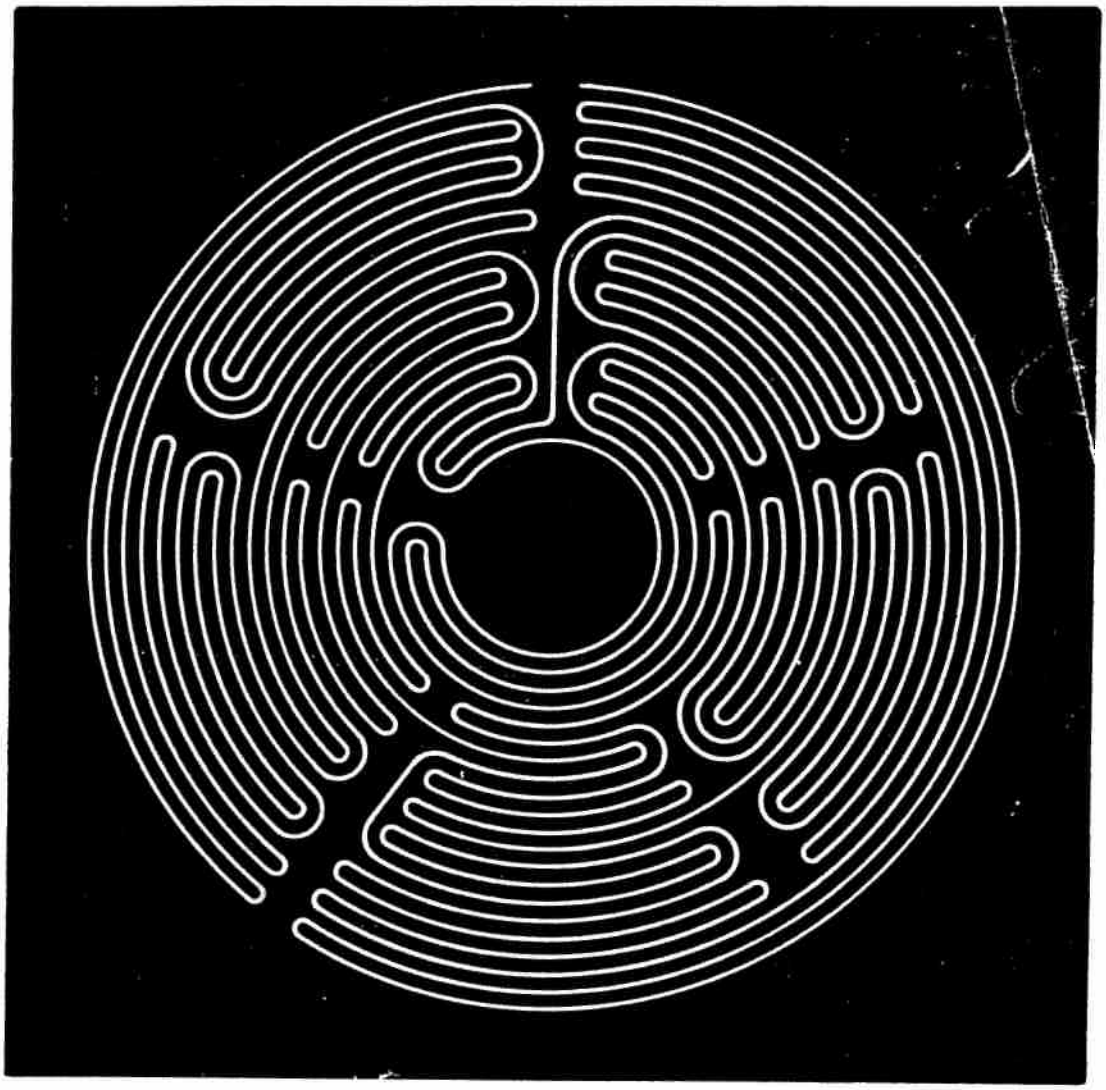
REPORT OF THE NATIONAL COMMISSION ON ORPHAN DISEASES

APPENDICES - VOLUME II



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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DEPARTMENT OF HEALTH & HUMAN SERVICES
NATIONAL COMMISSION ON ORPHAN DISEASES

Public Health Service

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FOREWORD

The task of preparing the Report to Congress from the National Commission on Orphan Diseases involved many different data gathering efforts. Several of the major tasks included collecting information from those individuals and organizations directly involved with activities related to rare diseases. These individuals and organizations were surveyed to determine their experiences with rare diseases and their needs based on these experiences. To complete this task, telephone interviews were conducted with physicians, investigators studying both rare and common diseases, and patients with a rare disease, members of their families or caregivers. These studies are presented in Volume I of the Appendices to the Report of the National Commission on Orphan Diseases.

The Commission also obtained essential information from separate surveys of pharmaceutical manufacturers, private and public foundations, voluntary rare disease organizations, and Federal agencies involved in rare disease research and development activities. The results from these surveys are presented in Volume II of the Appendices.

The results of these surveys are presented in summary format in the Commission's report to Congress. The studies are presented in their entirety to reflect the commitment and degree of involvement in the rare disease area as well as the needs of these individuals and organizations.

The Commission extends their gratitude to those individuals and organizations who responded to both the telephone and written surveys. The results generated from these surveys formed the basis for the recommendations adopted by the Commission and included in their report.

Stephen C. Groft, Pharm. D.
Executive Director

SURVEY OF FEDERAL AGENCIES:

EVALUATION OF RARE DISEASE RESEARCH ACTIVITIES SUPPORTED BY FEDERAL AGENCIES

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I. EXECUTIVE SUMMARY

In 1985, the National Commission on Orphan Diseases was established by an act of Congress to evaluate federally funded activities related to research on rare diseases. The results of the Commission's evaluation are to be presented in a report to Congress and will constitute an assessment of the status of federally supported rare disease research. The evaluation conducted by the Commission will be based on the examination of:

- Appropriateness of current Federal research priorities
- Effectiveness of grant and contract protocols to fund research
- Appropriateness of funding requirements for applicants
- Adequacy of resources and staff capabilities to conduct research
- Effectiveness of peer review of research projects
- Effectiveness of coordination between Federal and private sectors in supporting research
- Effectiveness of activities providing knowledge transfer between common and rare disease research

The Commission completed surveys of the Federal sector, foundations, voluntary organizations, and pharmaceutical manufacturers; and conducted telephone surveys of patients, physicians, and researchers. The synthesis of data from these surveys will provide the Commission with the information necessary to evaluate the current status of rare disease research and to make recommendations for policies for maintenance and/or enhancements of future research efforts.

This survey, which addressed 22 issues identified by the Commission, was designed to collect data on the mechanisms used by Federal agencies to:

- Stimulate and support research on rare diseases
- Evaluate existing funding programs
- Coordinate research activities with public sector and private sector agencies
- Transfer technologies and disseminate information to public and private sector researchers, physicians, and patients and their families

The Federal survey was sent to the 31 agencies previously identified by the Commission as being actively engaged in

research activities related to rare diseases. Twenty-eight agencies responded to the survey.

FINDINGS

Analyses of the survey data indicate that Federal agencies are currently conducting a significant amount of research of relevance to rare diseases. While few agencies target rare diseases as a research priority, many agencies support research projects that have important implications for rare disease diagnosis and treatment. This research is, in most cases, conducted without the benefit of special agency policies to stimulate or to support it. Agencies report that reliance on general agency policy is neither a deterrent to nor a stimulant for future rare disease research endeavors.

In the sections below, we present highlights of the findings. These highlights follow the organization of the survey: agency mission statements; general policies to encourage research on rare diseases; accomplishments, opportunities, and problems relating to rare disease research; funding of rare disease research; evidence of Federal agency cooperation with other public/private sector agencies; and techniques used to affect the transfer of information and technology.

Agency Mission

Few agencies have mission statements that specify rare disease as an agency focus. However, the Gillis W. Long Hansen's Disease Center (Hansen's Disease Center) located within the Health Resources and Services Administration and the Office of Orphan Products Development (OPD), located within the Food and Drug Administration (FDA),were both established to focus their research efforts on one or more rare diseases. The National Cancer Institute (NCI), the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), four institutes within the National Institutes of Health (NIH), are also committed to conducting a large proportion of their research in this area, as the disorders within their purview generally afflict small populations.

General Policies Encouraging Research On Rare Diseases

There is a great similarity in the way agencies stimulate interest in biomedical and behavioral research projects. Most agencies issue program announcements, Request for Applications

(RFAs), and Request for Proposals (RFPs) for this purpose. Several agencies send representatives to academic institutions to publicize agency research interests or to conferences and workshops to encourage individual scientists to submit research applications. The Department of Energy (DOE) encourages the submission of unsolicited proposals to conduct research in areas of special interest to the investigator. Agencies have not found it necessary to develop special mechanisms to stimulate research of rare diseases, indicating that existing policies are sufficient for this purpose.

Most agencies use a two tiered approach for the review of extramural grants. The first review is generally conducted by a specially convened group of scientists that is external to the agency; the second review is generally conducted by the agency's advisory council consisting of outstanding scientists and community leaders with relevant interests. The United States Agency for International Development (USAID) and the OPD at the FDA conduct a single review, relying on outside experts for this purpose. Contracts are more likely to have a single review conducted by experts in the field. There are no special review mechanisms for the review of applications that focus solely on rare disease research.

Several mechanisms are available to stimulate research training. These are the National Research Service Awards (NRSA) for individual and institutional training and the Research Career Development Awards (RCDA) supported by the NIH and the National Institute on Drug Abuse (NIDA). Other training grants are available from the Minority Access to Research Career Program (MARC), which aims to increase the number of minority scientists in biomedical research, and the Medical Scientist Training Program (MSTP), designed to increase the number of clinical researchers well trained in basic research, supported by the National Institute of General Medical Sciences. An additional award, the NRSA for Senior Fellows, is available to experienced researchers who wish to make major changes in the direction of their research careers. Agencies other than the NIH often have special awards available to support research training.

Agencies report that various measures are used to stimulate clinical research including: issuing RFAs and RFPs; making verbal requests to investigators to submit applications; and promoting information transfer activities, such as conferences, symposia, and workshops. No special activities have been developed to stimulate clinical research on rare diseases.

Agency funded biomedical/behavioral research generally has an evaluation component as part of the competition and award

process. Three agencies report that their research is monitored throughout the course of the project (i.e., process evaluation); and one agency reports that it assesses the overall merit of completed research projects (i.e., outcome evaluation). Program evaluations are conducted by all responding agencies.

Most agencies do not have a mechanism for extending the funding for research projects, other than through re-competition. The NIH, however, uses the following programs to provide longer term support: (1) the Method to Extend Research in Time (MERIT) awards, awarded to established investigators; (2) the First Independent Research Support and Transition (FIRST) Award, available to new investigators; and (3) the Javits Investigator Award, used by the NINCDS of the NIH.

Most agencies have developed mechanisms for encouraging research to move from basic into clinical and applied phases. Generally, these mechanisms include:the presentation of multidisciplinary workshops, conferences, and symposia at which clinicians are informed of basic science research results; the publication of agency interests in applied research through Program Announcements, RFAs, and RFPs; and the promotion of specific agency interests in Small Business Innovative Research (SBIR) announcements. The availability of NIH funded General Clinical Research Centers serves as a further stimulus for researchers interested in applied research projects, by providing the necessary facilities and ancillary services.

Only two agencies identified specific intramural policies that they have found to be a "facilitator" for research on rare diseases. Both policies involve the development of close communication links during the application and the working stages of projects. The OPD at FDA encourages scientists to maintain a policy of close communication with the agency, assisting them in conceptualizing projects; the NIDDK sponsors a program of regular meetings of intramural researchers to review research activities, conduct quality control, and exchange ideas.

Accomplishments And Problems In Rare Disease Research

The list of Federal accomplishments provided by respondents indicates that progress was made in FY 1987 in the development of diagnostic procedures, drugs, and therapies, as well as in the general understanding of disease categories (e.g., progress in genetic research). Most agencies reported accomplishments that were disease specific, but some reported accomplishments also had implications for common diseases.

A major barrier to research is that of locating a sufficiently large population for conducting clinical trials. Additional barriers include the difficulties involved in working with pharmaceutical firms, because of their reluctance to develop drugs that: (1) may not be marketable, (2) may not enhance their public image, or (3) for which the firm may be legally liable during clinical trials. A third barrier to rare disease research is the limited amount of funds available to support research projects, which must often vie with common diseases for funding.

Only eight of the responding agencies indicated that they had developed drugs that had not been adopted or marketed. Two of these agencies, the NIDA and USAID,indicated that the lack of progress in the development of drugs was largely attributable to the pharmaceutical industry.

All agencies that either provide patient services or include patients in clinical protocols, provide ancillary care. The most comprehensive set of in-hospital and post-hospital ancillary services is provided by NIH institutes through the Clinical Center.

Funding Of Rare Disease Research

Federal agencies indicated that approximately 1.3 billion dollars were obligated to rare disease research in FY 1987, and of this amount, 88.5 percent (or $1.15 billion) were obligated by NIH Bureaus, Institutes, and Divisions. Of these, the National Cancer Institute had the largest obligation, providing $662 million for research on rare forms of cancers.

Coordination With The Public/Private Sector And Transfer Of Information And Technology

All agencies engaging in rare disease activities have mechanisms for communicating with various Department of Health and Human Services (DHHS) agencies involved in this area. Communication links are established through participation in DHHS advisory councils or committees and through representation on the DHHS Orphan Products Board. Agencies engaged in product development activities (e.g., NIDA, OPD, NCI, and the NINCDS) often work cooperatively with independent pharmaceutical companies, the Pharmaceutical Manufacturers Association and the FDA. Institutes within the NIH have developed close working relationships with the faculties of leading universities and with voluntary associations.

Currently, there are four Federally funded clearinghouses and information centers to provide rare disease related information to the public. Only one of the four, National Information Center for Orphan Drugs and Rare Diseases (NICODARD), provides information on a full range of rare diseases. However, due to funding constraints, NICODARD had to severely limit its activities over the past 3 years. A fifth clearinghouse, one supported by NIDDK, serves health professionals, patients, and the general public. All NIH institutes report that they maintain information offices to disseminate publications in answer to public requests.

Several methods are used to transfer research technology to effect the development of innovative treatments for rare diseases. These include: publication of journal articles, newsletters, and technical publications; presentations made at voluntary association meetings; support of conferences, symposia, workshops, and cooperative agreements with industry; site visits to universities and international health agencies; stimulation of small business initiatives through the use of the Small Business Innovative Research (SBIR) Program; and the promotion of research through traditional grants and contracts. Technology transfer activities unique to specific agencies include the direct technical assistance provided to new researchers by NIDA and the technical assistance to potential researchers provided by the OPD.

II. INTRODUCTION

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A. BACKGROUND

Biomedical and behavioral research of rare diseases is an essential and important step in the promotion of our Nation's health. It has been estimated that as many as 20 million Americans suffer from approximately 5,000 rare diseases. The actual number and incidence of rare diseases occurring in this country is unknown.

Collectively, rare diseases affect many persons, individually, they often affect only a few. The small size of disease specific populations often may limit the amount and kind of research that can be conducted. In fact, finding a sufficient number of subjects for clinical research can be a great obstacle for investigators.

A small patient population also means a small consumer market, thus contributing to a reluctance among many pharmaceutical manufacturers to "adopt" (i.e., develop) therapeutic drugs or devices for the rare, "orphan" disease market, especially given the high cost of developing new drugs, estimated to range from $50 million to $80 million for each drug that eventually is marketed.

To provide incentives for commercial development of drugs for rare diseases, Congress passed the Orphan Drug Act in 1983. The Act included a definition for orphan diseases:

- The disease affects fewer than 200,000 persons in the United States
- The disease affects 200,000 or more persons, but there is no reasonable expectation that the cost of developing and marketing the therapeutic drug can be recovered through sales in the United States

The Orphan Drug Act also established the Orphan Products Board, consisting of representatives of relevant agencies within the Department of Health and Human Services (DHHS), to promote, evaluate and report annually to Congress on Federal and private sector activities in the orphan products development.

Two years later, in an amendment to the Orphan Drug Act, Congress established the National Commission on Orphan Diseases (Commission) to promote and evaluate activities related to research and dissemination of information on rare diseases. The Commission is composed of 20 members: 10 of whom are either

researchers or physicians specializing in rare diseases; 5 are persons with a rare disease; 4 nonvoting members are institute directors from the National Institutes of Health (NIH) and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); and 1 is a nonvoting member from the Food and Drug Administration (FDA).

The Commission is charged to evaluate the activities of Federal agencies and other public and private entities concerning:

- Basic research on rare diseases
- Applied and clinical research focusing on the prevention, diagnosis, and treatment of rare diseases
- Dissemination of information derived from such research to the public, health care professionals, researchers, and drug/medical device manufacturers
- Transfer of knowledge between rare disease research and other research fields

The Commission is to provide a comprehensive report of its findings and conclusions to the Secretary and to each House of Congress. The report will include recommendations and a long range plan for using public and private resources to improve research and to assist in the prevention, diagnosis, and treatment of rare diseases.

The findings from the survey described in this document will allow the Commission to evaluate Federal intramural and extramural research efforts in the area of rare disease; the amount of funding allocated to these activities; the level of coordination and cooperation existing within the Federal Government and among Federal agencies and the private sector; and the research achievements as well as initiatives planned for the future.

B. STUDY PURPOSE

The purpose of this study is to survey Federal agencies to identify the type and extent of involvement in biomedical and behavioral research relating to orphan (rare) diseases. The focus of the survey is the issues of interest to Congress, as specified by Public Law 99-91, Sec. 4(C), namely that the Commission's evaluation of the rare disease research activities determine:

- Appropriateness of Federal research priorities
- Effectiveness of grants and contracts to fund research
- Appropriateness of funding requirements for research grant applicants
- Adequacy of resource and staff capabilities to conduct research
- Effectiveness of peer review of research applications
- Effectiveness of coordination between Federal and private sectors in supporting research
- Effectiveness of activities promoting knowledge transfer between common and rare disease research

The findings of this survey will aid the deliberations of the Commission and will be included in the report to the Administration and the Congress.

