Diseases and Resources. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

IV. SCIENTIFIC BACKGROUND

The megakaryocyte is a unique cell that occurs only in mammals and that functions primarily to produce platelets. This polyploid cell yields several thousand anucleate platelets through precisely controlled cytoplasmic divisions. The exact mechanism that causes these divisions is not understood. Less is probably known about the megakaryocyte than about any other cell type in the bone marrow, except the stem cell. Among the reasons for this paucity of information is the fact that, over the years, less interest has been shown in megakaryocytes than in the precursors of other blood cells, probably because megakaryocytes constitute less than 0.4 percent of the cellular elements of the bone marrow and because attempts to isolate and concentrate them free of contamination by other cellular elements have only recently been successful.

Recent advances now make it possible to isolate and purify megakaryocytes in large quantities and to study and monitor the megakaryocytes and their precursor cells in culture techniques. Thus, many of the barriers to refined and carefully controlled studies of megakaryocytes have been overcome so that opportunity is available for rapid progress.

V. OBJECTIVES

This special grant program for the support of research in normal and pathological megakaryocytopoiesis and thrombocytopoiesis and the relation between megakaryocytes and thrombotic or hemorrhagic diseases is intended to encourage scientists to investigate the many unanswered questions about megakaryocytes and the production of platelets.

VI. SCOPE

Applications are invited that cover such topics as the morphological, biochemical, and regulatory mechanisms of megakaryocytopoiesis; the cytoplasmic sequestration of megakaryocyte to form platelets; the rate of platelet production; the genesis of platelet organelles; the function of lipid components in controlling the platelet demarcation process and the orientation of new membrane, the function of membrane receptors; and the participation of megakaryocytes in idiopathic thrombocytopenic purpura and other pathological conditions.

VII. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual research-project grant. Although \$500,000 for this program is included in the financial plans for fiscal year 1983, award of grants pursuant to this RFA is contingent upon receipt of funds for this purpose. It is anticipated that four to six grants will be awarded under this program. The specific amount to be funded will, however, depend on the merit and scope of the applications received and the availability of funds.

Upon initiation of the program, the DBDR will sponsor periodic meetings to encourage exchange of information among investigators who participate in this program. In the preparation of the budget for the grant application, applicants

should request travel funds for a two-day meeting each year, to be held in Bethesda, Maryland. Applicants should also include a statement in their applications indicating their willingness to participate in such meetings.

The award period for this grant activity must not exceed three years. At the end of the initial award period, renewal applications may be submitted for further competitive review through the regular grant programs of the National Institutes of Health. It is anticipated that support will begin on September 30, 1983.

The current policies and requirements that govern the research grant programs of the National Institutes of Health (NIH) will prevail.

VIII. REVIEW PROCEDURES AND CRITERIA

A. Review Method

All applications responding to this RFA will be reviewed for scientific and technical merit by an initial review group which will be convened by the Division of Extramural Affairs (DEA), National Heart, Lung, and Blood Institute (NHLBI), solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the 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 have it considered for the regular research grant programs of the NIH.

If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factors to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research-project grant applications, including the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator; the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed. An additional criterion will be the importance of the proposed research to the objectives of this RFA.

IX. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are encouraged to submit to the Review Branch of the Institute a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions. The Institute requests such letters for the purpose of providing an indication of the number and scope of applications to be received. A letter of intent is not binding, it will not enter into the review of any application subsequently submitted, and it is not a necessary requirement for application.

This letter should be received no later than February 15, 1983, and sent to:

Dr. Charles Turbyfill
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Applications

Submit applications on form PHS 398, the application form for the traditional research-project grant. This form is available in an applicant institution's office of sponsored research or business office or from the Division of Research Grants (DRG). Use the conventional format for research-project grant applications and ensure that the points identified in the Section on "Review Procedures and Criteria" are fulfilled.

To identify the application as a response to this RFA, check "yes" on Item 2 of page 1 of the application and enter the title: MEGAKARYOCYTOPOIESIS AND THROMBOCYTOPOIESIS and the RFA number NIH-NHL BI-DBDR-83G-G.

C. Application Procedure

Send or deliver the completed application and six (6) signed, exact photocopies of it to:

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

Send an additional twenty (20) copies of the application to:

Review Branch, DEA
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 5A15
Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible, but, after discussion with the applicant, it may be considered as a regular research-project grant application.

Timetable

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by the National Heart, Lung, and Blood Advisory Council	September 22-24, 1983
Anticipated award date	September 30, 1983

D. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

Walter R. Miller, M.D.
Blood Diseases Branch
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
National Institutes of Health
Federal Building - Room 5A12
Bethesda, Maryland 20205

Telephone: (301) 496-5911

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DBDR-83G-H

ETIOLOGY, PATHOGENESIS, AND TREATMENT OF APLASTIC ANEMIA

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. PURPOSE

The Division of Blood Diseases and Resources invites grant applications for a single competition for support of research on the etiology, pathogenesis, and treatment of aplastic anemia and related non-neoplastic stem cell disorders.

II. DISCIPLINES AND EXPERTISE

Among the disciplines and expertise that may be appropriate for this research program are epidemiology, cell biology, biochemistry, immunology, toxicology, and clinical medicine.