C. METHODOLOGY

The methodology for this survey had five distinct parts: identification of the Federal agencies that support research in rare diseases, design of the study and implementation plan, development and administration of survey instrument, analysis of the data, and preparation of the final report.

1. IDENTIFICATION OF RESPONDENT UNIVERSE

The Commission identified 31 Federal agencies that were likely to support projects related to orphan disease research. These include 24 agencies in the Public Health Service:

- The National Institutes of Health (NIH)
- Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA)
- Centers for Disease Control (CDC)
- Food and Drug Administration (FDA)
- Health Resources and Services Administration (HRSA)

The seven other Federal agencies that were identified include: the Veterans Administration (VA); the Department of Defense (DoD); the Department of Education (ED); the National Aeronautics and Space Administration (NASA); the Department of Energy (DOE); the United States Department of Agriculture (USDA);

and the United States Agency for International Development (USAID).

The Commission contacted each of these agencies and requested the name of a contact person to facilitate and coordinate the agency's participation in the survey. Contact persons would:

- Assist in the development of the survey questionnaire by reviewing the drafts, and suggest changes and clarification where appropriate
- Forward the final questionnaire to the appropriate agency respondents
- Provide correction and/or clarification of incomplete or unclear data in the completed questionnaire

Appendix B lists the agencies identified, and the designated agency contact persons.

2. STUDY AND IMPLEMENTATION PLAN

A survey plan, a rationale for the selected approach, and a schedule of the proposed activities were developed. The plan described the various tasks and subtasks of the project, quality control procedures for data verification, and a workplan for the staff.

3. QUESTIONNAIRE DEVELOPMENT AND DISTRIBUTION

The content of the questionnaire focused on the 22 issues of concern to the Commission and centered on the following:

- The Federal agencies' intramural and extramural rare disease research and information dissemination/transfer activities
- Scientific opportunities, including drugs and products under investigation,their potential uses, and efforts to get the products to the consumer
- The peer system for funding rare disease research, including the policies and processes regarding applications, awards, and renewals
- Special needs and requirements for rare disease research, and resource and personnel capabilities to meet such requirements.

The draft of the questionnaire was sent to the designated agency contacts and to the Commission for review and comment.

Meetings were also held with some of the agency contacts to review the questionnaire for content, format, ease of administration, and accessibility and comparability of the requested data. Based on the reviewers' suggestions, the questionnaire was revised and sent to the Commission for approval. Appendix C contains the final approved questionnaire.

The questionnaire was mailed to the agencies in January 1988 in two waves. The first mailing was to agencies outside of DHHS. Two weeks later, the remaining agencies received the questionnaire, with the NIH institutes also receiving a report of all rare disease extramural research projects supported by their respective institute. This report was prepared by the NIH Division of Research Grants through the use of CRISP (Computerized Retrieval of Information of Scientific Projects) to assist NIH respondents in answering project specific questions. Along with completing the questionnaire, Institute respondents were asked to review the CRISP report to update and/or correct their agency listings, and to comment on the key word identifiers used to access the reported projects to help in producing a more focused rare disease search strategy for future use.

Twenty-eight of the 31 agencies responded to the survey. NASA, USDA's Food Safety Division, and the National Institute of Environmental Health Sciences (NIEHS) reported that the survey was not relevant to their work. As questionnaires were returned, they were edited by Macro project staff to check for missing/incomplete data, and to note items needing additional information and clarification.

4. DATA ANALYSIS AND FINAL REPORT

The survey instrument consists of open ended questions that elicited qualitative information not amenable to statistical presentation. Therefore, content analyses of the data were conducted to isolate particular patterns or categories of information that could be presented as frequency distributions. Matrices were constructed summarizing the agency responses. These matrices provided the framework for the discussion of the major findings.

The remainder of this report presents the survey findings.

III. FINDINGS

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The findings from the orphan disease survey confirm the hypotheses of the Commission that: (1) orphan diseases are the focus of biomedical research activities in several Federal agencies, and (2) the activities are often embedded in more general agency research efforts. The majority of research activities in rare diseases are stimulated directly by the intramural and extramural efforts of several institutes within the NIH, which may focus their research on particular organs (e.g., National Heart Lung and Blood Institute, National Eye Institute), age groups (e.g., National Institute of Child Health and Human Development, National Institute on Aging), or diseases (e.g., National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases). Additionally, other Federal agencies contribute to the body of research knowledge, indirectly while pursuing non disease-oriented research (e.g., Department of Energy).

The following section presents survey findings for each agency. The agencies are grouped according to their research orientation, from the indirect to direct focus on diseases. Thus, the survey findings are first presented for agencies outside of the DHHS, followed by agencies within the Public Health Service (PHS), with the institutes of the NIH presented separately.

A. AGENCIES OUTSIDE OF DHHS

(1) United States Department Of Agriculture, Agricultural Research Service(ARS)

The ARS conducts research on agricultural subjects in response to industry needs and/or in response to "actual agencies' needs." The ARS reports that no research is conducted on human subjects and its work has little relevance to rare disease research.

All ARS research programs are conducted intramurally. Since they are not clinical or biochemical in nature, the ARS feels that its only contribution to rare disease research may come through the investigation of certain animal models. ARS in-house research programs undergo a review every 5 years.

(2) Department Of Defense (DoD)

The DoD supports research on infectious diseases that can be a threat to American personnel who are

deployed overseas. Most of the diseases, while prevalent in foreign countries, are rare in the United States (e.g., malaria), thus qualifying the DoD as an agency supporting biomedical research on rare diseases.

a. Stimulating Research In General--The Department stimulates interest in research on infectious diseases by issuing broad agency announcements that define the DoD's areas of interest and encourage the submission of pre-proposals. On occasion, the DoD will sponsor conferences to highlight areas of interest and stimulate additional research.

   Proposals are reviewed separately by the Army, Navy and Air Force.Extramural proposals are evaluated by either in-house or in-house and extramural committees for scientific merit, as well as military and program relevance; intramural proposals undergo a similar review process, but may include a program review.

b. Stimulating Biomedical/Behavioral Research Training In General--The individual services (Army, Navy, and Air Force) select research personnel for full-time training in areas of need. This training can include a residency in a Medical Treatment Facility (MTF) in which investigation programs are conducted on infectious diseases.

c. Stimulating Clinical Research In General--Clinical experience for those in the Medical Education Program is provided at the MTFs. Many of the overseas facilities of the Department have access to populations for clinical research through local health officials.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Ongoing research efforts are monitored by staff scientists. Applications for the renewal of research efforts undergo an outside peer review that focuses on the demonstration of scientific progress in the previous support phase. No findings of this review process are reported.

e. Programs To Ensure Longer Support For Researchers-There are none.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--There are none.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--The DoD's Medical Material Development Agency facilitates the transition of basic research to clinical applications. Clinical applications often involve the development of drugs or vaccines for infectious diseases of interest to DoD. Most of the infectious diseases are rare in the United States.

h. Recent Accomplishments In Research Concerned With Rare Diseases--Examples of FY 1987 accomplishments are: (1) a demonstration that calcium channel blocker drugs administered concurrently with antimalarials can restore sensitivity to resistant strains of malaria, thereby allowing further research on antimalarials to examine certain properties; and (2) the Army's use of an adenovirus vaccine that includes a genome for hepatitis B.

i. Scientific Opportunities For Additional Research--None were reported.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--The DoD finds that it is often difficult to locate a population with sufficient disease occurrence rates to conduct trials of drugs or vaccines. This difficulty occurs most often in third world countries where outbreaks of a disease are often not identified and/or tracked.

k. Potential Treatments/Products That Have Not "Moved Forward"--Botulinum toxin has not progressed in development, due to the rare occurrence of the disease it treats. The DoD reports that it has very little application in the population it serves.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--None are reported.

m. Obligations For Research In Rare Diseases--A total of $293 million was spent in FY 1987 for Army medical research. During this same period, the Army spent $85.8 million on (about 29 percent) infectious disease research, most of which relates to rare diseases. An exact ratio of rare disease research to total research expenditures cannot be estimated, as the number of infectious diseases of interest to the DoD that are rare in the United States cannot be established.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--The DoD coordinates its departmental activities by periodically convening the Armed Services Biomedical Research Evaluation and Management Committees and the Joint Technology Evaluation and Management Committees and the Joint Technology Coordinating groups. The purpose of these groups is to avoid duplications in research efforts. Departmental representation on DHHS advisory councils and committees serves to coordinate DoD biomedical research activities with other relevant Federal agencies. Also its policy of using civilian scientists on peer review panels and advisory boards serves to "bridge the gap" between public and private sector research.

o. Availability Of Documentation On Research Activities--Reports about DoD research are available through the National Technical Information Service (NTIS).

p. Methods For Stimulating The Transfer Of Technology-DoD uses the following mechanisms to stimulate the transfer of technology in rare disease/research:

- Publication of studies and findings in scientific literature
- Exchange of scientists with scientists from other countries
- Providing resources (e.g., personnel) to other nations
- Seminars and conferences

(3) Department Of Education, National Institute On Disability And Rehabilitation Research (NIDRR)

The NIDRR provides leadership and support for a broad national and international program of research on the rehabilitation of disabled individuals. The Institute disseminates information concerning new developments in rehabilitation procedures and methods and devices which help to improve the quality of life for disabled people.

a. Stimulating Research In General--The NIDRR stimulates extramural research through the announcement of the availability of grants (publicized in the Federal Register) and contracts (publicized in the Commerce Business Daily). NIDRR grant and fellowship applications undergo staff and peer review. The peer reviewers may be Federal employees with expertise in particular areas or non-Federal experts whose names are maintained on an NIDRR roster of expert scientists. Grants are evaluated based on their scientific, technical, and administrative merit. The review of RFPs follows procedures regulated by the Department of Education. The NIDRR does not support intramural research.

b. Stimulating Biomedical/Behavioral Research Training In General--The NIDRR sponsors the Mary E. Switzer Fellowship Program to support highly qualified persons to engage in scientific research related to the solution of the rehabilitation problems of the disabled. The Institute stimulates biomedical research training by awarding Field Initiated Research Projects and Small Innovations Grants.

c. Stimulating Clinical Research In General--Clinical research is stimulated by the award of grants and contracts funded through the Research and Demonstration Program. Some of the projects funded through the Program are carried out on a long-term basis at the Institute's Rehabilitation Research and Training Centers, which provide the setting for service delivery programs and research investigation.

d. Evaluating The Effectiveness Of Research Grants And Contracts--The evaluation of ongoing funded projects is left up to NIDRR senior scientific staff. Completed projects receive a technical peer review from a panel of experts and are then reviewed by the professional program staff of each office. This process is independent from the refunding process.

e. Programs To Ensure Longer Support For Researchers-There is no mechanism for extending research beyond the regular life of the grant. Rather, investigators must submit new applications to be considered for further support.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--Research is centered around the development of products for the disabled.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--No intramural research is supported.

h. Recent Accomplishments In Research Concerned With Rare Diseases--Not applicable.

i. Scientific Opportunities For Additional Research--Not applicable.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--Not applicable.

k. Potential Treatments/Products That Have Not "Moved Forward"--None were reported.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--The total obligation for research in FY 1987 was $56.2 million. NIDRR is not able to specify the allocation that supports research conducted on rare diseases.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--To

ensure the coordination of research activities with other agencies, all Federal agencies conducting rehabilitation research have representatives on the Interagency Committee on Handicapped Research(ICHR), chaired by the Director of NIDRR. The Committee, which holds formal quarterly meetings, serves to enhance the exchange of information and promotes joint research activities among participating agencies. NIDRR also coordinates research activities with manufacturers who are responsible for the development of equipment and devices for the rehabilitation of handicapped persons.

o. Availability Of Documentation On Research Activities--The NIDRR supports the National Rehabilitation Information Clearinghouse (NARIC), which responds to requests for information on rehabilitation issues from educators, manufacturers, researchers, families, and other interested parties.

p. Methods For Stimulating The Transfer Of Technology-NIDRR stimulates the transfer of technology through program development activities, professional education/training activities, conferences, seminars, and the preparation and dissemination of publications, audiovisuals, and other media materials.

(4) Department Of Energy (DOE)

The DOE supports the development of beneficial applications of energy-related technologies (e.g., radioactive nuclides, radiopharmaceuticals, imaging instrumentation and the use of particle beams) for the diagnosis, treatment and study of diseases. These technologies are very often highly relevant to rare disease research and therapeutic remedies.

a. Stimulating Research In General--The DOE does not support intramural research. Most of the research funded by DOE is initiated by unsolicited proposals from individuals who are seeking support in areas that might be relevant to the DOE interests. Occasionally, the DOE issues RFPs for specific research efforts. Proposals focusing on rare diseases are neither encouraged nor discouraged. Grant proposals are reviewed by ad

hoc external peer reviewers and then by in-house scientific panels. Such proposals are evaluated for scientific quality, relevance to the DOE mission, and the capability of the laboratory to conduct the proposed investigation. Since the emphasis of the Department is on methods and technology, impact of the research on rare diseases is not known. It is surmised, however, that the technologies have, at least, an indirect effect on both rare and common diseases.

b. Stimulating Biomedical/Behavioral Research Training In General--The DOE stimulates research training through its fellowship program that places scientists at the national laboratories. Although the results of research may have an impact on rare diseases, this is incidental to the overall focus of the supported research.

c. Stimulating Clinical Research In General--Epidemiological research is conducted by DOE and there is some testing of nuclear medicine. However,DOE does not support clinical research and does not have the equivalent of clinical trials.

d. Evaluating The Effectiveness Of Research Grants And Contracts--The DOE reports that they have no mechanisms for evaluating the effectiveness of their research grants and contracts; however, they note that research in the past appears to be very effective since many of the widely used instruments and radiopharmaceuticals currently used in nuclear medicine were developed at DOE laboratories.

e. Programs To Ensure Longer Support For Researchers-Typical DOE grants are for a 3-year program of research. They can be extended through the submission of a new proposal.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--When basic studies are sufficiently advanced to consider widescale clinical application, investigators are encouraged to apply to NIH or other agencies for continuation of their support.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--All research is extramural.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, DOE researchers successfully completed work on: the synthesis of a boron compound, which will be tested for use in boron neutron capture therapy of glioblastoma multiforme; the identification of synchrotron light sources that will be tested for use in angiography; and the use of proton beams to treat arterio-venous malformations.

i. Scientific Opportunities For Additional Research--Present scientific opportunities exist in the area of molecular epidemiology.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--Patient acquisition as research subjects may be a problem when studies proceed to the clinical stage (e.g., clinical studies on glioblastoma).

k. Potential Treatments/Products That Have Not "Moved Forward"--None were reported.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--The total research obligation for DOE's Office of Health and Environmental Research in FY 1987 was $196,565,000. Of the amount spent on nuclear medicine ($22,618,000), about $3.7 million was devoted to research technologies that relate to rare diseases. In FY 1987, approximately 2 percent of the research budget supported research related to rare diseases.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--Boron neutron capture research efforts are closely coordinated with the NIH Radiological Research Office through personal contacts and attendance at workshops.

o. Availability Of Documentation On Research Activities--The report, Research in Progress: Summaries of Projects Sponsored by the Office of Health and Environmental Research, published by the Office of Scientific and Technical Information, was not issued in 1987, but will be available in 1988.

p. Methods For Stimulating The Transfer Of Technology-DOE has a general policy of promoting technology transfer of products developed under their research program.

(5) United States Agency For International Development (USAID)

The USAID assists developing countries in achieving self-sustaining economic growth by improving the health and well-being of their population. Within the health sector, USAID's primary goal is to improve health status and life expectancy in USAID-assisted countries, with an emphasis on reduction of infant and child mortality.

USAID seeks to promote research on diseases of public health importance in the developing world, with special emphasis on those diseases for which there are inadequate research incentives. Some of these diseases have a low prevalence in the United States, and therefore meet the definitional standard for being classified as "rare."

a. Stimulating Research In General--USAID stimulates interest in research by issuing program announcements, RFAs, and RFPs. The Agency also jointly issues research announcements with other government agencies, primarily with the NIH and the PHS. The Office of the Science Advisor to the Administrator encourages the submission of proposals from institutions located in the developing world to carry out various parts of the overall research strategy. All research funded by USAID is extramural.

RFAs, RFPs, and unsolicited proposals are reviewed by technical committees comprised of both USAID and outside experts assembled by the office issuing the solicitation. Reviews of proposals

funded by the Office of Health are conducted by contractors and or consultants assembled to coordinate research programs on behalf of the Agency. Proposals submitted by developing countries, in response to solicitations from the Office of the Science Advisor, pass through a two-stage review process.

b. Stimulating Biomedical/Behavioral Research Training In General--Biomedical/behavioral research training is a component of the Tropical Disease Research and Diarrheal Disease Research Programs, Pediatric Diarrheal Disease Research Training Project, Development of International Linkages in Medical Education with African and Caribbean Countries Project, and the Asia Pacific Public Health Management Project.

   Most training activities conducted through these projects are oriented toward building institutional capacity in the specific developing countries.

c. Stimulating Clinical Research In General--Major clinical research activities focus on treating diarrhea and on vaccine testing. Projects with significant clinical research components include: the Malaria Vaccine Field Trials Project, Tropical Disease Research Project, Diarrheal Disease Research Programs, Vaccine Development and Health Research Participating Agency Service Agreement, Americares Foundation Project on Leprosy Research, the Malaria Immunity and Vaccine Research Project, and the Applied Diarrheal Disease Research Project.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Virtually all USAID's projects incorporate periodic evaluations in the project design. Evaluations are generally conducted by teams comprised of both USAID personnel and external experts selected by the office funding the project. Evaluations are comprehensive for each project. Reports of these activities are available on request.

e. Programs To Ensure Longer Support For Researchers-Most research activities funded by USAID are supported for no more than 2 to 3 years. The

Malaria Immunity and Vaccine Research Project is unique in that it has supported researchers for some 20 years.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--The bulk of USAID's investment in research is in applied research.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--No intramural research is conducted.

h. Recent Accomplishments In Research Concerned With Rare Diseases--Recent accomplishments (FY 1987) concerned with rare diseases include: (1) the development of a prototype vaccine against malaria; (2) the application of newly developed biotechnology to diagnostic methods for typhoid fever, diarrheal diseases, malaria, and tuberculosis; (3) the development of non-reusable needles and syringes; (4) the completion of field trials of a new measles vaccine; (5) a demonstration of the higher efficacy of a new vaccine against typhoid fever; (6) the documentation of longer protective immunity provided by a new oral cholera vaccine; (7) the development and testing of new oral rehydration solutions that reduce the volume, duration, and rate of diarrheal fluid losses.

i. Scientific Opportunities For Additional Research--Research will continue in similar areas.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--USAID research is undertaken primarily in or for less developed countries. The target population of many projects (i.e., infants and children) are often in a poor state of health--they are malnourished, live under unsanitary health conditions, and exhibit high levels of polyparasitism. This, and the ethical considerations of using children as research subjects, and the fact that their parents are often illiterate presents great problems for applied researchers. The lack of incountry laboratories, adequate equipment, and support from the private sector (especially pharmaceutical

firms) are viewed by USAID as additional problems.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are numerous potential treatments or products that appear to have useful applications for the prevention, diagnosis, and treatment of rare diseases which have not moved forward. Marketing of such products in many of the LDC countries, in many instances, is a more critical problem than technological development.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--In FY 1987, USAID had a$31,326,000 obligation for research projects, nearly all of which was related to rare disease research.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--Coordination of USAID health research within the Federal sector is primarily conducted through the Participating Agency Service Agreements (PASAs) with the Public Health Service. USAID works closely with the CDC senior staff assigned to the USAID/Washington Office, overseas USAID missions (particularly in Africa), and with the National Academy of Science's Institute of Medicine on various international health activities.

o. Availability of Documentation On Research Activities--USAID supports its own clearinghouse that focuses on USAID projects, programs, and projects.

p. Methods For Stimulating The Transfer Of Technology--USAID uses contracting mechanisms (including RFAs, RFPs, and PASAs) to encourage researchers in the transfer of basic research findings to clinical and applied phases. As a result, several USAID projects emphasize prompt application of new research findings and technologies.

(6) Veterans Administration (VA)

The VA's mission is to provide health care to eligible veterans. To support this mission, the VA

conducts biomedical, prosthetic and health service research, including research that focuses on rare diseases.

a. Stimulating Research In General--About 90 percent of the research proposals considered for VA Central Office funding are generated by VA clinicianscientists, mostly physicians, who are pursing their lines of interest in immediate or long-range health care for veterans. When special health problems arise (e.g., Acquired Immunodeficiency Syndrome or AIDS) the VA solicits research from interested investigators in the VA medical centers.

   All research conducted by the VA is intramural and conducted by VA clinician and non-clinician scientists. All proposals are first reviewed locally for scientific merit. Then, proposals requesting funds from the VA Central Office Research and Development Program are also reviewed by a merit review board (analogous to NIH study sections). Furthermore, proposals that will be jointly supported by both the VA and another Federal agency must undergo a third review to satisfy criteria set by the other funding source.

   The review process is identical for common and rare diseases.

b. Stimulating Biomedical/Behavioral Research Training In General--The VA stimulates biomedical and behavioral research training through: (1) its Career Development program, and (2) the special training programs that address specific needs. The Career Development program provides career support for the full spectrum of researchers--from beginners to well-established clinical research professionals. Currently, almost 200 physicians, dentists, and other doctoral level clinicians receive support through this program.

   The Career Development program applies to both common and rare disease research.

c. Stimulating Clinical Research In General--Most of the disease research supported by the VA is clinical in orientation. Seventy percent of the funded investigators are clinicians in VA

hospitals and clinics; additional clinical research is conducted in special research centers (e.g., the Geriatric Research Center and the Education and Clinical Care Center).

The clinical orientation of funded research is identical for common and rare diseases.

d. Evaluating The Effectiveness Of Research Grants And Contracts--There is no policy for the evaluation of grant and contract awards.

e. Programs To Ensure Longer Support For Researchers-Although the VA has not made a major effort to ensure longer term support for researchers, there has been a trend to support more projects for 5 years rather than the usual 3 years. Further, the time period for three of the Career Development Program award categories has recently been extended by 1 or 2 years.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--Such encouragement is not needed because the majority of VA researchers are already conducting clinical research.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--The majority of research projects funded by the VA are clinical in nature and include research on rare diseases. It is felt that a specific policy on this issue would not change the course of research.

h. Recent Accomplishments In Research Concerned With Rare Diseases--The VA has no mechanism for identifying specific research accomplishments concerned with rare diseases.

i. Scientific Opportunities For Additional Research--Not applicable.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--The VA does not specify"rare diseases" as a separate entity and, thus, it cannot identify problems specific to rare disease research.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--The VA provides outpatient followup to assure that discharge plans are successfully implemented. These plans include making and monitoring referrals to community agencies, identifying and working with community self support groups, and providing case management services.

m. Obligations For Research In Rare Diseases--In FY 1987, the VA spent $194,722,360 to support research and training activities. Of this amount, $20,578,080 was spent on rare disease research activities. In FY 1987, approximately 10.6 percent of the VA research budget was spent on activities related to rare diseases.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--The VA coordinates its research with other Federal agencies through its participation on all NIH councils, the Orphan Products Board, and the congressionally mandated Cooperative Medical Research Program.

o. Availability Of Documentation On Research Activities--None are available.

p. Methods For Stimulating The Transfer Of Technology-VA researchers publish widely in professional and scientific journals.

B. DEPARTMENT OF HEALTH AND HUMAN SERVICES AGENCIES (Excluding NIH

(1) Health Resources and Services Administration, Office of Maternal and Child Health (OMCH)

The OMCH, through its responsibility for the administration of Title V of the Social Security Act, has a long standing history in dealing with rare diseases afflicting the youth. Its Maternal and Child Health Program works jointly with State health departments to provide screening programs for newborns, and the Genetic Disease Program funds State and

Regional Genetic Service Networks that link outreach primary care units to tertiary centers for prenatal diagnosis, testing, counseling, and treatment and management of a variety of genetic conditions.

(2) Gillis W. Long Hansen's Disease Center (Hansen's Disease Center).

The Hansen's Disease Center's work is totally devoted to the study of Hansen's Disease or leprosy, which in the United States is considered to be a rare disease.

a. Stimulating Research In General--The Hansen's Disease Center issues RFPs to stimulate clinical research in Regional Hansen's Disease Programs.The RFPs are reviewed by the Hansen's Disease Research Advisory Committee. The review criteria are based on NIH format and procedures. All RFPs are for intramural (Hansen's Disease Center and Regional Hansen's Disease Program) research.

b. Stimulating Biomedical/Behavioral Research Training In General--Research training is stimulated through the process of accepting postdoctoral fellows and graduate students to study at the Hansen's Disease Center Laboratories.

c. Stimulating Clinical Research In General--All research supported through the RFA process are clinical in nature.

d. Evaluating The Effectiveness Of Research Grants And Contracts--There is no mechanism for conducting evaluation.

e. Programs To Ensure Longer Support For Researchers-Not applicable.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--Not applicable.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--All research supported by the Hansen's Disease Center focuses on a rare disease.

h. Recent Accomplishments In Research Concerned With

Rare Diseases--The Hansen's Disease Center reports three research accomplishments in FY 1987. They include: (1) development of in vitro measures of metabolism of M. leprae, (2) identification of macrolides as active in M. leprae, and(3) 15 percent serologic prevalence of leprosy in wild armadillos.

i. Scientific Opportunities For Additional Research--The accomplishments of FY 1987 present the following opportunities for additional research:(1) attempting in vitro cultivation of M. leprae, (2) clinical trials of newer macrolides in leprosy, and (3) potential field trials of anti-leprosy vaccines in armadillos.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--There are no problems.

k. Potential Treatments/Products That Have Not "Moved Forward"--A product that has potential for treating Hansen's Disease, but which has not "moved forward" is thalidomide. It is still distributed under investigational new drug (IND) mechanisms for leprosy.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--All Hansen's Disease Center and Regional Hansen's Disease program patients are tracked through the National Hansen's Disease Register. All are referred to a Regional Center or to other known Hansen's Disease care providers. They are referred to clinical investigators, as needed, for thalidomide.

m. Obligations For Research In Rare Diseases--The total FY 1987 agency obligation of $2,300,000 supported research in a rare disease.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--There is no formal coordination with either the Federal sector or the private sector, although some informal coordination exists.

o. Availability Of Documentation On Research Activities--Educational efforts to inform the

public about Hansen's Disease include: (1) publication of The Star, prepared by patients at Carville and circulated to about 80,000 people;(2) publication of the International Journal of Leprosy; and (3) publication of a textbook entitled Leprosy.

p. Methods For Stimulating The Transfer Of Technology--Information transfer is accomplished through: (1) seminars held by the Hansen's Center Training Branch, (2) the national research conference held every other year, and (3) regular publications in scientific literature.(2)

(3) Centers For Disease Control (CDC)

The CDC serves as the national center for developing and applying disease prevention and control, environmental health, and health promotion and health education activities designed to improve the health of the people of the United States. It is responsible for controlling the introduction and spread of infectious disease in the United States. It also provides consultation and assistance to other nations and international agencies.

a. Stimulating Research In General--CDC stimulates research by issuing RFAs and RFPs, developing collaborative arrangements with other institutions, and working with State and local health agencies. This protocol is applicable to research in both common and rare diseases.

Proposals for extramural projects are reviewed in accordance with applicable provisions of the Federal Procurement Regulations; intramural projects are prioritized and reviewed within each Center/Institute/Program Office, using a variety of approaches. The impact of the CDC review process on rare disease research is unknown, as CDC does not keep a database by disease.

b. Stimulating Biomedical/Behavioral Research Training In General--This is not done by CDC.

c. Stimulating Clinical Research In General--CDC does not stimulate clinical research.

d. Evaluating The Effectiveness Of Research Grants

And Contracts--Evaluations of the effectiveness of research grants and contracts is performed on a project-to-project basis.

e. Programs To Ensure Longer Support For Researchers--Not applicable.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--Not applicable.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--CDC does not perform extensive clinical research

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, CDC conducted research on the following rare diseases: poliomyelitis, malaria, plague, Kawasaki syndrome, and rabies.

i. Scientific Opportunities For Additional Research--Continuing efforts in similar areas are underway.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--No problems have been encountered.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none to report.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable. CDC does not provide direct patient services.

m. Obligations For Research In Rare Diseases--In FY 1987, a total of $65,394,000 was spent on extramural and intramural research. Information on the expenditure for rare disease research is not available.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--CDC coordinates its research activities with several other Federal agencies, both on a formal and informal basis. These collaborations are generally at the working level and may not include the exchange of resources. Rare disease research

topics are included in these collaborations.

o. Availability Of Documentation On Research Activities--CDC uses the Morbidity and Mortality Weekly Report (MMWR) to inform other researchers and practitioners of data on diseases of low prevalence and to report on outbreaks of rare diseases.

p. Methods For Stimulating The Transfer Of Technology-In addition to the MMWR, CDC reports on research at conferences and publishes results in a scientific journal.

(4) Alcohol, Drug Abuse And Mental Health Administration: National Institute on Drug Abuse (NIDA)

NIDA studies the bio-psychosocial bases of drug abuse and the development of new treatment and prevention methodologies. While drug abuse affects millions of people, the number of people in treatment (with a specific pharmacology) at any given time may be under 200,000, qualifying the research performed on possible therapies to be classified as research devoted to rare diseases.

a. Stimulating Research In General--NIDA stimulates research by issuing program announcements, RFAs, and RFPs. There is no specific Institute research program on rare disease, although therapies developed for limited numbers of patients may be considered to be rare disease oriented.

Extramural proposals receive a two-tiered peer review by nongovernment experts and the National Advisory Council on Drug Abuse; intramural proposals are reviewed by an outside advisory committee and receive an internal review for programmatic appropriateness. There has been no specific attempt to investigate the impact of the review process on therapies that target small populations

b. Stimulating Biomedical/Behavior Research Training In General--NIDA stimulates research training through its National Research Service Awards, fellowships, and training grants. These mechanisms for the support of training would be applicable to rare disease if: (1) some (or all)

forms of drug abuse were specifically included in the enacting legislation, or (2) therapies (specially pharmacotherapy) for which the estimate of numbers of patients making use of them, falls within the target number for affected populations.

c. Stimulating Clinical Research In General--The Institute does not have a general clinical research program. All research is specifically targeted to the identification, treatment, and prevention of drug abuse, and the basic sciences that form the foundation for these investigators.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Each contract and grant supported by NIDA undergoes an annual review. The review is conducted by the NIDA project officer who evaluates the effectiveness of the project and submits his findings to the institute and agency. Funding for each project year is contingent upon this review.

NIDA holds several meetings (15-20 per year), which allow researchers to discuss their projects and their research findings with other research scientists (primarily other NIDA grantees). "Technical review" meetings serve to provide a prospective evaluation of the projects; "research analysis utilization reviews" provide a retrospective evaluation.

e. Programs To Ensure Longer Support For Researchers-The Institute has a MERIT award program and will be funding up to 5 percent of its extramural program through this award. This award system used by NIDA and most NIH institutes allows for initial funding of 5 years and additional support (3 to 5 additional years) to be provided researchers who have in the past demonstrated success in their research endeavors. Potential awardees are "invited" to compete for these awards by submitting a progress report and a budget projection.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--There is no specific program to encourage research to move from basic to applied phases. One of the major areas of concern to NIDA is the development

of newer treatment and prevention methodologies for patients affected by drug abuse.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--NIDA's intramural facility has the resources to perform small-scale human studies in the potential utility of new pharmacotherapies for drug abuse subcategories.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, NIDA successfully tested a depot preparation of the drug naltrexone in humans, and completed a review of studies of potential carcinogenicity of LAAM.

i. Scientific Opportunities For Additional Research--Innovative treatments for a variety of different forms of drug abuse is likely to follow the acquisition of fundamental knowledge of drug-receptor mechanisms.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--NIDA reports that its greatest problems lie in the fact that pharmaceutical firms are reluctant to become involved with drug abuse. Public relations efforts on this problem have not been successful as pharmaceutical firms fear that the manufacture of products for drug abusers will have an overall negative impact on sales.

k. Potential Treatments/Products That Have Not "Moved Forward"--Progress on the development of the drug LAAM has been slow. This is in spite of the fact that the drug may have some therapeutic advantage over methadone for a specific sub-population of opiate abusers.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not Applicable

m. Obligations For Research In Rare Diseases--NIDA reports that it cannot respond to this question since it does not have a categorical rare disease or orphan drug program. NIDA does fund research into the use of pharmacologic agents, many of which may influence the treatment of certain kinds

of drug abuse.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--NIDA participates in DHHS activities which involve orphan drugs and when appropriate, meets with Federal agencies such as DEA and FDA. NIDA also works cooperatively with academic institutions, private foundations, and various committees conducting activities on drug abuse.

o. Availability Of Documentation On Research Activities--The NIDA Research Monograph Series contains papers describing funded research projects.

p. Methods For Stimulating The Transfer Of Technology--NIDA distributes information through a variety of newsletters, technical publications, staff presentations at professional meetings, conferences, staff site visits, and direct technical assistance. The technical review and research analysis utilization reviews, described earlier, also serve to transfer research findings and stimulate additional research.

(5) Alcohol, Drug Abuse and Mental Health Administration: National Institute of Mental Health (NIMH)

The NIMH is charged with improving the mental health of the American people, fostering the understanding, treatment, and rehabilitation of the mentally ill, and preventing mental illness. The Institute supports research at universities, hospitals, mental health centers, and other research facilities across the country. Basic research and clinical studies in psychiatry, psychology, neurogenetics, neurochemistry, neurophysiology, and cellular and molecular biology are conducted in NIMH facilities.

a. Stimulating Research In General--The NIMH stimulates research by issuing program announcements and RFAs. The Institute views the availability of clinical center grants and intramural research hospitals to be an additional stimulant to research. The NIMH encourages research in rare diseases through its grant announcement process, training mechanisms, scientific presentations and workshops, and the

rare disorder component included in a number of clinical center grants.

A two-tiered approach is used to review all grant applications. Research grants are first reviewed for scientific and technical merit by an initial review group (IRG) composed primarily of non-Federal scientists convened by the NIMH. Following this process, the National Advisory Mental Health Council reviews the proposal, guided by its knowledge of Institute policy and program priorities.

Intramural research projects are generated by the scientific staff and reviewed at the level of Branch (for clinical) or Laboratory Chief (for basic). Those proposals that require additional resources to implement are shared with the Scientific Director who consults with the Deputy Director and Associate Directors for Clinical and Basic Research to make the final decision on its award.

b. Stimulating Biomedical/Behavioral Research Training In General--NIMH uses NRSAs to fund institutional training grants and individual research fellowships. The Institute also provides Research Scientist Development Awards (RSDA), which are designed to foster the development of outstanding scientists by providing funds for research and training on a full-time basis up to 5 years.