III. ADMINISTRATIVE BACKGROUND

The Blood Diseases Branch of the Division of Blood Diseases and Resources supports research in red blood cell disorders in order to foster the development of new knowledge for diagnosis, treatment, and prevention. One component of the program is erythropoiesis and stem cell kinetics, in which there is emphasis on aplastic anemia. Because there are few projects directed towards studies of aplastic anemia, the Branch is attempting to promote the program and accelerate progress through this RFA.

IV. SCIENTIFIC BACKGROUND

Non-neoplastic abnormalities in the hematopoietic process may lead to a decrease in the production of one or more of the several cell types produced in the bone marrow. For example, pure red cell aplasia, Diamond-Blackfan anemia, transient erythroblastopenia of childhood, refractory anemia, acquired sideroblastic anemia, and paroxysmal nocturnal hemoglobinuria are diseases associated with suppression of red blood cells. Abnormal erythropoiesis may also result in an overproduction in

The programs of the National Heart, Lung, and Blood Institute are identified in the Catalog of Federal Domestic Assistance, No. 13.830, Blood Diseases and Resources. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

the number or function of hematopoietic stem cells, as occurs in polycythemia vera. Neutropenia and thrombocytopenia are deficiencies in granulocytes and platelets, respectively. When production of two or more of these cell types is significantly reduced the disease is usually referred to as aplastic anemia. Data suggest an incidence of between 500 and 2,500 cases annually in the United States. It is a serious illness and patients with severe aplasia have a particularly grave prognosis: median survival is less than 6 months and 80 percent of patients die within 1 to 2 years. Survivors rarely improve, and most need continued transfusions of blood products.

Aplastic anemia encompasses a very heterogeneous group of disorders with numerous etiologies and varied natural histories. It can be inherited, but more often it is acquired as a result of reactions to drugs, chemicals, toxins, radiation, or infection. Patients with an inherited predisposition to bone marrow failure are classified as having constitutional aplastic anemia and perhaps the most common disorder in this group is Fanconi's anemia. Patients with Fanconi's anemia are born with one or more of the following characteristic physical abnormalities: hypoplastic thumb or radius, hyperpigmentation, microcephaly, hypoplasia of the kidney and spleen, vision abnormalities, and mental and sexual retardation. Hematologic abnormalities usually develop after the age of five (1).

Unfortunately, the acquired types are frequently idiopathic. The exact mechanisms responsible for bone marrow failure are not yet understood because of the complexity of the hematopoietic system. One can conceive of numerous chances for failure in various stages of hematopoiesis.

While bone marrow transplantation continues to be a rational therapy for some patients with aplastic anemia (2,3), it remains a high-risk procedure, especially for older patients. For most patients with aplastic anemia, bone marrow transplantation is inappropriate. This group includes those who lack histocompatible sibling donors and patients with a moderate form of the disease for whom the risks of transplantation are unwarranted.

Antithymocyte globulin (ATG), a form of therapy directed at the immune system, represents a new and promising clinical treatment for aplastic anemia. This treatment involves injection of ATG or antilymphocyte serum obtained from horses immunized with human thymus lymphocytes. As found in early European trials (4) and in a recent American study (5), therapy with ATG is effective in 30 to 40 percent of patients with severe aplastic anemia.

The mechanism of action of ATG is unknown. Speculation centers on its effect on a pathologic suppressor lymphocyte or killer cell, resulting in suppression of normal hematopoietic development. Alternatively, normal hematopoiesis may require a constant balance between helper and suppressor cell effects, and this balance may be upset in patients with bone marrow failure. The success of ATG therapy and results of numerous recent *in vitro* studies point to an involvement of the immune system in aplastic anemia. ATG may function by affecting a primary cell-cell interaction or toxic humoral effect or hematologic improvement may be the result of secondary phenomena, such as the ability of serum sickness to stimulate production of hematopoietic factors.

REFERENCES

- (1) Schroeder, T.M., Tilgen, D., Kruger, J., Vogel, F.: Formal genetics of Fanconi's anemia. *Human Genet* 32:257, 1976.
- (2) Camitta, B.M., Storb, R., Thomas, E.D.: Aplastic anemia: pathogenesis, diagnosis, treatment, and prognosis. *N. Engl. J. Med.* 306:645, 712, 1982.
- (3) Young, N.: Aplastic anemia: research themes and clinical issues. *Progress Hematol* 12:227, 1981.
- (4) Speck, B., et.al.: Treatment of severe aplastic anemia with anti-lymphocyte globulin or bone marrow transplantation. *Brit. Med. J.* 282:860, 1981.
- (5) Champlin, R., Gale, R.P.: Anti-thymocyte globulin treatment for aplastic anemia: a randomized controlled study. *Blood* 58:40a, 1981.

V. OBJECTIVES

This special grant program for the support of research on the etiology, pathogenesis, and treatment of aplastic anemia and other non-neoplastic bone marrow abnormalities is intended to encourage scientists to investigate the many unanswered questions about aplastic anemia.

VI. SCOPE

Applications are invited that cover such topics as (but not limited to) the following as they relate to aplastic anemia and other non-neoplastic bone marrow disorders:

- o the effects of helper and suppressor T-cells;
- o the function of the natural killer cell;
- o the involvement of viruses, drugs, chemicals, and toxins;
- o the regulation of stem cell differentiation and self-renewal;
- o the importance of cell-cell interactions;
- o the effect of the bone marrow microenvironment;
- o the effects of growth factors and inhibitors;
- o the mediation of bone marrow failure by immunological mechanisms;
- o the mechanism of action of ATG in treating aplastic anemia; and
- o the usefulness of monoclonal antibodies directed against defined T-lymphocyte subsets as a possible alternative to ATG therapy.