NIMH recently developed a special mental health clinical training grant called the Individual Faculty Scholar Award. The grant is designed to enhance the infrastructure of academic institutions by training clinical faculty who will then remain within an academic setting to foster these skills in future psychiatric nurses, psychologists, social workers, and psychiatrists.

c. Stimulating Clinical Research In General--The Division of Intramural Research of the NIMH has as its primary mission to carry out comprehensive long-term innovative biologic research on processes related to the causes, diagnosis, treatment and prevention of mental disorders as well as the biological and psychosocial factors

that determine human behavior and development.Clinical investigations conducted by these researchers are facilitated by the availability of the NIH Clinical Center where patients and their families are included in often lengthy protocols.

d. Evaluating The Effectiveness Of Research Grants And Contracts--An evaluation of the Preventive Intervention Research Center program is currently underway. An initial evaluability assessment was conducted involving experts in the areas of research, dissemination and management. Recommendations included use of annual structured site visits to assess research quality, program progress, accomplishments, and problems.

e. Programs To Ensure Longer Support For Researchers--The NIMH uses the MERIT award system to ensure longer term support for researchers.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--The NIMH has two divisions devoted to encouraging applied and clinical research. The Division of Clinical Research funds studies on both rare and less rare mental disorders, with specific branches focusing on disorders of childhood, disorders of aging, affective and anxiety disorders, prevention research, and the study of epidemiology and psychopathology. A second division, the Division of Biometry and Applied Sciences, funds research in the areas of service delivery, economic influences on mental health service provision, research related to antisocial and violent behavior, and research on minority populations.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Current policies for intramural research may restrict the expansion of clinical research on rare diseases because: (1) there are a small number of beds available for any single research project, and (2) the Board of Scientific Counselors, which can provide additional input for proposed projects, meets only about once in every three years.

h. Recent Accomplishments In Research Concerned With

Rare Diseases--In FY 1986, the NIMH funded research projects focusing on: pervasive developmental disorders in children, genetic and environmental factors in the transmission of Tourette disorders, the relationships between depression in youths and adults, the biomedical and physiological correlates of psychiatric illness, childhood psychopathology, cognitive impairment in obsessive-compulsives, and the efficacy of two drugs in treating various types of social phobias.

i. Scientific Opportunities For Additional Research--The institute expects to fund new research in areas similar to those listed above.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--Progress in research in rare diseases is hampered by the lack of qualified investigators with appropriate backgrounds to conduct studies.

k. Potential Treatments/Products That Have Not "Moved Forward"--Therapies and products for the treatment of obsessive-compulsive disorders are still in the early stages of development. Specific products that may be potentially useful in treating these disorders include: clomipramine, fluoxetine and fluvoxamine. Products used for the treatment of social phobias, such as monoamine and certain benzodiazepines, are also in the experimental stages.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Ancillary services to patients with rare diseases who participate in research protocols include: support groups, identification of the availability of various forms of ongoing community assistance, followups with the community physician, the transfer of patient records, and expense-paid followup evaluations at the Clinical Center. In addition, the Clinical Director's office maintains a list of available protocols for individuals with a variety of illnesses so that they can be referred if an active protocol is not available in their particular areas. When children with rare diseases have completed their protocol, clinic

staff make visits to the child's community, if it is within the geographic area.

m. Obligations For Research In Rare Diseases (FY 1986 data)--In FY 1986, NIMH had a $353.8 million obligation for research activities. Many of these activities included research on the 20 mental disorders that NIMH identifies as being rare.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--No effort to coordinate rare disease research has been attempted.

o. Availability Of Documentation On Research Activities--The National Clearinghouse for Mental Health Information was disbanded in 1981 due to budget cutbacks. In its place, the NIMH now maintains the Office of Scientific Information, which directs the acquisition and dissemination of mental health information. In addition, the office prepares reports and public information materials, and responds to requests from the lay public, clinicians, and the scientific community. Because of continued funding difficulties, many of these publications are out-of-date.

p. Methods For Stimulating The Transfer Of Technology--The NIMH stimulates the transfer of technology by supporting conferences and workshops on various mental disorders. In FY 1987, the NIMH conducted a workshop on autism and a conference on psychiatric co-morbidity. The latter included discussions on obsessive compulsive disorder and social phobia.

(6) Food And Drug Administration: Office Of Orphan Products Development (OPD)

The OPD promotes the development of safe and effective products for the prevention, diagnosis or treatment of rare diseases/conditions. Its mission is to implement the orphan drug provisions of the Food Drug and Cosmetics Act and to manage grant programs to support clinical studies on the use of drugs, biologics, medical devices, and medical foods for rare diseases/conditions. Other FDA agencies that conduct research related to rare diseases include: (1) the Center for Devices and Radiological Health's Division

of Life Sciences, which assesses the human health effects of radiation; (2) the Center for Biologic Evaluation and Research, which conducts research directed at understanding mechanisms of disease pathogenesis and disease prevention; and (3) the Center for Drug Evaluation and Research, which develops animal models for evaluating the short- and long-term effects of drugs, and improvements in drug evaluation methodologies.

a. Stimulating Research In General--The OPD stimulates extramural research by issuing RFAs in the Federal Register, placing grant announcements in the NIH Guide to Research, and mailing grant announcements to researchers who have demonstrated an interest in participating in the FDA grant program. In addition, the FDA invites industrial sponsors, research institutions, rare disease organizations, and professional groups to submit grant applications through the Orphan Products Grants Program.

   Extramural grant applications are reviewed by field reviewers selected from an OPD consultant list containing over 300 names of experts in over 35 medical specialty areas. The selection of the field reviewer is based on the expert's: recent clinical research completed in the field, history of publication in appropriate medical journals, absence of real or apparent conflict of interest, balance between research expertise and clinical background, educational background, institutional affiliation, etc. Applications for intramural research projects are reviewed by a broad array of government, industry, and academic scientists.

b. Stimulating Biomedical/Behavioral Research Training In General--OPD stimulates biomedical/behavioral research training through its participation at symposia and through its support of disease-specific workshops and conferences, such as those sponsored by the National Organization for Rare Disorders (NORD), Pharmaceutical Manufacturers Association Commission on Drugs for Rare Disease, and the NIH.

c. Stimulating Clinical Research In General--OPD's grant program has a heavy emphasis on clinical research.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Since the Orphan Products Grants Program is a relatively new program, few grant studies have actually been completed. Most of the proposals that are funded are project- and product-specific and thus a defined time limit is strictly adhered to.

e. Programs To Ensure Longer Support For Researchers-No such programs have been established.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--The entire Orphan Product Grants Program was established to encourage movement of research from basic to clinical and applied research. In addition, FDA has established a program to provide protocol assistance to sponsors of studies of drugs intended for the treatment of rare diseases/conditions. Through this program, study sponsors receive guidance on the appropriateness of the nature of the study, as well as guidance on meeting the FDA New Drug Application Approval requirements.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--The most important FDA policy to facilitate clinical research is that of open communications on all aspects of research. Non-FDA scientists from industry or from academia are encouraged to bring problems in the initiation of studies to FDA's attention. Once a problem is identified, a dialogue ensues whereby actions to resolve the problem become a joint venture.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, the FDA funded studies on: (1) immune serum globulin; (2) standards and analytic methods for quality control of hepatitis B vaccine and hepatitis B immune globulin; (3) exposure of blood and blood products in hemophiliacs; (4) possible adulteration of blood and blood products with components of plastic containers; (5) the putative agent responsible for non- A non-B hepatitis; (6) the relationship of measles infection and immunization to the development of subacute sclerosing

panencephalitis; (7) rabies vaccine potency testing;(8) the potential usefulness of products derived from genetic engineering and monoclonal antibodies in treatment of viral diseases; (9) the development of new techniques for preventing bacterial meningitis; (10) the interaction of tetanus toxin with cells; (11) specific skin and serological tests for use in the diagnosis of TB and related mycobacterial infections; (12) the role of mycoplasma and ureaplasma in human diseases; (13) techniques for preventing atypical pneumonia; (14) whole cell and acellular vaccines for pertussis;(15) treatments for infantile seizure disorders; (16) the toxicity of a chelation therapy for Wilson's disorder; (17) therapies for pneumococcus, pertussis, rubella, and meningococcus; (18) technologies for the assessment of endotoxins; and (19) the development of a polysaccharide vaccine.

i. Scientific Opportunities For Additional Research--Many of the programs listed above are in their early stages and work will continue.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--Difficulties encountered in the development and implementation of basic or clinical research on products for rare diseases/conditions include: (1) obtaining sources of raw materials to develop a drug or device or medical food without commercial potential,(2) locating persons who are afflicted with rare disorders to serve as subjects for clinical studies, (3) finding grant field reviewers who are knowledgeable in the various specialties proposed in the applications, and (4) managing the difficulties that arise when products under investigation are modified during the course of examination.

k. Potential Treatments/Products That Have Not "Moved Forward"--Treatments which have not progressed include the use of sulfur hexaflouride gas for com -plex retinal detachment surgery, and the use of adhesives in the Cyanoacrylate family of products for corneal perforation and arteriovenous malformations.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--Of FDA's FY 1987 $99,862,000 obligation for research, $83,000,000 was related to product testing, compliance, analytical methods, and standards development. Of the remaining $16,862,000 spent on research, about $5,862,000 (35 percent) was obligated to rare disease research.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--Coordination with the Federal sector occurs through FDA's membership on the DHHS Orphan Products Board and its interaction with Federal agencies through: joint funding, review of grant applications; obtaining access to drugs, devices, or medical foods; location of potential subjects with rare diseases; communication with experts in the research community; and joint sponsorship of conferences.
The FDA coordinates with the private sector through its attendance at meetings of the Pharmaceutical Manufacturers Association and the Pharmaceutical Industry Association. The FDA also interacts with many of the 300 plus rare disease organizations, including NORD.

o. Availability Of Documentation On Research Activities--FDA sponsors the NICODARD, which is operated under contract by the Office of Disease Prevention and Health Promotion.

p. Methods For Stimulating The Transfer Of Technology-Transfer of technology is stimulated through the incentives of the Orphan Drug Act.

C. DEPARTMENT OF HEALTH AND HUMAN SERVICES--THE NATIONAL INSTITUTES OF HEALTH

(1) Division Of Research Services (DRS)

The DRS supports the NIH research program by providing centralized services to the NIH. These services include: expertise in biomedical engineering, medical library and translation services, medical illustration and photographic services, and the

provision and care of research animals.

a. Stimulating Research In General--Not applicable. The DRS only responds to request for assistance or collaboration from researchers in NIH intramural programs.

b. Stimulating Biomedical/Behavioral Research Training In General--The DRS participates in the NIH National Research Council's Resident Research Associateships Program by offering postdoctoral research opportunities in chemical engineering, applications of laser technology to medicine, physiological applications of biomechanics, biological application of computerized analytical electron microscopy, bioinstrumentation, animal-model development, and embryo cryopreservation.

c. Stimulating Clinical Research In General--Not applicable.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Not applicable.

e. Programs To Ensure Longer Support For Researchers-Not applicable.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--Not applicable.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Not applicable.

h. Recent Accomplishments In Research Concerned With Rare Diseases--Not applicable.

i. Scientific Opportunities For Additional Research--Not applicable.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--Not applicable.

k. Potential Treatments/Products That Have Not "Moved Forward"--Not applicable.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge-Not Applicable.

m. Obligations For Research In Rare Diseases--Not applicable.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector-Not applicable

o. Availability Of Documentation On Research Activities--Not applicable.

p. Methods For Stimulating The Transfer Of Technology-DRS has used cooperative agreements with industry to stimulate the transfer of technology. It has also held conferences, and provided services to professional societies and scientific publications.

(2) Fogarty International Center (FIC)

The FIC supports and coordinates international activities at the National Institutes of Health. Its activities include awarding of international research fellowships and scholarships, facilitating international health scientist exchanges; and promoting international studies. While the work of the FIC does not focus on a disease, organ or condition, programs supported by FIC sometimes may be associated with rare diseases.

a. Stimulating Research In General--The FIC uses two mechanisms for stimulating research. It announces program offerings through the NIH Guide for Grants and Contracts, and it sends RFAs and RFPs to specific organizations thought to have the relevant capabilities. This process is used to stimulate research in both common and rare disease.

Extramural research fellowship applications are reviewed by NIH study sections and then by the FIC Advisory Board. Intramural projects, notably in the FIC International Studies Program, are reviewed by the FIC senior staff, the Advanced Studies Working Group of the FIC Advisory Board, and then by the full membership of the FIC Advisory Board. The FIC reports that this review

process has no impact on rare disease research.

b. Stimulating Biomedical/Behavioral Research Training In General--The FIC stimulates biomedical/behavior research training through its international fellowship and scholar awards, which encourage U.S. scientists to conduct research in other countries and provide opportunities for scientists from other countries to conduct collaborative research in the U.S. Scientists who come to this country for training typically continue their collaborative research with U.S. scientists after their return home.

c. Stimulating Clinical Research In General--Not applicable.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Evaluation studies of FIC's research fellowship programs are conducted regularly. A study of the Senior International Fellowship program was completed in 1986; a followup of former International Research Fellows is underway. The research training/fellowship programs are evaluated primarily on the basis of process (i.e., the extent to which they successfully completed their project), research career accomplishments, professional achievements, continuing collaboration, success rate in obtaining future NIH awards, etc.

e. Programs To Ensure Longer Support For Researchers-The International Research Fellowship Award is being changed in FY 1989 from a 1-year award to an award for which applicants can apply for either 1 or 2 years of support.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--Not applicable.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Not applicable.

h. Recent Accomplishments In Research Concerned With Rare Diseases--Not applicable.

i. Scientific Opportunities For Additional Research--

Not applicable.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--Not applicable.

k. Potential Treatments/Products That Have Not "Moved Forward"--Not applicable.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--Not Applicable.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--FIC administers the Foreign Scientist Assistance Program for NIH, which includes programs for FDA and ADAMHA, and collaborates with the National Science Foundation and the National Academy of Sciences by providing references for international fellowships. The FIC also works with several agencies of foreign nations (Finland, France, Ireland, Norway, Sweden, and Switzerland) in the administration of postdoctoral research programs.

o. Availability Of Documentation On Research Activities--Not applicable.

p. Methods For Stimulating The Transfer Of Technology-Not applicable.

(3) National Cancer Institute (NCI)

The NCI conducts and supports research and other activities designed ultimately to decrease morbidity and mortality from neoplastic diseases. It does this by extensive programs in basic and clinical research, and a variety of programs in early detection, prevention, cancer control, and information transfer. Although several cancers such as lung, breast, and colon cancers have prevalence rates that exceed the Department's definition of rare diseases, many others clearly fall into this category.

a. Stimulating Research In General--The NCI uses program announcements,RFAs, and RFPs to stimulate the submission of grants and contracts. These

mechanisms apply equally to common and rare diseases. Most investigator-initiated grant proposals are reviewed under the aegis of the Division of Research Grants. Program project grants and the clinical trials program undergo peer review coordinated by the Division of Extramural Activities, NCI. Contract proposals are reviewed according to established NCI and NIH procedures. Proposals for intramural research are reviewed by each Division's Board of Scientific Counselors.The review processes have no impact on rare versus non rare disease research.

b. Stimulating Biomedical/Behavioral Research Training In General--NCI research manpower training programs are designed to recruit and develop well trained investigators in the basic and clinical disciplines necessary for cancer research. Special health professional education programs are designed to stimulate and improve cancer teaching in schools of nursing and public health as well as in medical and dental schools. Besides disseminating knowledge, these funded programs serve to encourage students to pursue careers in cancer research. As such, the program stimulates research training in all areas of cancer, including those that are considered to be rare diseases.

c. Stimulating Clinical Research In General--NCI stimulates clinical research in several ways. It funds a large grant portfolio in clinical oncology and developmental therapeutics, supports a large multi-center clinical trials program that involves hundreds of hospitals and thousands of physician investigators, provides "core grants" to support a network of comprehensive and clinical centers that are important sites of clinical research activity, and supports intramural programs in clinical oncology. All these mechanisms apply equally to common and rare diseases.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Both grants and contracts have proven to be successful mechanisms for the conduct of NCI-supported scientific research. Grants are the mechanisms of choice when the research proposal is initiated by an outside investigator, no substantial involvement between the NCI and the

investigator is required, and there is no expectation of receiving a specified service or end product. In contrast, contracts are procurements initiated by the NCI for the express purpose of acquiring a specific service or end product. Because basic research continues to be the highest priority of the NCI, the research project grant mechanisms receive the largest share of the NCI budget.

e. Programs To Ensure Longer Support For Researchers--The NCI has recently initiated an Outstanding Investigator Grant for selected scientists and physicians with particularly distinguished track records.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--NCI's entire clinical research program can be viewed as a mechanism that encourages the translation of basic applications into clinical and applied phases. For example, the Division of Cancer Treatment has major responsibility for seeing to it that advances in tumor cell biology, pharmacology, and tumor immunology are translated into programs in developmental therapeutics.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--NCI has long been conducting intramural research that falls into the rare disease category. Hodgkin's Disease, the various non--Hodgkin's lymphomas, cutaneous T-cell lymphoma, AIDS, islet cell carcinomas, adrenocortical carcinoma, and the whole spectrum of childhood cancers are but a few examples.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, the NCI conducted research in the areas of: cancer biology, cancer causation, cancer detection and diagnosis, and prevention. Clinical trials were conducted on: prostate cancer, rectal cancer, and bladder cancer. In this same period, the NCI conducted radiotherapy clinical trials and biological response modifiers clinical trials.

i. Scientific Opportunities For Additional Research--Research will continue in similar areas.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--A problem that may impede research in rare diseases is the difficulty of finding a sufficiently large population for clinical trials. NCI has minimized this problem through the use of "cooperative" clinical trials.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--NCI patients staying at the NIH Clinical Center receive all ancillary services provided by the Center, including support group meetings, referrals, followup visits with researcher physicians, and assistance locating other experimental treatments.

m. Obligations For Research In Rare Diseases--In FY 1987, NCI obligated $1,402,790,000 to intramural and extramural research. Of this amount, $662,018,000 or 47 percent, was for research on rare forms of cancer or cancer in children.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--NCI works closely with other Public Health Service agencies including the FDA and the National Center for Health Statistics. It also has extensive collaborations with the National Institute of Allergy and Infectious Diseases. Its nongovernmental collaborations include long-standing extensive collaborations with many pharmaceutical companies to develop potential cancer treatment modalities.

o. Availability Of Documentation On Research Activities--NCI supports the Physician's Data Query (PDQ), a computerized database that provides physicians with state-of-the-art statements concerning the best available therapy for a wide variety of cancers. In addition, PDQ contains a protocol file that permits physicians to know which experimental treatments are available at many locations around the country.

p. Methods For Stimulating The Transfer Of

Technology-Through the International Cancer Information Center, the NCI sponsors a large number of projects and publications devoted to information dissemination and technology transfer. In addition, the NCI publishes the Journal of the National Cancer Institute, supports a cancer database (the PDQ), and provides a number of abstracting services and other databases for use by researchers.