VII. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual research-project grant. Although \$500,000 for this program is included in the

financial plans for fiscal year 1983, award of grants pursuant to this RFA is contingent upon receipt of funds for this purpose. It is anticipated that four to six grants will be awarded under this program. The specific amount to be funded will, however, depend on the merit and scope of the applications received and the availability of funds.

Upon initiation of the program, the Division of Blood Diseases and Resources will sponsor periodic meetings to encourage exchange of information among investigators who participate in this program. In the preparation of the budget for the grant application, applicants should request travel funds for one two-day meeting each year, to be held in Bethesda, Maryland. Applicants should also include a statement in their applications indicating their willingness to participate in such meetings.

The award period for this grant activity must not exceed three years. At the end of the initial award period, renewal applications may be submitted for further competitive review through the regular grant programs of the National Institutes of Health. It is anticipated that support will begin on September 30, 1983.

The current policies and requirements that govern the research grant programs of the National Institutes of Health will prevail.

VIII. REVIEW PROCEDURES AND CRITERIA

A. Review Method

All applications responding to this RFA will be reviewed for scientific and technical merit by an initial review group which will be convened by the Division of Extramural Affairs (DEA), NHLBI, solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the 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 have it considered for the regular research grant programs of the NIH.

Projects focused on immunologic etiologies or immunologic forms of therapy are of interest to the National Institute of Allergy and Infectious Diseases (NIAID). Applications of this type may be jointly assigned to the NIAID.

Basic research on hematopoiesis which does not emphasize studies on aplastic anemia or other non-neoplastic bone marrow abnormalities may be of interest to the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) and will be assigned accordingly.

If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factors to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research-

project grant applications, including the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator; the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed. An additional criterion will be the importance of the proposed research to the objectives of this RFA.

IX. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are encouraged to submit to the Review Branch of the Institute a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions. The Institute requests such letters for the purpose of providing an indication of the number and scope of applications to be received. A letter of intent is not binding, it will not enter into the review of any application subsequently submitted, and it is not a necessary requirement for application.

This letter should be received no later than February 15, 1983, and sent to:

Dr. Charles Turbyfill
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Applications

Submit applications on form PHS 398, the application form for the traditional research-project grant. This form is available in an applicant institution's office of sponsored research or business office or from the Division of Research Grants (DRG). Use the conventional format for research-project grant applications and ensure that the points identified in the Section on "Review Procedures and Criteria" are fulfilled.

To identify the application as a response to this RFA, check "yes" on Item 2 of page 1 of the application and enter the title: "ETIOLOGY, PATHOGENESIS, AND TREATMENT OF APLASTIC ANEMIA" and the RFA number "NIH-NHL BI-DBDR-83G-H."

C. Application Procedure

Send or deliver the completed application and six (6) signed, exact photocopies of it to:

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

Send an additional twenty (20) copies of the application to:

Review Branch, DEA, NHLBI
National Institutes of Health
Westwood Building - Room 5A15
Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible, but, after discussion with the applicant, it may be considered as a regular research-project grant application.

Timetable

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by the National Heart, Lung, and Blood Advisory Council	September 22-24, 1983
Anticipated award date	September 30, 1983

D. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

Dr. Alan S. Levine
Red Blood Cell Program Administrator
Blood Diseases Branch
Division of Blood Diseases and Resources
Federal Building - Room 5A12
Bethesda, Maryland 20205

Telephone: (301) 496-5911

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DL D-83G-I

EXTRACELLULAR MATRIX INTERACTIONS IN THE

NORMAL AND DISEASED LUNG

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: April 15, 1983

I. PURPOSE

The Division of Lung Diseases (DLD), National Heart, Lung, and Blood Institute (NHLBI), invites grant applications for research on the cellular and the biochemical aspects of the extracellular matrix in normal and diseased lung. The objective of this special grant program is to improve our understanding of the role of the interactions of extracellular matrix components in maintaining normal lung functions, changes in the organization and composition of these components in various pulmonary diseases and the subsequent repair processes.

Applications received in response to this request will be reviewed in a single competition.

II. DISCIPLINES AND EXPERTISE

Among the disciplines and expertise that may be appropriate for this research program are cell biology, molecular biology, biochemistry, immunology, cellular physiology, and pulmonary pathology.

III. SCIENTIFIC BACKGROUND

The mammalian lung comprises a number of cell types and subtypes surrounded and supported by extracellular matrices consisting primarily of collagen, elastin, proteoglycans, fibronectin, and other as yet poorly characterized components. These extracellular components are believed to account for many of the mechanical properties of the lung. Recent studies of non-pulmonary systems have clearly demonstrated that the concept of the extracellular matrices as inert supporting materials secreted by cells to serve as mere scaffoldings is no longer valid. They are now perceived as biologically active components of the tissues, in

This program is described in the Catalog of Federal Domestic Assistance, No. 13.838, Lung Diseases. Awards will be made under the authority of the Public Health Service Act 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

constant communication with cells they surround and capable of influencing metabolism, shape, size and ultimate fate of these cells.