(4) National Institute Of Neurological And Communicative Disorders and Stroke (NINCDS)

The NINCDS conducts, fosters, and supports research and research training on the causes, prevention, diagnosis, and treatment of neurological, sensory, communicative, and muscle disorders, many of which affect relatively few individuals. The Institute invests the major portion of its funds in investigator initiated basic and clinical research in broad research areas that affect a number of specific disorders. The Institute is responsible for the study of approximately 600 neurological and communicative disorders.

a. Stimulating Research In General--The NINCDS issues program announcements,RFAs, and RFPs to stimulate research. In addition, Institute staff attend national scientific meetings and encourage investigators to submit applications for research. Extramural grant applications are subjected to peer review conducted by the Division of Research Grants, followed by a second-level review by the NINCDS Advisory Council. Extramural contracts receive a concept review and a technical merit review conducted by an external advisory group. Intramural projects are first reviewed by the Board of Scientific Counselors and then by the NINCDS Advisory Council. The application review process developed by the NINCDS ensures that research applications for common and rare diseases receive both scientific and programmatic review.

b. Stimulating Biomedical/Behavioral Research Training In General--The NINCDS provides support for research training in two ways. It sponsors postdoctoral training grants, or NRSAs awarded to academic institutions. It also supports individual researchers through its award of:

National Research Service Awards for Postdoctoral Fellows, Research Career Development Awards, and Clinical Investigator Development Awards.The mechanism for stimulating research training is identical for common and rare diseases.

c. Stimulating Clinical Research In General--The Institute stimulates clinical research by issuing program announcements, RFPs, RFAs, and announcing their research interests at national scientific meetings.

d. Evaluating The Effectiveness of Research Grants And Contracts--There is no administrative evaluation of the effectiveness of research.

e. Programs To Ensure Longer Support For Researchers--The Javits Investigator Award is used to provide up to 7 years of support for innovative projects.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--The NINCDS sponsors multidisciplinary workshops, conferences and symposia to acquaint clinicians with basic science research results to encourage research in applied phases.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Intramural scientists are encouraged to keep informed of the latest research in their specialty areas.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, the NINCDS supported research on the following neurological and communicative disorders: juvenile myoclonic epilepsy, Gaucher's disease, laryngeal papillomatosis, William's syndrome, profound hearing loss, hydrocephaly, metachromatic leukodystrophy, neurofibromatosis, Duchenne muscular dystrophy, myasthenia gravis, Creutzfeldt-Jacob disease, and Huntington's disease.

i. Scientific Opportunities For Additional Research--The Institute expects to fund new research in areas similar to those listed above.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--The development and implementation of rare and non-rare disease research has been hindered by limitations of funds to support research needs and staff requirements.

k. Potential Treatments/Products That Have Not "Moved Forward"--A NINCDS report that summarizes this issue is in a forthcoming publication.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--NINCDS inpatient hospital staff provides the following services for all patients, and specifically for those with a rare disease: (1) support services to patients and to family members of "out of town patients," (2) close and continuing contact with the referring physician, (3) in selected cases, NINCDS assumes responsibility for long-term continuing comprehensive care for outpatients, (4) for selected diseases, NINCDS coordinates local support groups (e.g., Parkinson's disease and dystonia), and (5) in selected cases, NINCDS provides assistance in obtaining social services or medical assistance.

m. Obligations For Research In Rare Diseases--Of the $454,600,000 total obligation for extramural and intramural research in FY 1987, the NINCDS spent $103,910,000 (or 23 percent) on projects related to rare diseases.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--NINCDS coordinates its activities with other Federal agencies through its participation in interagency coordinating committees, interagency review of grant applications, and its participation on study sections.

o. Availability Of Documentation On Research Activities--The NINCDS regularly publishes informational materials for physicians and patients that highlight the research status of various diseases. Fact Sheets and Hope Through Research are examples of this activity.

p. Methods For Stimulating The Transfer Of

Technology-To stimulate the transfer of technology, the Institute participates in grant and direct operation supported workshops, maintains patient rosters of genetic diseases, and conducts consensus development conferences.

(5) National Institute Of Diabetes And Digestive And Kidney Diseases (NIDDK)

The NIDDK is responsible for research on a wide range of diseases--mostly of a serious and chronic nature--including diabetes and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and diseases of the kidney, urinary tract and blood. While many of these are among the major diseases afflicting mankind,many others are relatively rare. Ongoing NIDDK research indicates that many major diseases under investigation are heterogeneous groupings of more specific conditions, each affecting a more circumscribed and smaller number of patients.

a. Stimulating Research In General--The NIDDK stimulates research by issuing programs announcements, RFAs, RFPs, and interagency agreements. A new mechanism, that of small grants, was introduced to facilitate support of pilot size research projects in rare diseases. Other mechanisms used to stimulate research in rare diseases are the conferences and workshops organized by the Institute (or its divisions) to bring the state-of-the art for a particular disease to the attention of researchers.

Extramural biomedical and behavioral grant applications receive a dual peer review--an initial scientific review by non-NIH scientists in study section, and a second review by the Institute's National Advisory Council. Proposals are reviewed for scientific merit, evaluation of applicant qualifications, adequacy of the research environment, and significance of the proposed problem to be studied. Contracts receive a technical merit review by a group of non-NIH scientists. Intramural research projects are reviewed by the Institute's Board of Scientific Counselors.

b. Stimulating Biomedical/Behavioral Research Training In General--The Institute stimulates

biomedical/behavioral research training by sponsoring individual and institutional NRSAs. These applications are reviewed under the standard peer review process. Applicants who choose programs of research on rare diseases can apply under the standard NIH procedures for all training grants.The Institute also stimulates research training through the distribution of training related brochures or other publications at scientific meetings. These brochures/publications are used by NIDDK staff to convey information and counsel potential candidates on available training options. A particular brochure, Sources of Research Training Support could be adapted to the needs of the rare disease research community.

c. Stimulating Clinical Research In General--Clinical research is stimulated through the publication of program announcements, RFAs, RFPs and program staff interaction with applicants and grantee institutions to encourage application submission. Clinical research is emphasized in the intramural programs and in the general clinical research center programs, both of which include work on rare diseases.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Evaluation of research relies on the general NIH system of periodic review of progress and of subsequent applications. In addition, the Institute's Divisions have conducted evaluations by outside experts. The result has been a continual fine-tuning of the process.

e. Programs To Ensure Longer Support For Researchers--The Institute uses the MERIT award to ensure longer support for a select group of investigators who qualify under Institute criteria.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--To encourage research to move from basic applications into clinical and applied phases, the NIDDK organizes and/or supports workshops and conferences on the state-of-the-art in various diseases, including rare diseases. Often these activities are followed by the preparation of relevant program announcements, RFAs and RFPs to further stimulate interest.

The Institute also issues SBIR Grant Program Announcements to emphasize areas of applied research in rare diseases of interest to the Institute.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Much of NIDDK's intramural research is devoted to rare diseases because they fall within the scope of the Institute's responsibility for studying metabolic and endocrine disorders. A particular NIDDK policy that facilitates clinical research on rare diseases is the institution of a program of regular meetings to review research activities. These meetings allow for personnel to be involved in the quality control process and encourages the "cross-fertilization" of ideas. Such a program has been a stimulant to the extensive program now conducted by NIDDK in cystic fibrosis.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, NIDDK conducted research in areas such as: enzyme replacement therapy for rare inherited metabolic disorders, rare disorders of fatty acid oxidation, sphingolipidoses, ornithine transcarbamylase (OTC) deficiency, hereditary amyloidosis, biotinidase deficiency, Lesch-Nyhan syndrome, methylmalonic acidemia, Zellweger syndrome, cystic fibrosis, parathyroid adenoma, primary biliary cirrhosis, cystine kidney stones, polycystic kidney disease, and hemochromatosis.

i. Scientific Opportunities For Additional Research--Among the new initiatives for future research are plans to expand protected enzyme replacement therapy to other rare metabolic diseases, and develop new cell and mouse models for study of rare diseases. The initiation of the Genome Mapping and sequencing project will enhance knowledge of the genetic basis of inherited metabolic diseases, and hopefully, will translate into direct applications for the prevention, diagnosis, study, and treatment of several groups of rare diseases.

j. Problems Encountered In The Development And

Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--The usual difficulties of research (i.e., the need for more funding, trained personnel, and institutional support of interdisciplinary teams) are magnified for researchers intent on conducting research on rare diseases. These difficulties are compounded by those unique to rare disease research including: the numbers of such diseases, the complexity of the diseases, the difficulty of obtaining adequate numbers of clinical cases, the difficulty of competing with common diseases research required by national priorities, and the difficulty of promoting therapies that lack the profitability of those developed for more common diseases.

k. Potential Treatments/Products That Have Not "Moved Forward"--The development of specific gene and gene product therapies for rare diseases has not moved forward as fast as it would have without the difficulties described above.

l. Provision Of Ancillary Service During A Hospital Stay and After Discharge--Ancillary services provided to hospital patients include: support group meetings and referrals, the transfer of patient records to the primary physician, followup visits with researcher/physician, and assistance with locating other experimental treatments.

m. Obligations For Research In Rare Diseases--In FY 1987, NIDDK obligated a total of about $500 million for research. Of this amount, $73.1 million, or 15 percent was obligated for rare disease research.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--Coordination within the NIH and with other health-related agencies is carried out through standing interagency coordinating committees. Coordination with the private sector is carried out by programs of technology transfer. All these benefit from workshops, conferences, and publications supported by the Institute, and all are applicable to rare diseases. The NIDDK Program Director for Metabolic Diseases has been especially active in facilitating cooperation and information sharing

with the voluntary agencies represented in NORD.

o. Availability Of Documentation On Research Activities--NIDDK supports the National Kidney and Urologic Diseases Information Clearinghouse which serves health professionals, patients, and the general public. The Institute also provides NORD with publications that may be sent out to patients to answer queries.

p. Methods For Stimulating The Transfer Of Technology--NIDDK stimulates the transfer of technology through cooperative ventures and contracts with the private sector, workshops, consensus conferences, seminars, and publications.

(6) National Heart, Lung, And Blood Institute (NHLBI)

The NHLBI provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; in the uses of blood; and in the management of blood resources. It conducts and supports, through research in its own laboratories and through extramural research grants and contracts, an integrated and coordinated program that includes basic investigations, clinical trials, epidemiologic studies, and demonstration and education projects.

a. Stimulating Research In General--The NHLBI stimulates research by issuing program announcements, RFAs and RFPs. It also conducts meetings and workshops, conferences and symposia to permit the exchange of ideas and stimulate innovative research.

Extramural grant applications are reviewed by peer reviewers using both standing and ad hoc committees. Extramural contract applications receive a concept and technical merit review from an external advisory group.Intramural projects are reviewed by the Board of Scientific Counselors. The review process for rare and non-rare diseases is identical.

b. Stimulating Biomedical/Behavioral Research Training In General--NRSAs are awarded to provide research training for early pre-doctoral and early postdoctoral individuals to give them the opportunity to broaden their scientific knowledge

and thereby extend the potential for qualified researchers to advance in the health-related areas. Awards designed for more advanced and more independent researchers include: the Research Career Development Awards, Clinical Investigator Awards, Academic Investigator Awards,Physician Scientist Awards, and Minority School Faculty Development Awards. In addition, the program supports Minority Biomedical Research Support grants in conjunction with the Division of Research Resources.

c. Stimulating Clinical Research In General--Clinical research is stimulated through the publication of program announcements, RFAs, RFPs and through the conduct of meetings, workshops, conferences, and symposia which permit the interchange of information among investigators.

d. Evaluating The Effectiveness Of Research Grants And Contracts--The NHLBI evaluates the effectiveness of research grants and contracts through peer review and expert panels.

e. Programs To Ensure Longer Support For Researchers-To ensure longer term support for researchers, the NHLBI uses the MERIT Award.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--The NHLBI sponsors multidisciplinary workshops, conferences, and symposia to acquaint clinicians with basic science research results to encourage research to move from basic applications into clinical and applied phases. It also supports Research Centers programs, which emphasize a multidisciplinary approach to specific health problems, including sickle cell diseases.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Intramural scientists are encouraged to keep informed of the research in their specialty areas through review of literature and attendance at lectures and conferences. The basic research done in the NHLBI Intramural program is often applicable to rare as well as non-rare diseases.

h. Recent Accomplishments In Research Concerned With

Rare Diseases--In FY 1987, the NHLBI supported research on heart and vascular diseases (i.e.,hereditary cardiomyopathies and myocarditis, hereditary forms of hyperlipidemia, congenital cardiac and vascular malformations, and Kawasaki disease), lung diseases (i.e., neonatal respiratory distress syndrome, idiopathic pulmonary fibrosis, familial emphysema, cystic fibrosis, sarcoidosis, apneas, and primary pulmonary hypertension), and blood diseases (i.e., sickle cell disease, Cooley's anemia, hemophilia, thrombotic thrombocytopenic purpura,and pheochromocytoma).

i. Scientific Opportunities For Additional Research--The NHLBI is continuing investigations on LDL-pheresis to reduce low-density lipoprotein cholesterol levels in blood, balloon angioplasty as a treatment for certain congenital cardiac malformations, and intravenous gamma globulin to prevent aneurysms in Kawasaki disease. Various surfactant preparations are being tested for treatment of neonatal respiratory distress syndrome, broncheolar lavage is being tested for management of idiopathic pulmonary fibrosis, an animal model is being developed for familial emphysema, a program is being initiated on cardiopulmonary disorders of sleep (apnea), and a center of cystic fibrosis research is being established (with NIDDK). Studies on manipulation of fetal hemoglobin synthesis in sickle cell disease are ongoing, as are studies on improving the success of bone marrow transplantation in Cooley's anemia, anti-platelet agents in thrombotic thrombocytopenic purpura, and improved diagnosis of pheochromocytoma.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--There are none.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable

m. Obligations For Research In Rare Diseases--In FY 1987, the NHLBI obligation for extramural and

intramural research was $891,027,000. Of this amount, $104,000,000 (or 12 percent) was appropriated to research in rare diseases.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--The Institute works with other NIH Institutes and Federal agencies in its programs. The Interagency Technical Committee (IATC), under the chairmanship of the Director of NHLBI, coordinates all Federal programs related to heart, blood vessel, lung, and blood diseases and blood resources among 16 participating Federal agencies. The Institute also maintains continuing relationships with institutions and professional associations; international, national, State, and local officials; voluntary agencies and organizations. For health professionals and the lay public, the Institute conducts education programs with special emphasis on collecting and disseminating materials on disease prevention.

o. Availability Of Documentation On Research Activities--A wide variety of reports and other documentation on NHLBI research activities are available from the NHLBI Office of the Director and Communications and Public Information Branch. Some of this documentation includes information on rare diseases.

p. Methods For Stimulating The Transfer Of Technology-The NHLBI uses cooperative ventures or contracts, workshops, consensus groups, conferences, seminars, and the preparation of publications to stimulate the transfer of technology.

(7) National Institute Of Allergy And Infectious Diseases (NIAID)

The NIAID conducts and supports research to study the causes of allergic,immunologic, and infectious diseases, and to develop better means of preventing,diagnosing, and treating illnesses. While the NIAID has no mandate to study orphan diseases or develop orphan drugs, many of the diseases that are the focus of Institute study have a prevalence of less than 200,000 persons.

a. Stimulating Research In General--The Institute issues program announcements,RFAs, and RFPs to stimulate research in both common and rare diseases.

Extramural research applications are reviewed by peer reviewers, using both standing and ad hoc committees; intramural applications are reviewed by the Board of Scientific Counselors. The Institute finds that the review process has no impact on the study of rare diseases.

b. Stimulating Biomedical/Behavioral Research Training In General--The NIAID funds training for pre-doctoral and postdoctoral Ph.D. researchers and clinical research fellowships for M.D.s. The funding supports training in both common and rare disease research.

c. Stimulating Clinical Research In General--The NIAID uses the General Clinical Research Centers (GCRCs) to conduct clinical trials for both common and rare diseases. Contracts, cooperative agreements and grant mechanisms are used to support clinical trials research. The process is the same for both rare and non-rare diseases.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Not applicable.

e. Programs To Ensure Longer Support For Researchers-NIAID presents MERIT awards to superior established investigators. The initial funding is for 5 years, and can be extended for an additional 3 to 5 years.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--NIAID uses two mechanisms to encourage the progression from basic research applications into clinical and applied phases. First, it maintains animal models of human illnesses that are to be used for preclinical evaluation of experimental therapies. Second, it supports clinical trials for experimental therapies for common and rare infectious and immunologic disorders.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare

Diseases--NIAID does not know of any existing policies.

h. Recent Accomplishments In Research Concerned With Rare Diseases--The NIAID supports research on a number of rare diseases in both its intramural program and its extramural program through the grant and contract mechanisms. These rare diseases include: viral diseases (AIDS, juvenile recurrent respiratory papillomatosis, neonatal herpes, congenital cytomegalovirus infections, hepatitis A, herpes encephalitis, and North American viral encephalitides); bacterial diseases (pertussis, hemophilus influenza b meningitis, group B streptococcal neonatal sepsis, and neisserial meningitis); systemic fungal diseases (cryptococcal infections, coccidioidomycosis, candidiasis, blastomycosis, and histoplasmosis); parasitic diseases (schistosomiasis, leishmaniasis, and malaria); and rare diseases of the immune system (chronic granulomatous diseases of childhood).

i. Scientific Opportunities For Additional Research--None are reported.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--NIAID finds that industrial sponsors are not always willing to assume liability risks during the clinical trial phases of development.

k. Potential Treatments/Products That Have Not "Moved Forward"--DHPG, a treatment for cytomegalovirus infection, has not progressed in its developmental stages.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--In FY 1987, a total of $523,127,000 was obligated by NIAID for extramural and intramural activities. Of the $211,567,826 that was obligated for research in rare diseases, $69,042,943 was for non-AIDS related research. Approximately 13 percent of the research budget supported non-AIDS

rare disease research

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--NIAID coordinates its research when applicable with other institutes and other Federal agencies. It also works with industrial and academic scientists to evaluate experimental therapies pre-clinically and clinically for the purpose of expediting the licensure and availability of effective treatments.

o. Availability of Documentation On Research Activities--NIAID supports an Information Office to respond to requests for information from the public and physicians.

p. Methods For Stimulating The Transfer Of Technology-To stimulate the transfer of technology, NIAID: supports basic research on drug design and discovery; funds preclinical evaluation of experimental therapies; sponsors clinical trials of promising novel therapies; conducts workshops, conferences and seminars; and publishes research findings.