For many types of cells, attachment to collagenous matrix influences growth as well as differentiation. Such interactions of cells with matrix are mediated by glycoproteins which are specific for each cell type and its matrix. For example, attachment of fibroblasts, chondrocytes and epithelial cells is mediated by fibronectin, chondronecin and laminin respectively. These glycoproteins conceivably link specific groups on the matrix molecules with putative receptors on cell surfaces. There is evidence from non-pulmonary systems, that these attachment proteins are more than passive interlocks, and play regulatory roles in cellular functions. Such specific attachment glycoproteins may be similarly associated with lung tissue.

In emphysema, where the pathology is clearly related to the derangement of the pulmonary connective tissue protein elastin, there has been little investigation into the role of matrix interactions in the development of the lesion. Since elastase from the polymorphonuclear leukocytes, which is implicated in the degradation of elastin, also digests other matrix components such as fibronectin, collagens, proteoglycans, etc., these macromolecules may influence elastin degradation.

Examples of specialized extracellular matrices are provided by the basement membranes surrounding epithelial and endothelial cells. Recent studies with glomerular basement membranes suggest that an important function of the alveolar and capillary basement membranes, namely, the regulation of transport of molecules from endothelium to interstitium and from interstitium to alveolus, may be influenced by the interaction among the basement membrane components. Furthermore, alveolar and capillary basement membranes contain anionic components, such as heparan proteoglycans as do glomerular basement membranes and it is possible that "increased permeability" pulmonary edema is analogous to the basement membrane-related permeability changes noted in diseased kidney. The role of pulmonary basement membrane components, individually or in combinations, in the regulation of permeability needs to be better understood.

Extracellular matrix component interactions may also influence the repair processes, by directing the spatial orientation of cells following lung tissue injury. For example, it has long been suspected that the exposed basement membrane, free of attached cells, is somehow responsible for the type II cell proliferation and differentiation associated with lung repair. In experimental emphysema, elastin levels, which decrease following elastase treatment, eventually return to approximately normal levels. However, the new elastin appears to be morphologically abnormal. This could be due to changes either in temporal synthetic sequence of the various matrix components which may prevent development of appropriate interactions or in the controlled degradation of other components.

In recent years considerable information on the biochemistry of individual components of the pulmonary extracellular matrix has become available. However, little is known of their interactions and organization, and neither a plausible structural model of the matrices nor a correlation of biochemical organization with morphology and function have been developed.

IV. OBJECTIVES AND SCOPE

It is the intent of this RFA to encourage study of the roles of the various components of pulmonary extracellular matrix in the maintenance of normal lung function, in the development of physiologic and structural abnormalities in acute and chronic disease states and in induction of subsequent repair processes.

Applications are invited for studies designed to investigate the regulation of biosynthesis and interactions of the pulmonary extracellular matrix components, and their role and fate in disease and repair. Studies may be undertaken in any species but they should have clear relevance to human pulmonary biology and pathology. In all instances, the perceived relationship and importance of the proposed work to the improved understanding of human pulmonary diseases should be made explicit. New approaches and multidisciplinary research efforts are encouraged.

Some unanswered questions relevant to the biology of the pulmonary matrix are listed below in order to provide a perspective of the scope of research that would meet the goals of this program.

A. Matrix Assembly

Even though the synthesis of individual components of extracellular matrices from various organ systems is being elucidated, the total picture of matrix synthesis is far from clear, especially in the lung. To delineate the changes in the amounts and sequential synthesis of the components of the extracellular matrix during disease and repair, a thorough understanding of the factors influencing both the de novo synthesis and turnover of the matrix components is required. Some questions that need to be answered in this regard are: How does the synthesis of matrix by fully differentiated cells differ from that during embryonic development? What are the feedback controls that induce the cells to turn on or off the synthesis of extra cellular matrix components? Is there a temporal sequence for the synthesis of various extracellular matrix components? What is the relationship between molecular and supramolecular structures of extracellular matrix and macroscopic tissue organization and function in normal and diseased lung?

B. Biological Functions

The components of the extracellular matrix are believed to be in constant communication with the cell, influencing the performance and functions of the organ. However, little is known regarding the mechanisms of such communication and function. For example: What are the mechanisms of matrix cell communication in the pulmonary tissue? What is the nature of the receptor(s) on cell surface that react with extracellular matrix components? What is the nature and role of the basement membrane components, alone or in combination, in influencing the alveolar permeability?

C. Disease and Repair

It has been shown that repair processes following tissue injury involve both qualitative and quantitative changes in the extracellular matrix

components. A clear understanding of these changes could help development of intervention strategies. The following questions need to be addressed in this regard: What types of perturbations are caused in the interactions of pulmonary matrix components during disease? How do cells respond to such perturbations? What are the roles of the various extracellular matrix components in the repair processes following or during pulmonary disease? What factors prevent normal repair processes or cause misrepair to operate in diseased lung?

It is not required that all of these questions be dealt with in a single proposal. Investigators are encouraged to consider other relevant questions and approaches which would expand our understanding of the role of the pulmonary extracellular matrix in normal and diseased lung.