(8) National Institute Of Child Health And Human Development (NICHD)

The NICHD supports programs focused on the reproductive, developmental,and behavioral processes that determine the health of children, adults, families, and populations. The NICHD has no special program targeted toward orphan product development per se. However, in the course of dealing with the many rare genetic disorders addressed in its intramural and extramural programs, scientists may use or develop orphan products to diagnose or treat a disorder of interest to the Institute.

a. Stimulating Research In General--NICHD uses program announcements, RFAs,RFPs, and staff programming to stimulate research.Extramural grant applications receive a study section peer review and a review by the NICHD Advisory Council. Extramural contracts are reviewed by an external advisory group to provide concept and merit review. Intramural projects are reviewed by the Board of Scientific Counselors and the NICHD Advisory Council.

Research applications for the study of common or rare diseases receive the same scientific and programmatic review.

b. Stimulating Biomedical/Behavioral Research Training In General--Biomedical/behavioral research training is stimulated through the use of program announcements, RFAs, RFPs, and staff programming.

c. Stimulating Clinical Research In General--Clinical research is stimulated through the use of program announcements, RFAs, RFPs, and staff programming.

d. Evaluating The Effectiveness Of Research Grants And Contracts--The Institute does not conduct evaluations of the effectiveness of research grants and contracts above and beyond that provided by the peer review system during the competitive renewal consideration of the award, and that provided by staff in reviewing the annual progress report.

e. Programs To Ensure Longer Support For Researchers-NICHD uses the MERIT award to ensure longer term support for researchers.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--To encourage research to move from basic applications into clinical and applied phases, the NICHD relies on program announcements, RFAs, RFPs, and staff programming.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Intramural scientists in all clinical branches address numerous rare diseases. New Federal policies permitting government scientists to obtain and share in royalties from licenses encourage rare and common disease product development.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, NICHD supported research on the following rare diseases: adrenal insufficiency, Cushing's syndrome, central precocious puberty, cervical dystocia, congenital

adrenal hyperplasia, cystinosis, fetal alcohol syndrome, fibrodysplasia ossificans progressiva, glycogen storage disease (Type I), homocystinuria, hyperprolactinemia, hypogonadotropic hypogonadism, hypopituitary dwarfism, immune deficiency syndromes, mucopolysaccharide storage diseases, Nelson's syndrome, osteogenesis imperfecta, maternal phenylketonuria, renal Fanconi syndrome, respiratory distress syndrome, Salla disease, sudden infant death syndrome, urea cycle enzymyopathies, immunologic infertility, amennorrhea, and premature ovarian failure. Effective treatments have been developed for precocious puberty (LHRH analogs), cystinosis (cysteamine), glycogen storage disease (starch), and some urea cycle disorders.

i. Scientific Opportunities For Additional Research--Scientific opportunities cannot be planned for or predicated. Rather, they evolve out of NICHD's ongoing work on developmental endocrinology and developmental genetics.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--There are none beyond the limited availability of funds for clinical trials.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none. The Institute, through support of clinical trials, has moved all these products forward.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--The NICHD relies on the Clinical Center Social Work Department to provide necessary services to patients with rare diseases and their families. In addition, staff physicians and nurses insure continuity of care when responsibility for patient care moves to the community physician.

m. Obligations For Research In Rare Diseases--In FY 1987, NICHD had a total research obligation of $366,651,000, of which $55,856,515 (or 15 percent) was devoted to rare disease research.

n. Coordination Of Research Activities With The

Federal Sector And With ThePrivate Sector--The coordination of NICHD rare disease research is through participation in all PHS activities relating to the rare diseases, especially the FDA.

o. Availability Of Documentation On Research Activities--These are described in the NIH annual report, Report on the Rare Disease and Condition Research Activities of the National Institutes of Health.

p. Methods For Stimulating The Transfer Of Technology--Support of clinical trials to demonstrate efficacy, and obtaining patents and issuing licenses.

(9) National Institute Of General Medical Sciences (NIGMS)

The NIGMS supports broad-based, fundamental research and research training that is not targeted to any specific organ system or disease. In this way, the Institute helps supply new knowledge, theories, and concepts for disease-targeted studies supported by other NIH components. NIGMS funded research with relevance to rare diseases falls mainly within two programs: the Genetics Program and the Pharmacological Sciences Program.

a. Stimulating Research In General--NIGMS uses the full range of funding mechanisms available to the NIH institutes. When appropriate, it issues program announcements and RFAs to stimulate research training grant applications in areas of high program relevance. The NIGMS also stimulates research through their participation in scientific meetings, interpersonal contacts with current and potential grantees, articles and speeches, and through the seminars and workshops they sponsor. NIGMS does not attempt to stimulate research on rare diseases, because their mission is to support nondisease-targeted research and research training.

NIGMS only funds extramural research. Applications submitted in response to program announcements and RFAs are reviewed by peer viewers who rank the proposed studies. The recommendation of the peer reviewers (research scientists) are then reviewed by the NIGMS

Advisory Council.

The peer review process provides staff with an assessment of a research grant's scientific merit. Meritorious applications, including those relating to rare diseases are considered for funding.

b. Stimulating Biomedical/Behavioral Research Training In General--Biomedical/behavioral research training is stimulated through the program announcement, RFA and program clarification process described above. In addition, NIGMS staff members make visits to campuses to discuss research training programs and encourage the submission of training grant applica -tions. NIGMS also has two special training programs that address shortage areas among biomedical researchers: (1) the Minority Access to Research Careers Program, which aims to increase the number and capabilities of minority scientists engaged in biomedical research; and (2) the Medical Scientist Training Program, which is designed to increase the number of clinical investigators who have been well trained in basic research.

c. Stimulating Clinical Research In General--NIGMS does not support clinical research per se, although a small amount of clinical investigation does take place within NIGMS-funded research centers focused on burn and trauma research and genetics research.

d. Evaluating The Effectiveness Of Research Grants And Contracts--NIGMS relies on the NIH peer review system to evaluate grants when they are submitted for renewal. If reviewers find that the research continues to have scientific merit and funds are available, the project is renewed; if the project is not deemed to have enough scientific merit, the grant is terminated or it is returned to the investigator for amendment and resubmission.

e. Programs To Ensure Longer Support For Researchers- NIGMS participates in the NIH programs to provide longer-term support to established investigators. It awards the MERIT to investigators who have conducted exemplary research in the past and the FIRST award to new researchers.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--The NIGMS programs that encourage the research transition from basic to applied phases include: burn and trauma research centers, genetics research centers, and the pharmacological sciences centers. In addition, NIGMS supports Small Business Innovation Research (SBIR) to encourage the private sector to develop clinical applications for basic research findings.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Not applicable.

h. Recent Accomplishments In Research Concerned With Rare Diseases--NIGMS maintains the NIGMS Human Genetic Mutant Cell Repository, which provides a resource for investigators studying genetic disorders. The repository maintains and distributes cell lines from patients and families with a wide variety of genetic disorders and from normal persons whose tissues serve as controls. In FY 1987, the NIGMS also supported research in two genetic diseases: Hermansky Pudlak syndrome and mitochondrial diseases.

i. Scientific Opportunities For Additional Research--The Human Genetic Mutant Cell Repository provides the scientific opportunity for additional research on genetic disorders.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--There are none.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--In FY 1987, NIGMS had a $555.4 million obligation for research of which $876,556, or less than 1 percent, was directed toward research of rare diseases.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--NIGMS coordinates its research with other Federal agencies,such as the DOE and the National Science Foundation (NSF). It also has communication links with several relevant private sector organizations.

o. Availability Of Documentation On Research Activities--Not applicable.

p. Methods For Stimulating The Transfer Of Technology--NIGMS engages in the following activities to stimulate the transfer of technology: conducts conferences and workshops; prepares publications and articles; and sends senior staff to make presentations at scientific meetings.

(10) National Eye Institute (NEI)

The NEI conducts and supports research, training, health information dissemination and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of the blind. NEI supports basic and clinical research on the eye and visual system in health and disease, including rare diseases, through a program of research grants, individual and institutional research training awards, career development awards, core grants, and contracts to public and private research institutions and organizations.

a. Stimulating Research In General--NEI uses program announcements, RFAs, and RFPs to stimulate research. It also sends Institute staff to attend national scientific meetings to encourage investigators to submit applications. These procedures are used to stimulate research in both common and rare diseases.
Grant applications are submitted to peer review for scientific merit and are then reviewed by the National Advisory Eye Council. Contract applications are reviewed by an external advisory group that provides concept review and technical merit review. Intramural projects are periodically reviewed by NEI Board of Scientific

Counselors.

b. Stimulating Biomedical/Behavioral Research Training In General--NEI sponsors research training by awarding postdoctoral training grants to academic institutions. It supports individual training through postdoctoral awards such as Research Career Development Awards and Clinical Investigator Development Awards. The same mechanisms are used for both rare and non-rare disease research.

c. Stimulating Clinical Research In General--Clinical research is stimulated through the publication of program announcements, RFAs, and RFPs. It applies to both common and rare diseases.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Administrative and scientific evaluation of the effectiveness of research is accomplished by NEI's ongoing planning and evaluation activities in conjunction with the National Advisory Eye Council, which has produced a series of five, sometimes multi-volume, reports.

e. Programs To Ensure Longer Support For Researchers-The NEI provides MERIT and the FIRST awards to ensure longer term support.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--NEI sponsors multidisciplinary workshops,conferences, and symposia to acquaint clinicians with basic science research activities and to encourage the move from basic to applied phases.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Intramural scientists are encouraged to keep informed of developments in their specialty areas.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, NEI supported research on the following rare diseases that affect the eye: retinopathy of prematurity, retinoblastoma, retinitis pigmentosa, macular corneal dystrophy, secondary glaucomas, and motor neuro-ophthalmic disorders.

i. Scientific Opportunities For Additional Research--None were reported.

j. Problems Encountered In The Development And Implementation Of Basis Or Clinical Research Concerned With Rare Diseases--None were reported.

k. Potential Treatments/Products That Have Not "Moved Forward"--None were reported.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--The total research obligation for the Institute in FY 1987, was $210,128,000. Of this amount, $28,555,000, or 14 percent, was spent on rare diseases research.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--The NEI coordinates its research activities with other Federal agencies through attendance at various NIH and interagency meetings, by providing representatives to various standing committees, and by disseminating information about its activities through publication of long- range plans and annual reports. The NEI also coordinates its activities with professional, commercial, voluntary, and philanthropic organizations, both nationally and internationally.

o. Availability Of Documentation On Research Activities--NEI conducts a comprehensive program of public and professional information and education on common and rare diseases affecting the eye. After NEI-supported clinical trials have produced results, the NEI makes special efforts to disseminate this information to health professionals and consumers in such a way as to encourage their rapid and appropriate utilization.

p. Methods For Stimulating The Transfer Of Technology-The NEI supports the transfer of technology through the sponsorship of: workshops, conferences, symposia, and publication of research results.

(11) National Institute On Aging (NIA)

The NIA conducts and supports biomedical, social and behavioral research, training, health information dissemination, and other programs with respect to the aging process. The Institute does not focus on rare diseases per se, since most diseases affecting the aged involve a large segment of the population. However, certain rare conditions/diseases are studied as they relate to the process of aging or the diseases of aging.

a. Stimulating Research In General--The NIA stimulates research by means of program announcements, RFAs, and RFPs, as well as by program staff interaction with applicants and grantee institutions to encourage application submissions. However, the NIA does not currently issue any requests for research that specifically target rare diseases.

Extramural biomedical and behavioral grant applications receive a dual peer review--an initial scientific review by non-NIH scientists and a second review by the National Advisory Council on Aging. Proposals are reviewed for scientific merit, evaluation of applicant qualifications, adequacy of the research environment, and significance of the proposed problem to be studied. Extramural contracts receive a technical merit review by a group of non-NIH scientists. Intramural biomedical and behavioral research projects are reviewed by the NIA Board of Scientific Counselors.

Applications on rare disease are reviewed through the same process.

b. Stimulating Biomedical/Behavioral Research Training In General--The NIA sponsors individual and institutional NRSA awards. Award applications are reviewed under the standard peer review process. Scientists who wish to apply for rare disease research training follow the same procedures.

c. Stimulating Clinical Research In General--Clinical research is conducted by the NIA intramural program in the NIH Clinical Center and in the Gerontology Research Center. While rare diseases are not targeted per se, they could be studied in relation to the study of the process of aging or diseases of aging. Extramural clinical research is stimulated through the use of program announcements, RFAs, RFPs, and staff programming. Any research involving a rare disease could be initiated after undergoing standard peer review procedures.

d. Evaluating the Effectiveness of Research Grants and Contracts--Not applicable.

e. Programs To Ensure Longer Support For Researchers-The MERIT and LEAD Awards provide long-term support for qualified researchers.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--The NIA stimulates clinical research to move from basic research to applications by sponsoring workshops and conferences to disseminate basic research findings that might be suitable for research into clinical applications. The NIA supports interventions and other clinical trials. The NIA also relies on program announcements, RFPs, and RFAs, and staff programming to encourage research to move from basic to applied phases.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--There are no policies that govern intramural research other than procedures established for concept review by the Board of Scientific Counselors.

h. Recent Accomplishments In Research Concerned With Rare Diseases--There are none.

i. Scientific Opportunities For Additional Research--The NIA expects to fund new research in areas related to its mission.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--No specific problems

have been encountered.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--There are none.

m. Obligations For Research In Rare Diseases--In FY 1987, the NIA obligated approximately $168,842,000 to extramural and intramural research. The obligation for research related to rare diseases was $1,569,485, or close to 1 percent of the total research obligation.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--The Institute works with other NIH components if a research application has relevance to the interests of other Bureaus, Institutes, and Divisions (B/I/D). NIA also coordinates with the private sector when funding is a shared responsibility.

o. Availability Of Documentation On Research Activities--The NIA conducts an extensive program of public and professional information about NIA-supported research findings and their applications.

p. Methods For Stimulating The Transfer Of Technology--The NIA uses workshops and consensus development conferences to stimulate the transfer of technology, although rare diseases have not yet been specifically targeted.

(12) Division Of Research Resources (DRR)

The DRR was created to strengthen and enhance the research environment of institutions engaged in biomedical research by developing and supporting a variety of essential research resources. These resources are used by investigators who possess active NIH or PHS grants and are engaged in health- related research, including research related to rare diseases. The programs of the DRR include: Biomedical Research Technology Program, which provides access to the latest technologies from the physical sciences, mathematics, and engineering; General Clinical Research Centers,

which support specialized clinical research units, usually within larger hospitals; Animal Resources Programs, which support the effective use of laboratory animals and the seven Regional Primate Research Centers; Minority Biomedical Research Support Program, which increases the participation of ethnic minorities in the biomedical science; Biomedical Research Support Program, which enhances the effectiveness and efficiency of biomedical research and behavioral research related to health at institutions receiving PHS grant support; and Shared Instrumentation Program, which makes available to institutions, major instrumentation on a shared-use basis for groups of PHS-funded investigators.

a. Stimulating Research In General--Each program within the DRR announces the availability of resource support in the NIH Guide for Grants and Contracts, which is published weekly.

   The review of a new, competitive renewal, or supplemental grant application involves three steps: (1) consideration by a site visit, panel review, or mail review; (2) consideration by the program subcommittee; and (3) consideration by the National Advisory Research Resources Council.

   While the focus of research conducted using DRR resources is a decision made by the local institutional review committee and/or the investigator using the resource, the very nature of the activities funded by NIH dictate that many of the resources requested will be used to facilitate research related to rare diseases.

b. Stimulating Biomedical/Behavioral Research Training In General--The DRR stimulates research career development through three of its multidisciplinary programs, the Animal Resources Program, which supports both institutional training programs and postdoctoral fellowships to encourage the search for animal models; the General Clinical Research Centers Programs, which provides support for 202 physicians who have completed sub-specialty training to enhance their career development and provide the opportunity for them to acquire sophisticated biomedical research technologies; and the Minority Biomedical Research Support Program, which provides institutional

grants to enable the participation of minority faculty and students in biomedical research and related enrichment activities.

c. Stimulating Clinical Research In General--The DRR encourages multi-disciplinary research to facilitate transfer of basic science advances into clinical research and then to standard medical practice through the GCRC Program. The GCRC Program provides the setting for investigators funded by other components of the NIH and other Federal, State, and private sources to conduct clinical trials.

d. Evaluating The Effectiveness Of Research Grants And Contracts--An evaluation of the DRR Shared Instrumentation Program is under contract and currently under way. An evaluation of the General Research Centers Program is now being planned and will also be conducted under contract.

e. Programs To Ensure Longer Support For Researchers--DRR does not support the MERIT award or any other mechanism specifically designed to ensure longer term support.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--DRR encourages research to move from basic to clinical applications through the General Clinical Research Centers Program. In addition, DRR supports small businesses through SBIR grants.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--The DRR has no intramural programs.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, DRR programs provided support for research in the following rare diseases: Animal Resources Program (Duchenne-like muscular dystrophy, X- linked severe combined immunodeficiency, alpha mannosidosis, Wilson's disease, and multiple sclerosis); Biomedical Research Technology Program (short stature, sickle cell anemia, neurogenetic diseases); General Clinical Research Centers Program (amyloidosis, Kawasaki syndrome, Werdnig-Hoffman disease, porphyrias, hereditary hemochromatosis, and

Wilson'sdisease); Minority Biomedical Research Support Program (infant apnea and sudden infant death syndrome); and Biomedical Research Support Program (group b Beta-hemolytic streptococcal disease, X-linked lymphoproliferation syndrome, and Wilms' tumor).

i. Scientific Opportunities For Additional Research--DRR will continue to conduct additional research in the areas specified above.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--Historically, the major problems encountered in the conduct of biomedical research have been the rapid rate of obsolescence of biomedical research equipment and the difficulty of acquiring state-of-the-art research equipment at low cost.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--In FY 1987, DRR had an obligation of $313,070,000 for extramural research. Approximately 10 percent, or $30,389,402 of this amount went to the support of rare disease research.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--DRR provides resource support to institutions whose researchers are engaged in biomedical research and possess active NIH or PHS grants. These same investigators may also receive support from the private sector.

o. Availability Of Documentation On Research Activities--DRR maintains the Research Resources Information Center, which regularly prepares several publications highlighting recent research, responds to requests from categorical organizations, and provides free bulk reprints regarding researchrelated activities.

p. Methods For Stimulating The Transfer Of

Technology-The DRR stimulates the transfer of technology through its activities in the General Clinical Research Centers, Small Business Innovation Research grants, and the Research Resources Information Center.

(13) National Institute Of Dental Research (NIDR)

The NIDR conducts and fosters research on the cause, diagnosis, and treatment of dental and oral diseases. Several rare diseases have been or are currently under study by the intramural program.

a. Stimulating Research In General--NIDR stimulates research through program announcements, RFAs, RFPs; presentations at research meetings, workshops, conferences; and individual and group consultations with the external research community.

Extramural research grant applications are generally reviewed by the DRG study sections. RFAs and other small grant applications are reviewed by peer groups convened by the NIDR Scientific Review Branch. Extramural contract solicitations are reviewed by external consultants to the Institute. Intramural research projects are reviewed by Laboratory and Branch Chiefs, followed by the Board of Scientific Counselors.

b. Stimulating Biomedical/Behavioral Research Training in General--NIDR stimulates biomedical research by maintaining close contacts with research institutions; making announcements in relevant research journals; and making presentations at meetings, conferences and symposia.

The process is similar for both common and rare diseases.

c. Stimulating Clinical Research In General--NIDR has developed a Dentist Scientist Award (individual and institutional) to train clinical dental scientists. This award is available for both rare and common diseases.

d. Evaluating The Effectiveness Of Research Grants And Contracts--NIDR evaluates the effectiveness of

research grants and contracts through peer review, expert panels, and bibliometrics.

Generally, NIDR grants and contracts have produced high quality outputs (e.g., publications and patents) and have been cited as making major contributions to the advancements of knowledge in both dental and medical fields. NIDR programs which have been evaluated include: Periodontal Diseases, the National Caries Program, and Craniofacial Anomalies.

e. Programs To Ensure Longer Support For Researchers--NIDR uses the MERIT award to ensure longer support for researchers.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--NIDR encourages research to move from basic to applied phases by using RFPs, RFAs, publications, and sponsoring consensus development conferences, workshops, and symposia.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--One policy that could be used by the Institute to facilitate clinical research on rare dental diseases is to identify patients in the Clinical Center who may have an oral disease associated with the disease under treatment.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, NIDR intramural researchers were involved with improving the diagnosis of patients with genetic and congenital disorders with attention directed towards the characterization and management of dental-craniofacial manifestations. Disorders examined included: ectodermal dysplasia, osteogenesis imperfecta, neurofibromatosis, precocious puberty, and nevoid basal cell carcinoma.

i. Scientific Opportunities For Additional Research--Scientific opportunities for additional research lie in the craniofacial synostosis disorders as Crouzon's syndrome, Apert's syndrome, and Pfeiffer's syndrome. Another area for research is hemifacial microsomia.

j. Problems Encountered In the Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--A problem experienced by NIDR researchers is that of securing an adequate patient population for research purposes.

k. Potential Treatments/Products That Have Not "Moved Forward--There are none.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--In FY 1987, the total NIDR obligation for extramural and intramural research was $110,910,000. The obligation for rare disease-related disorders was $1,128,360 or 1 percent of the total.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--There are none.

o. Availability Of Documentation On Research Activities--There are none.

p. Methods For Stimulating The Transfer Of Technology-NIDR sponsors workshops, conferences, and seminars to stimulate the transfer of technology. It also encourages its staff to make submissions to journals and other publications.

(14) National Institute Of Arthritis And Musculoskeletal And Skin Diseases (NIAMS)

The NIAMS conducts and supports basic and clinical research on many forms of arthritis and musculoskeletal and skin diseases. Many of the diseases included in its research may be classified as rare diseases. The NIAMS Office of Prevention, Epidemiology and Clinical Applications is responsible for coordinating and tracking rare and orphan disease research activities, including transfer of relevant technologies. The Office of Scientific and Health Communication is responsible for developing information items and responding to inquiries, often regarding rare or orphan diseases.

a. Stimulating Research In General--The NIAMS

stimulates research by means of program announcements, RFAs, RFPs, as well as by program staff interaction with applicants and grantee institutions to encourage application submissions.Extramural biomedical and behavioral grant applications receive a dual peer review--an initial scientific review by non-NIH scientists in study sections, and a second review by the NIAMS National Advisory Council. Proposals are reviewed for scientific merit, evaluation of applicant qualifications, adequacy of the research environment, and significance of the proposed problem to be studied. Contracts receive a technical merit review by a group of non-NIH scientists. Intramural research projects are reviewed by the NIAMS Board of Scientific Counselors.

This review process is identical for both common and rare disease research.

b. Stimulating Biomedical/Behavioral Research Training In General--NIAMS stimulates biomedical/behavioral research training by sponsoring individual and institution NRSA awards. These applications are reviewed under the standard peer review process. Applicants who chose programs of research on rare diseases can apply under the standard NIH procedure for all training grants.

c. Stimulating Clinical Research In General--Clinical research is stimulated through the publication of program announcements, RFAs, RFPs, and program staff interaction with applicants and grantee institution to encourage application submission.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Not applicable.

e. Programs To Ensure Longer Support For Researchers-NIAMS uses the MERIT award to ensure longer support for a select group of investigators who qualify under Institute criteria.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--NIAMS sponsors multidisciplinary workshops,conferences, and symposia to acquaint

clinicians with basic science research results.

g. Policies For Intramural Research That could Be Used To Facilitate Clinical Research On Rare Diseases--Intramural staff are encouraged to keep informed of developments in their particular specialty areas.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, NIAMS supported research on over 80 rare diseases including: epidermolysis bullosa, pemphigus, the ichthyoses, osteogenesis imperfecta,Ehlers-Danlos syndrome, Marfan's syndrome, Duchenne's muscular dystrophy, Lyme disease, polymyositis/dermatomyositis, arthritis in children, scleroderma, Sjogren's syndrome, and Reiter's syndrome.

i. Scientific Opportunities For Additional Research--The Cooperative Systematic Studies in the Rheumatic Diseases, a consortium of clinical centers across the United States, provides a unique resource for conducting clinical trials in rheumatology. The Centers maintain blood specimens from the patient volunteers enrolled in its studies in long-term storage in a serum bank for future research requests.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--A major problem encountered by researchers, particularly those doing epidemiologic and clinical research, is finding sufficient numbers of subjects with rare disorders.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--Not applicable.

m. Obligations For Research In Rare Diseases--In FY 1987, the NIAMS obligation for extramural and intramural research was $138,685,000. Of this amount, $20,636,000, or 15 percent, was directed towards research in rare disease related conditions.

n. Coordination Of Research Activities With The Federal Sector And With ThePrivate Sector--NIAMS staff participates in interagency coordinating committees; reviews dually assigned grant applications; and attends study sections. Staff members also work with professional advisory boards of lay organizations.

o. Availability Of Documentation On Research Activities--The NIAMS supports the National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse.

p. Methods For Stimulating The Transfer Of Technology--NIAMS uses workshops and consensus development conferences to stimulate the transfer of technology.

(15) National Center For Nursing Research (NCNR)

The NCNR conducts, supports, and disseminates information respecting basic and clinical nursing research, training, and patient care. Its purpose is to accomplish both short- and long-term improvements in nursing practice, patient health, and recovery from illness. Its programs are expected to complement other NIH supported research and to further the mission of NIH as a whole.

a. Stimulating Research In General--NCNR issues program announcements and RFAs to stimulate research.

NCNR does not specify program announcements by a disease taxonomy;however, a rare disease may be included in the focus of a research endeavor.In times of pandemics (i.e., AIDS), NCNR requests rare disease research in order to further the mission of NIH as a whole and to complement other NIH supported research.

Extramural biomedical and behavioral grant applications receive a dual peer review--an initial scientific review by non-NIH scientists and a second review by the NCNR Advisory Council. Proposals are reviewed for scientific merit, evaluation of applicant qualifications, adequacy of the research environment, and significance of the proposed problem to be studied.

b. Stimulating Biomedical/Behavioral Research Training In General--NCNR stimulates biomedical research training through the NRSA research training program and the Career Development Programs. New NCNR directions in research training include an increasing emphasis on postdoctoral research training and the initiation of two Career Development Awards.

c. Stimulating Clinical Research In General--NCNR stimulates biopsychosocial clinical research through conferences, seminars, and staff representatives at national meetings. As the NCNR does not specify programs by disease taxonomy, clinical research in rare diseases may or may not be included in funded research.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Since the NCNR is relatively new, evaluation processes for research grants and contract mechanisms are still being developed.

e. Programs To Ensure Longer Support For Researchers-Not applicable. The NCNR is too new to have investigators who qualify for the MERIT award.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--The NCNR places a strong emphasis on clinical research, and the application of basic science to clinical practice. The majority of supported grant awards are clinical in nature.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--NCNR does not have intramural programs.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, the NCNR supported research in chemotactic receptor loss during renal dialysis, malignant melanoma, and congenital cardiovascular malformations.

i. Scientific Opportunities For Additional Research--Bacterial opsonic activity of plasma and peritoneal fluids obtained from chronic ambulatory peritoneal dialysis patients and controls will be

examined for IgG, C3 and fibronectin content. Differences/similarities of gram-negative/positive bacteria in plasma and peritoneal fluid will be noted.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--NCNR does not focus on rare disease per se, and thus cannot identify specific problems relating to the support of rare disease research.

k. Potential Treatments/Products That Have Not "Moved Forward"--The electric nerve muscle stimulator, CNS control units for quad/paraplegics, and the voice synthesizer for amyolateriosclerosis patients are examples of treatments/ products that have not progressed through developmental stages.

l. Provision Of Ancillary Service During A Hospital Stay And After Discharge--No such services are provided.

m. Obligations For Research In Rare Diseases--In FY 1987, the NCNR obligation for extramural research was $18,150,000. The obligation for similar research activities focusing on rare diseases was $2,573,869, or 14 percent of the total.

n. Coordination Of Research Activities With The Federal Sector And With The Private Sector--NCNR coordinates with other NIH institutes if a research application for funding is relevant to the interests of other B/I/Ds. The Institute also works with the private sector when funding is a shared responsibility.

o. Availability Of Documentation On Research Activities--None available.The institute is too new.

p. Methods For Stimulating The Transfer Of Technology--There are none. NCNR does not focus on diseases, but rather on health care. Their contribution to a technology transfer activity would deal with such topics as: pain, immobility, labored breathing, etc.

(16) Warren Grant Magnuson Clinical Center (Clinical Center)

The Clinical Center provides patient facilities for clinical investigations; conducts research in clinical care, hospital administration, and related areas; and supervises residency and other training programs.

a. Stimulating Research In General--Not applicable.

b. Stimulating Biomedical/Behavioral Research Training in General--The Clinical Center staff supervise residency and other training programs.

c. Stimulating Clinical Research In General--The Clinical Center provides the setting for clinical research.

d. Evaluating The Effectiveness Of Research Grants And Contracts--Not applicable.

e. Programs To Ensure Longer Support For Researchers-Not applicable.

f. Programs To Encourage Research To Move From Basic Applications Into Clinical And Applied Phases--Not applicable.

g. Policies For Intramural Research That Could Be Used To Facilitate Clinical Research On Rare Diseases--Not applicable.

h. Recent Accomplishments In Research Concerned With Rare Diseases--In FY 1987, the Clinical Center staff conducted research on osteogenesis imperfecta, developed and evaluated a bracing system to permit children to ambulate, and developed a general rehabilitation program for infants and children. Research on polymyositis resulted in the development of an assessment tool to evaluate strength and function in patients.

i. Scientific Opportunities For Additional Research--Not applicable.

j. Problems Encountered In The Development And Implementation Of Basic Or Clinical Research Concerned With Rare Diseases--There are none.

k. Potential Treatments/Products That Have Not "Moved Forward"--There are none.

l. Provision of Ancillary Service During A Hospital Stay And After Discharge--The Clinical Center provides ancillary services to all patients admitted through the programs of the intramural research staff. The Clinical Center's Social Work Department maintains separate organizational sections to provide social services to patients with the following: cancer, arthritis and metabolic disorders, neurological disorders, and cardiovascular disease.

m. Obligations For Research In Rare Diseases--In FY 1987, the Clinical Center had a $127,000 obligation for its work on osteogenesis imperfecta and polymyositis.

n. Coordination Of Research Activities With The Federal Sector And The Private Sector--The Clinical Center coordinates its work with all other NIH institutes.

o. Availability Of Documentation On Research Activities--None.

p. Methods For Stimulating The Transfer Of Technology--The Clinical Center participates in various activities to encourage the transfer of technology. These activities include: publications in peer reviewed journals; presentations at special society meetings (e.g., Academy of Physical Medicine and Rehabilitation, and the American Rheumatism Association); and cooperation with the Osteogenesis Imperfecta Society.

IV. DISCUSSION OF THE FINDINGS

IV. DISCUSSION OF THE FINDINGS

The analyses of survey data provided by the 28 responding Federal agencies indicate that a substantial amount of research on rare diseases is being conducted. In some instances, agencies target rare/orphan diseases as a research priority; in others, agencies focus their research on broad topics that have but incidental implications for rare disorders and their therapies. The data indicate that progress is being made in the identification, diagnosis, and treatment of several rare disorders afflicting small segments of the population. This progress, however, is generally realized without the benefit of special agency policies to stimulate and support such research, or mandates to disseminate and apply the findings.

The following sections compare the agencies' rare disease activities, highlighting those activities deserving further attention. The interpretation of the findings presented in this and the previous chapter has been based on the understanding that the majority of responding agencies have broad agency missions that often preclude the maintenance of records that are disease-specific, or that designate rare diseases as a research priority. Consequently, responses to survey questions, in most instances, were based on estimates by the respondents.

A. FEDERAL COMMITMENT TO RESEARCH ON RARE DISEASES

Each of the Federal agencies responding to the survey demonstrated some level of commitment to the study of rare diseases, as indicated by the amount of funding support, and by the number of research activities and accomplishments. However, the results also show that the type and level of pertinent activities and obligated funding vary considerably from agency to agency and in no way can be predicted from agencies' stated missions or research orientation. Table 1 illustrates the proportion of each agency's research obligation committed to rare disease research activities.

The agency respondents reported over $1.3 billion obligated for rare disease research activities in FY 1987. The NIH institutes assumed most of the obligations, representing 88.5 percent or $1.15 billion of the total amount (see Figure 1 and Table 2), with NCI commanding the largest proportion for the investigation of rare forms of cancer (see Figure 2 and Table 3). Among agencies outside of DHHS, DoD provided the most support to research related to rare diseases, with a reported obligation of $85.5 million for research of infectious diseases that are of concern to the military.