V. EXCLUSIONS

Studies of nonpulmonary systems, and solely biochemical or morphometric studies of individual components of extracellular matrix exclusive of the nature and effects of their interactions will not be considered responsive to this announcement. Investment of major effort towards isolation of biochemical components or establishment of new cell lines is not encouraged. Studies dealing with lung cancer are also excluded from this program.

VI. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual, research project grant. Although approximately \$800,000 is included for this program in the financial plans for fiscal year 1983, award of grants pursuant to this RFA is contingent upon receipt of funds for this purpose. It is anticipated that six to eight grants will be awarded under this program. The specific amount to be funded will, however, depend on the merit and scope of the applications received and the availability of funds. Since a variety of approaches would represent valid responses to this announcement, it is anticipated that there will be a range of costs among individual grants awarded.

Upon initiation of the program, the DLD will sponsor periodic meetings to encourage exchange of information among investigators who participate in this program. In the preparation of the budget for the grant application, applicants should request travel funds for a one-day meeting each year, most likely to be held in Bethesda, Maryland. Applicants should also include a statement in their applications indicating their willingness to participate.

Applicants should plan and execute their own research programs and are requested to furnish their own estimates of the funds and time required to achieve the objectives of the proposed research project; however, the award period for this activity must not exceed three years. At the end of the initial award period, renewal applications may be submitted for further competitive review through the regular grant period of the NIH. It is anticipated that support will begin on September 30, 1983.

The current policies and requirements that govern the research grant programs of the NIH will prevail, including the requirement for cost sharing.

VII. REVIEW PROCEDURES AND CRITERIA

A. Review Method

All applications submitted in response to this RFA will be reviewed for scientific and technical merit by an initial review group, which will be convened by the Division of Extramural Affairs (DEA), NHLBI, solely to review these applications. Upon receipt, applications will be reviewed for their responsiveness to the objectives of this RFA. If an application is judged unresponsive, the applicant will be contacted and given an opportunity to withdraw the application or permit administrative transfer for consideration in the regular grant program of the NIH.

If a proposal submitted in response to this RFA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

B. Review Criteria

The factors to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research project grant applications, including the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed.

VIII. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are asked to submit a one-page letter of intent that includes a brief synopsis of the proposed research and identification of any other participating institutions. Such letters are requested for the purpose of obtaining an indication of the number and scope of applications to be received. A letter of intent is not binding, and it will not enter into the review of any application subsequently submitted, nor is it a necessary requirement for application. This letter should be received no later than February 15, 1983, and sent to:

Dr. Charles L. Turbyfill
National Heart, Lung, and Blood Institute
Westwood Building - Room 553
Bethesda, Maryland 20205

B. Format for Applications

Submit applications on form PHS 398, the application form for the traditional research project grant. This form is available in the applicant institution's office of sponsored research or from the Division of

Research Grants (DRG). Use the conventional format for research project grant applications and ensure that the points identified in the section on "Review Procedures and Criteria" are fulfilled.

To identify the application as a response to this RFA, check "yes" on item 2 of page 1 of the application and enter the title "EXTRA MATRIX INTERACTIONS IN THE NORMAL AND DISEASED LUNG" and the RFA number NIH-NHLBI-DL D-83G-I.

C. Application Procedure

Send or deliver the completed application and six (6) signed, exact photocopies of it to:

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

Send an additional twenty (20) copies of the application to:

Review Branch, DEA
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 5A15
Bethesda, Maryland 20205

Applications must be received by April 15, 1983. An application not received by this date will be considered ineligible.

D. Timetable

Letter of intent	February 15, 1983
Application receipt date	April 15, 1983
Review by National Advisory Council	September 22-24, 1983
Anticipated award date	September 30, 1983

E. Inquiries

Inquiries regarding this announcement may be directed to the program administrator:

Dr. Zakir Bengali
Airways Diseases Branch
Division of Lung Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 6A11
Bethesda, Maryland 20205

Telephone: (301) 496-7332

ANNOUNCEMENT

AVAILABILITY OF ANIMALS WITH INHERITED RETINAL DEGENERATIONS

NATIONAL EYE INSTITUTE

The National Eye Institute encourages research directed toward finding the causes of and preventing human hereditary retinal degenerations. An NEI contract supports the development of strains of dogs with progressive retinal atrophy and the breeding and distribution of these animals for research purposes. Irish setters exhibiting rod-cone dysplasia and miniature poodles with progressive rod-cone degeneration will continue to be made available to qualified investigators. Investigators interested in obtaining animals are encouraged to contact the NEI. A brief research protocol will be requested and it will be competitively reviewed for scientific merit by a selection committee. There will be no charge for the animals, but shipping and other research related costs will be the responsibility of the individual investigator. For further information please contact:

Jack A. McLaughlin, Ph.D.
Retinal and Choroidal Diseases Branch
National Eye Institute
National Institutes of Health
Building 31 - Room 6A51
Bethesda, Maryland 20205

Telephone: (301) 496-5983

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

RFA-NIH-NHLBI-DHVD-83G-J

SPECIALIZED CENTERS OF RESEARCH IN ISCHEMIC HEART DISEASE (IHD-SCORs)

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: July 18, 1983

I. PURPOSE

The Division of Heart and Vascular Diseases (DHVD) of the National Heart, Lung, and Blood Institute (NHLBI), intends to renew the IHD-SCOR program. These centers include multidisciplinary fundamental and clinical research directed at the reduction of death and disability from ischemic heart disease. The characteristics of Specialized Centers of Research in Ischemic Heart Disease as well as the requirements and format of applications submitted in response to this RFA are covered in subsequent pages. Applications received in response to this request will participate in a single competition. It is open to all interested investigators, those presently involved, and those now interested in participating.

II. DISCIPLINES AND EXPERTISE

This request for grant applications will be of interest to groups engaged in cardiovascular research, particularly those whose investigations include fundamental studies. Investigators in some or all of the following disciplines may wish to participate: biochemistry, biomedical engineering, biophysics, biostatistics, computer sciences, endocrinology, epidemiology, immunology, molecular biology, pathology, pharmacology, and physiology. The request will also be of interest to those involved in clinical investigation of ischemic heart disease, particularly as it relates to the application of basic research findings to the prevention, diagnosis and treatment of myocardial ischemia. Investigators in some or all of the following clinical disciplines may wish to participate: cardiology, radiology, nuclear medicine, and cardiovascular surgery.

This program is described in the Catalog of Federal Domestic Assistance No. 13.837, Heart and Vascular Diseases. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

III. BACKGROUND

A. The Coronary Heart Disease Program

The Ischemic Heart Disease Specialized Centers of Research (SCORs) are part of the Coronary Heart Disease Program of the DHVD, NHLBI. The Institute and Division have responsibility for the design and administration of research leading to the reduction of death and disability from ischemic heart disease. The Program is intended to foster the development of new knowledge and to support the translation of research results into preventive, diagnostic and therapeutic maneuvers which will have wide clinical application.

The Program supports a wide range of research activities directed towards this goal. These activities cover the research spectrum from fundamental studies to clinical investigations. The mechanisms of support include, in addition to the SCORs, individual research grants, program projects, clinical trials and patient registries.

The SCORs are microcosms of the Program in that they include all aspects of these research activities. SCORs have the advantage that these various activities are coordinated in a single center and across a loose confederation of centers leading to close interaction and rapid dissemination of research findings for the mutual benefit of SCOR investigators, the general cardiovascular community and ultimately the patient with coronary heart disease.

B. History of the SCOR Concept

The IHD-SCORs evolved from the Myocardial Infarction Research Units (MIRU's) which were established in 1967 and expanded in 1968. These units were largely clinical in orientation. Early recognition of the need for balanced fundamental and applied research within centers for the study of ischemic heart disease led to the IHD-SCOR concept. Thus specialized centers were sought in which fundamental and clinical research could be coordinated in a manner that would facilitate the development of new knowledge and its expeditious transfer to prevention and treatment of coronary heart disease.

The first competition for such centers results in the establishment, in 1975, of nine specialized Centers of Research in Ischemic Heart Disease funded for a period of five years. All centers pursued, with varying intensity, both basic and clinical research. A renewal competition in 1979 resulted in the establishment of the current eight centers; funding for these grants will terminate in 1984.

C. Definition of a SCOR

A Specialized Center of Research (SCOR) is an identifiable unit within a sponsoring institution with a strong commitment to this activity. Each SCOR conducts its own research program based on local interest and talents. Each research program consists of a sustained series of investigations aimed at the

reduction of death and disability from ischemic heart disease through better understanding of the etiology and pathogenesis of various ischemic syndromes and ultimately leading to improved prevention, diagnosis and treatment.

A SCOR consists of a cluster of individual, but related, research projects, each with high scientific merit and clear research objectives. A SCOR may address more than one issue; however, a broad range in topics is not a requisite. A SCOR may also include one or more core resources, which perform specialized service activities such as biochemical analysis, pathology, or data management. These activities are shared by several or all investigators. The core investigators, in addition to performing service functions, may also conduct research projects.

Investigators participating in a SCOR must be of recognized ability, capable of conducting independent research, and willing to make long term commitments to the goals of the SCOR. SCOR scientists should have access to facilities where innovative fundamental and clinical investigations can be conducted.

D. SCOR Director

The SCOR Director must provide strong, effective administrative and scientific leadership. The Director is responsible for the organization and operation of the center and for communication with the NHLBI on all scientific and operational matters. The SCOR Director is responsible for maintaining high quality research throughout the five-year funding period. New projects may be incorporated into the program at any time at the discretion of the Director with final review and approval by NHLBI. SCOR grantees are thus encouraged to pursue promising research leads. By the same token, if a Director deems it advisable to discontinue a project, NHLBI staff should be consulted before implementing the decision. Each SCOR Director must encourage and support close collaboration between individual SCOR investigators by means of frequent seminars and scientific meetings.

Each SCOR Director must establish both internal and external advisory committees which will periodically assess the overall program as well as the progress of individual projects. The external advisory committee must consist of expert consultants from outside the grantee institution and must meet annually. The NHLBI program officer may attend their meetings as an observer.

E. Interactions Among SCORS

Active collaboration among the individual SCORS is a most important aspect of the SCOR program. SCOR Directors meet at least once each year to review progress, discuss common problems, and plan collaborative efforts. An annual meeting of SCOR investigators is coordinated by NHLBI and the SCOR Directors. The purpose of the meeting is to encourage exchange of information among SCOR investigators, and to help plan future directions. Topics for formal presentation by SCOR investigators are chosen by the Directors and NHLBI staff.

F. Relation to the NHLBI

A SCOR is a grant-in-aid which differs from other research grants in its goal orientation. The award of a SCOR grant will establish a special relation between the NHLBI and the grantee institution. The NHLBI will designate a scientific program officer who will monitor the program and when necessary provide advice to the Director and staff of each SCOR.

Scientific progress will be evaluated annually by the Institute by review of progress reports included in noncompeting renewal applications. Interim evaluations will also be conducted by the DHVD.

IV. OBJECTIVES AND SCOPE

This solicitation for applications for SCORs on ischemic heart disease emphasizes a continuing trend in the SCOR program toward the inclusion of more research that is directed toward the elucidation of fundamental mechanisms involved in the manifestations and sequelae of myocardial ischemia. Therefore, the proposed program should include fundamental as well as clinically oriented research and should provide for a mutually supportive interaction between the basic scientists and clinical investigators. The individual projects should be correlative or complementary in terms of the topic or topics chosen within the general area of ischemic heart disease. It is hoped that new applicants will participate in the competition and that it will be possible to fund some smaller centers. It is unlikely, however, that an application with less than three projects would be responsive. Emphasis in proposed projects should be on the development of innovative approaches, the elaboration of new and significant hypotheses, and the generation of novel strategies to resolve current issues.

The unsolved problems in research related to ischemic heart disease are many. A catalog of these problems would be lengthy and probably not useful in this document. The following brief discussion of research topics is intended to offer a few examples of the kinds of research sought and to emphasize the importance of fundamental, new, and innovative research in this second renewal of the IHD-SCOR program.

Many basic structural and functional characteristics of the coronary circulation, both large and small vessels, under normal and hypoxic conditions are poorly understood. The pathophysiology of ischemic injury, the time course, and means to modify and prevent severe ischemic injury and necrosis in the coronary circulation itself are important research topics. The roles of coronary endothelial injury, spasm and thrombosis in the genesis of acute ischemic events are poorly understood. The therapeutic control of inadequate coronary flow during acute ischemia might be a clinically oriented project of importance to pursue in parallel with basic studies.

Topics of substantial importance are the mechanisms involved in triggering acute ischemic events such as sudden cardiac death and acute infarction with or without associated coronary occlusion. The local and systemic factors leading to acute thrombosis and spasm in epicardial coronary arteries are only dimly perceived. Refinement of diagnostic technique to predict the likelihood of acute events and to promote understanding of the etiology and pathophysiology of such events would be of value in the design of new preventive and therapeutic maneuvers. Both fundamental and applied studies are needed in this area.

The development of collateral vessels in response to chronic ischemia, and following an acute event is of interest, particularly with regard to the mechanisms which initiate the process. The factors which lead to exuberant collateral development in some individuals and the paucity of such vessels in others are unknown and involve fundamental biologic processes such as growth and differentiation. Elucidation of control mechanisms might ultimately permit endogenous bypass of epicardial coronary lesions.

While the study of heart function has produced much new knowledge in recent years, these advances have uncovered many areas that demand further study, particularly at the cellular level. The sequence of events leading from reversible to irreversible damage of the heart muscle cell in ischemia needs further elucidation in order to design more effective pharmacologic modalities for interruption of this process. For example, further studies are needed of ischemic metabolic changes and the manner in which ischemic conditions modify the contractile and electrophysiologic properties of cardiac tissue. Another example concerns the role of various subcellular organelles in maintaining these properties and the role which impaired function of these organelles plays in the development of irreversible damage to heart muscle cells. Therapy designed to protect the integrity of cellular organelles might be pursued both in the laboratory and the clinic.

Disturbances in protein synthesis and degradation in heart muscle as a result of acute or chronic oxygen or substrate deprivation may play a role in the loss of contractile function. Little attention has been paid to the factors in ischemia which might disturb the balance of protein turnover. Moreover little attention has been paid to cardiac hypertrophy which results from chronic myocardial ischemia. Hypertrophy is a fundamental biologic process which is poorly understood.

The relationship of the nervous system to cardiac function under normal and ischemic conditions is an important topic for further fundamental research. Central nervous system effects upon the coronary circulation and heart function are not well understood. Furthermore, information on the effect of central nervous system stimulation of the ischemic heart and whether this is a significant factor leading to arrhythmias and sudden death is of paramount importance in view of the continued prevalence of instantaneous sudden cardiac death and the fact that under the best of circumstances only 20-40 percent survive this catastrophic event. The importance of fundamental understanding of these processes is crucial to effective preventive efforts.

Much remains unknown concerning the complex mechanisms which mediate control of the heart by both the sympathetic and parasympathetic limbs of the autonomic nervous system. The manner in which this control may be exerted by various biochemical entities at the cellular and molecular level to affect contractile and electrophysiological properties requires further clarification. This is of particular importance given the recent clear demonstration that beta-blockade reduces mortality in survivors of myocardial infarction.

The clinicopathologic features of various ischemic heart disease syndromes need to be further clarified in order to define risk groups, to develop prognostic criteria and ultimately to design and evaluate pharmacologic interventions. Topics of current interest include continuing efforts to reduce oxygen demand by the heart

while maintaining function, the maintenance of an adequate energy supply in the face of hypoxia and the control of cellular injury and the inflammatory process. These are examples of areas where the results of basic findings are close to providing new leads for the treatment of patients.

V. EXCLUSIONS

No support will be provided for large clinical trials or for programs containing exclusively clinical studies or fundamental studies without at least one clinically oriented project. While the development of new instrumentation may be a part of the SCOR, support for development alone, will not be funded. Similarly, funds will not be provided for the purchase and installation of very expensive, new equipment. Institute staff should be consulted if an applicant has questions regarding this limitation.

VI. MECHANISM OF SUPPORT

The support mechanism will be the research grant-in-aid for a period of five years commencing January 1, 1985. However, it will differ from other research grants in the expected communication between centers and periodic structured review of progress by the NHLBI.

Applicants are expected to furnish their own estimates of the time required to achieve specific objectives of the proposed work, a schedule for completion of the work, and an outline of the phases or segments into which the proposed program can be logically divided. The IHD-SCOR will plan, direct and execute its own research program, but any substantial modifications in it must be mutually agreed upon by the IHD-SCOR institution and the NHLBI.

Additionally, a yearly two-day meeting of SCOR investigators will be held, most likely in Bethesda, Maryland, and applicants should include a request for travel funds for this meeting in each year of the budget. Applicants should also include a statement in the application indicating willingness to participate in such meetings.

Although this solicitation is included in the plans for Fiscal Year 1985, support of grants pursuant to this request for applications is contingent upon ultimate receipt of appropriate funds for this purpose. The current program includes eight grants which have a total annual funding base of approximately \$13 million (including indirect costs). At this time, it is not possible to predict whether future funding will be at the current level or at a lower level. This will be influenced by the amount of funds available to the Division, by the overall merit of proposals, and by their relevance to the program objectives. It is the intent of this solicitation to include some smaller centers and to emphasize fundamental, new, innovative research. A variety of approaches would be responsive to this solicitation; accordingly, it is anticipated that there will be a range of costs among individual grants awarded.

VII. REVIEW PROCEDURES AND CRITERIA

The applications will be evaluated in national competition with each other. Primary review will be conducted by a review group of predominantly non-federal consultants with selected scientific expertise and may involve a site visit. Secondary review will be by the National Heart, Lung, and Blood Advisory Council

Applications considered non-responsive will be returned to the investigator. Major factors to be considered in the evaluation of responsive applications will include:

1. The scientific merit of each proposed project, including the novelty, originality and feasibility of the approach and the adequacy of the experimental design;
2. The technical merit and justification of each core unit;
3. The competence of the investigators to accomplish the proposed research goals, their commitment, and the time they will devote to the program;
4. The adequacy of facilities to perform the proposed research including the laboratory and clinical facilities and the proposed instrumentation and data management systems, when needed;
5. The integration of the various projects and core units into an effective center, and the adequacy of plans for interaction and dissemination of information among investigators;
6. The qualifications, experience and commitment of the SCOR Director and the ability to devote adequate time and effort to provide effective leadership to the center;
7. The scientific and administrative structure of the program, including adequate internal and external procedures for monitoring the proposed research and for providing ongoing quality control and scientific review;
8. The institutional commitment to the program, and the appropriateness of its resources and policies for the administration of a research program of the type proposed;
9. The willingness to work cooperatively with other Specialized Centers of Research in Ischemic Heart Disease and with the NHLBI; and
10. The appropriateness of the budget for the proposed program.

VIII. METHOD OF APPLICATION

A. Letter of Intent

Prospective applicants are encouraged to submit a one-page letter of intent which includes a synopsis of proposed areas of research and identification of any other participating institutions. This letter should be received no later than April 4, 1983, and should be addressed to:

Dr. Charles L. Turbyfill
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 553
5333 Westbard Avenue
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, and it will not enter into the review of any proposal subsequently submitted, nor is it a necessary requirement for application.

B. Application Procedure

In addition to the signed original and six copies to be mailed to the Division of Research Grants (DRG) (see PHS 398 instructions p. 8), three copies should be sent or delivered to:

Review Processing Section
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building - Room 5A15
5333 Westbard Avenue
Bethesda, Maryland 20205

To ensure their review, applications must be received by July 18, 1983

C. Format for Applications

Form PHS 398 (Revised May 1982) should be used, but since this form is used primarily for the traditional project-grant application, several sections have to be modified and expanded so that this form can be used to provide the additional information needed for the Ischemic Heart Disease Specialized Centers of Research Application.

A SPECIAL SUPPLEMENT IS AVAILABLE CONTAINING SPECIFIC GUIDELINES FOR THE PREPARATION OF AN IHD-SCOR APPLICATION. PROSPECTIVE APPLICANTS SHOULD SUBMIT A WRITTEN REQUEST FOR THESE GUIDELINES TO THE PROGRAM OFFICIAL LISTED BELOW.

D. Timetable

Letter of intent	April 4, 1983
Application receipt date	July 18, 1983
Review by the National, Heart, Lung, and Blood Advisory Council	May 17-19, 1984
Notification of applicants	May 25, 1984
Anticipated award date	January 1, 1985

IX. INQUIRIES

Inquiries about the Ischemic Heart Disease SCOR program should be addressed to:

Eugene R. Passamani, M.D.
Associate Director for Cardiology, DHVD
National Heart, Lung, and Blood Institute
National Institutes of Health
Federal Building - Room 3C12
Bethesda, Maryland 20205

Telephone: (301) 496-1081