TABLE 1
AGENCY OBLIGATIONS FOR RARE DISEASE RESEARCH

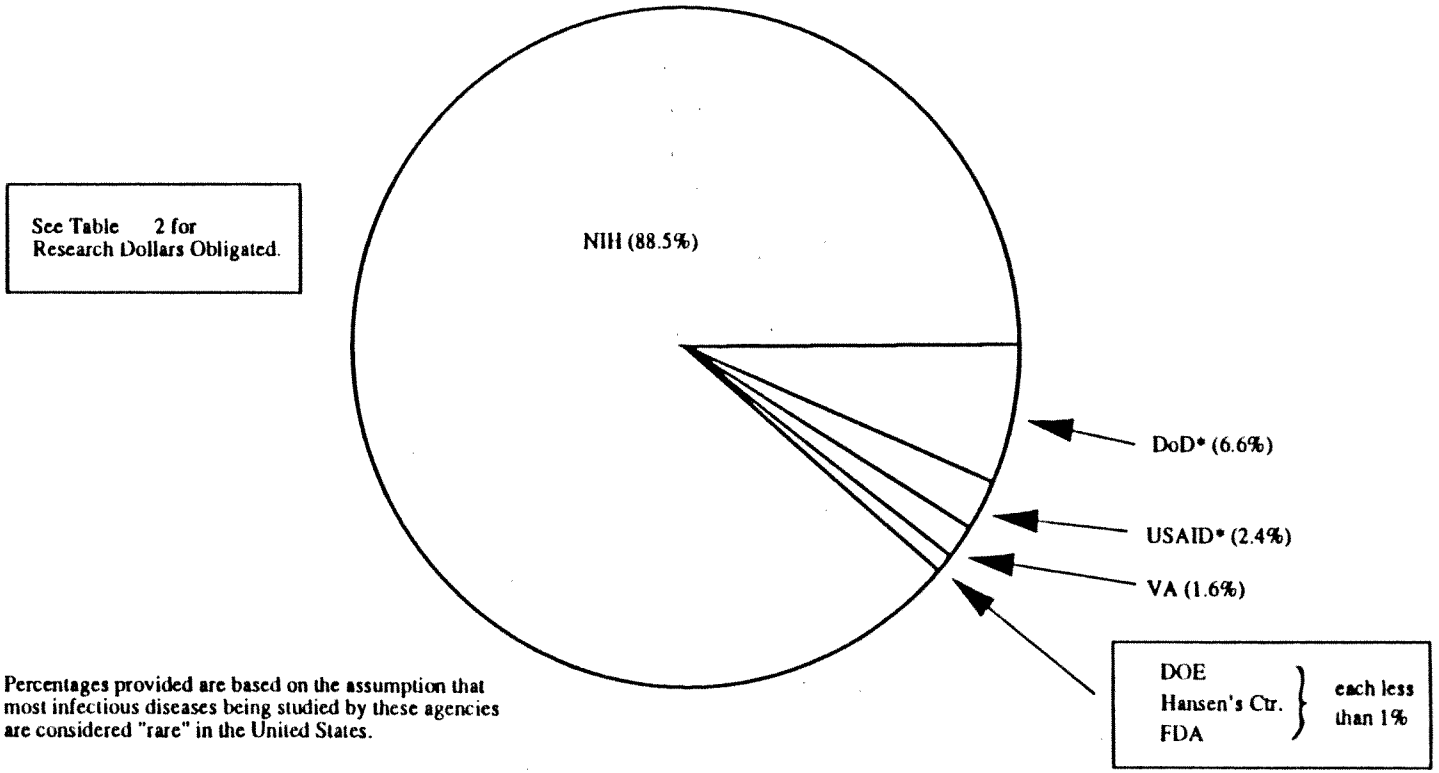
Agency	Rare Disease Research Obligation (in millions)	Percent of Total Research Obligation
Outside of DHHS		
Department of Agriculture	*	*
Department of Defense	85.8 (1)	*
Department of Education	*	*
Department of Energy	3.7	2.0
Agency for International Development	31.3	100.0
Veterans Administration	20.6	10.6
DHHS (excluding NIH)		
Centers for Disease Control	*	*
Health Resources & Services Administration		
Hansen's Center	2.3	100.0
Office of Maternal & Child Health	*	*
Alcohol, Drug Abuse & Mental Health Admin.		
National Institute on Drug Abuse	*	*
National Institute of Mental Health	*	*
Food and Drug Administration	5.9	35.0
DHHS (NIH)		
Division of Research Services	*	*
Fogarty International Center	*	*
National Cancer Institute	662.0	47.0
National Institute of Neurological, Communicative Disorders and Stroke	103.9	22.8
National Institute of Diabetes, Digestive Diseases and Kidney	73.1	15.0
National Heart, Lung & Blood Institute	104.0	12.0
National Institute of Allergy and Infectious Diseases	69.0	13.0
National Institute of Child Health and Human Development	55.9	15.2
National Institute of General Medical Science	.876	< 1.0
National Eye Institute	28.6	14.0
National Institute on Aging	1.6	1.0
Division of Research Resources	30.3	10.0
National Institute of Dental Research	1.1	1.0
National Institute of Arthritis, Musculoskeletal & Skin Diseases	20.6	14.9
National Center for Nursing Research	2.6	14.0
Clinical Center	.127	*

* Data are unavailable.

(1) Obligation for research in infectious diseases, most of which are rare in the United States

FIGURE 1

PERCENTAGE OF RESEARCH DOLLARS OBLIGATED BY FEDERAL AGENCIES REPORTING RESEARCH ACTIVITIES ON RARE DISEASES: FY 1987



* Percentages provided are based on the assumption that most infectious diseases being studied by these agencies are considered "rare" in the United States.

(Note: Data are not available for OMCH, NIDA, NIMH, USDA, CDC, ED.)

TABLE 2

RESEARCH DOLLARS OBLIGATED BY FEDERAL AGENCIES REPORTING RESEARCH ACTIVITIES ON RARE DISEASES: FISCAL YEAR 1987

Federal Agency	Total Dollar Amount Obligated	Percent of Total Federal Obligation
DEPARTMENT OF HEALTH AND HUMAN SERVICES:		
Health Resources and Services Administration		
G.W.L. Hansen's Disease Center	$ 2,300,000 (est.)	0.18
Office of Maternal and Child Health	*	*
Food and Drug Administration	5,862,000	0.45
Alcohol, Drug Abuse, and Mental Health Administration		
National Institute on Drug Abuse	(1)	*
National Institute of Mental Health	*	*
National Institutes of Health		
National Cancer Institute	662,018,000	50.9
National Heart, Lung, and Blood Institute	104,000,000	8.0
National Institute of Neurological and Communicative Disorders and Stroke	103,910,000	7.9
National Institute of Diabetes and Digestive and Kidney Diseases	73,100,000	5.6
National Institute of Allergy and Infectious Diseases	69,042,942 (1)	5.3
National Institute of Child Health and Human Development	55,856,515	4.3
Division of Research Resources	30,389,402	2.3
National Eye Institute	28,555,000	2.2
National Institute of Arthritis and Musculoskeletal and Skin Diseases	20,636,000	1.6
National Center for Nursing Research	2,573,869	0.20
National Institute on Aging	1,569,485	0.12
National Institute of Dental Research	1,128,360	0.09
National Institute of General Medical Sciences	876,556	0.07
Warren Grant Magnuson Clinical Center	127,000	0.01
Fogarty International Center	*	*
Division of Research Services	*	*
Centers for Disease Control	*	*
Subtotal	$1,161,945,129	89.22

TABLE 2 (CONT'D)

Federal Agency	Total Dollar Amount Obligated	Percent of Total Federal Obligation
DEPARTMENT OF DEFENSE	85,800,000 (2)	6.6
DEPARTMENT OF ENERGY	3,716,700	0.29
DEPARTMENT OF AGRICULTURE:		
Agricultural Research Service	*	*
DEPARTMENT OF EDUCATION:		
National Institute of Disability and Rehabilitation Research	*	*
INDEPENDENT AGENCIES:		
United States Agency for International Development	31,326,000	2.4
Veterans Administration	20,578,080	1.6
TOTAL	$1,303,365,909	100.0**

(1) Non-AIDS related research.

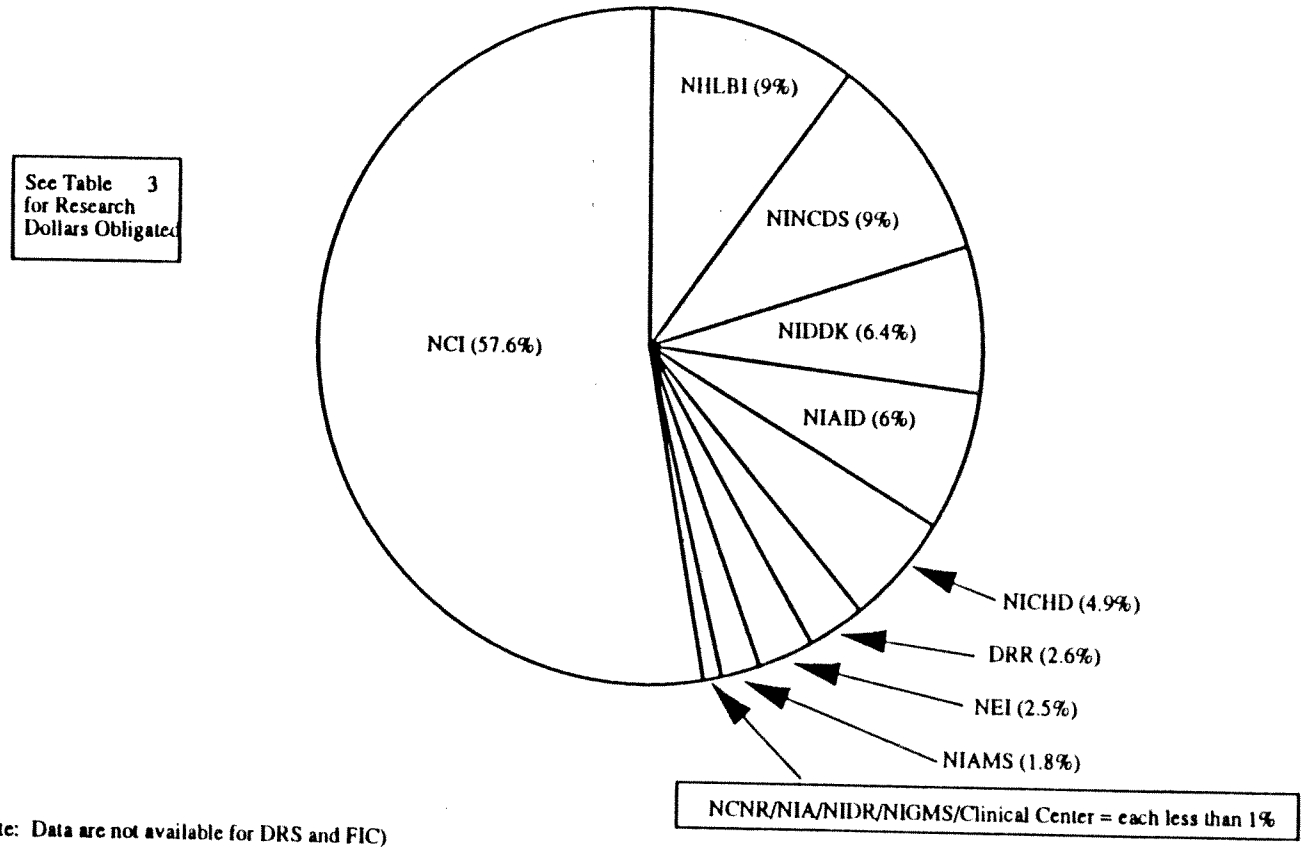
(2) Expenditures for "infectious disease research." Most diseases studied may be considered rare by the survey's definition since they are rare in the United States.

* Data are unavailable.

** Percentages do not add to 100.0 because of rounding.

FIGURE 2

PERCENTAGE DISTRIBUTION OF NIH OBLIGATIONS FOR RARE DISEASE RESEARCH: FY 1987



(Note: Data are not available for DRS and FIC)

TABLE 3

RESEARCH DOLLARS OBLIGATED BY NIH INSTITUTES
TO RESEARCH ACTIVITIES ON RARE DISEASES: FY 1987

Agency	Total Dollar Amount Obligated	Percent of Total NIH Obligation
National Cancer Institute	$ 662,018,000	57.6
National Heart, Lung, and Blood Institute	104,000,000	9.0
National Institute of Neurological and Communicative Disorders and Stroke	103,910,000	9.0
National Institute of Diabetes and Digestive and Kidney Diseases	73,100,000	6.4
National Institute of Allergy and Infectious Diseases	69,042,942 (1)	6.0
National Institute of Child Health and Human Development	55,856,515	4.9
Division of Research Resources	30,389,402	2.6
National Eye Institute	28,555,000	2.5
National Institute of Arthritis and Musculoskeletal and Skin Diseases	20,636,000	1.8
National Center for Nursing Research	2,573,869	0.2
National Institute on Aging	1,569,485	0.14
National Institute of Dental Research	1,128,360	0.10
National Institute of General Medical Sciences	876,556	0.08
Warren Grant Magnuson Clinical Center	127,000	0.01
Fogarty International	*	*
Division of Research Services	*	*
TOTAL	$1,153,783,129	100.0**

(1) Non-AIDS related research.

* Data are unavailable.

** Percentages do not add to 100.0 because of rounding.

The reported dollar amounts in almost all instances are gross estimates for the following reasons:

- It was often impossible to separate the proportion of an agency's work that relates specifically to rare diseases and then attach a "price tag."
- Many grants studying a particular disorder do so in the context of studying other disorders as well. The reported award amounts, therefore, often pertain to the grant as a whole, even though a given rare disease may be only a subfocus.

Given these caveats, the reported dollar amounts still do not translate easily into "agency commitment," as the size of an agency's obligations to rare disease research is greatly affected by the actual funds available and by the size of the Research and Development budget.

To overcome these difficulties, an attempt was made to compare the proportion of agency research dollars committed to rare disease research (i.e., amount obligated to rare disease research/amount obligated to all research) based on the data provided. Unfortunately, such an analysis was found to be very misleading as: (1) complete financial data are not available for all agencies, and (2) there are no standard data available for comparison; in some instances, obligations were reported for an agency/ institute as a whole, and in other cases, for an office within an agency. The assessment of an agency's commitment, therefore, can only be made by simultaneously examining the several variables that constitute commitment: obligations, activities, and accomplishments.

The organization's stated mission appears not to be necessarily reflective of commitment to rare disease research and related services. In fact, most agencies do not include the study of rare diseases in their mission statement but conduct such research as a by-product of their stated mission. For example, a large proportion of the research on the etiology, diagnosis, and treatment of rare diseases is conducted by the NIH institutes as an "extension" of their mission. These institutes obligate anywhere from one to 47 percent of their research dollars to fund between 8 and 625 separate research projects on rare diseases.

B. ENCOURAGEMENT AND SUPPORT OF RESEARCH IN RARE DISEASES

The Federal Government plays a major role in promoting and supporting biomedical research. It awards grants and contracts

to finance medical research in general, stimulates research training through individual and institutional awards, supports the development of clinical centers conducive to applied research, and disseminates research findings to encourage the progression of basic research to clinical applications. Agencies report that the measures used to stimulate and support research for rare and common diseases are virtually identical.

(1) Stimulation Of Research In General

All survey respondents report that Federal research interests are announced in a variety of publications in the form of program announcements, RFAs and RFPs. These formal announcements serve to inform scientists of the government's intent to fund specific areas of research and to stimulate creative technology in these areas. The NIH institutes supplement these research promotion mechanisms with a more personalized approach, often sending senior staff members to major academic research centers and to conferences and symposia to promote research and solicit the submission of applications.

The NIH institutes offer various types of grants to support researchers. For example, the FIRST Award provides support for biomedical investigators who have just completed research training, and who need support to develop research capabilities and to demonstrate the merit of research ideas. Similarly, newly trained physicians and clinical investigators can receive support to help them make the transition from research training to independent investigation (Physician Scientist Award and Clinical Investigator Award, respectively).

NIH grant support is also available to experienced researchers. The RCDA is a special salary grant to enhance the health-related research capabilities of individuals who have demonstrated outstanding potential as independent researchers, but who need to be freed from some of the teaching and administrative duties assigned to junior faculty. Senior fellowships, such as the NRSA for Senior Fellows, are designed for experienced scientists who wish to make major changes in the direction of their research careers, to broaden their capabilities, or to enlarge their command of an allied research field.

The NIH also offers a limited number of awards to selected investigators who have demonstrated superior competence and outstanding productivity during their previous research endeavors. This award, known as the MERIT, relieves the selected candidates from writing frequent renewal applications by providing the opportunity to gain up to 10 years of support in two segments.

DHHS agencies tend to use a combination of funding approaches, frequently relying on both extramural and intramural funding to stimulate research projects. Agencies outside of DHHS are more likely to promote either extramural or intramural projects, but not both. The type of funding approach, however, does not appear to be related to any commitment or lack of commitment to disease research, or to the resulting list of pertinent agency accomplishments.

Extramural research is generally funded for short durations, typically for 2 to 3 years. However, NIH and NIDA provide initial research funding for 5 years through such mechanisms as the MERIT Award, and the FIRST Award. MERIT award recipients are also eligible for an additional 3 to 5 years of support, based on a review of accomplishments during the initial period. The other agencies have no similar mechanism in place to support research for extended periods, although the VA indicates that it is now funding most research projects for up to 5 years.

(2) Stimulation Of Research Training

Research training is generally stimulated through the award of special training grants or fellowships. These awards are made either to institutions or to individuals. Individual awards are given to postdoctoral researchers who have applied research experience in clinical settings. Institutional awards support the expansion of biomedical research training at the institution's medical facility. Training awards are made in response to the submission of research training applications and undergo a rigorous review by a combination of peer and senior staff.

Research training grants are awarded only by agencies with their own medical research centers, intramural research hospitals/clinics or laboratories. These agency-supported facilities serve as settings for clinical trials of new therapies and treatments, and for developing diagnostic technologies.

As the number of researchers continue to decrease, more effective programs are needed to promote or support research training. It does appear, however, that providing persons with both the money and the facilities to be trained is an effective combination that may stimulate disease-related research. Whether an increase in their availability would affect the quantity or quality of research remains yet to be answered.

(3) Stimulating The Progression From Basic Research To Applied Phases

Most agencies rely on informal means to promote the progression of basic research into applied phases, such as supporting clinical facilities, publishing research findings, and funding symposia or seminars to disseminate information on promising research outcomes. A few agencies, however, have developed specific means to facilitate research transfer: the FDA's Office of Orphan Products Development (OPD), the DOE, and the NIH institutes.

The FDA's protocol is unique. The entire OPD Grants Program was established to encourage movement of research from basic to clinical and applied phases. Thus, project funding is contingent on the applicant's submission of a complete description of an executable clinical trial, and on the availability of human research subjects. The result of this policy is that all grant applicants are aware that a clinical phase must be included in their research plan; those who cannot meet this requirement do not apply. In addition, FDA also provides "meaningful assistance" to initial investigators by helping them design a study protocol. While receiving this assistance, the investigators are informed of the Orphan Products Grants Program and invited to apply.

The DOE encourages individual investigators to continue their research by counseling them about the applicability of their work, and advising them on how to obtain funding for the applied phase of research. This policy has helped transfer newly developed technologies to clinical centers for testing and eventual use.

A policy adopted by the institutes at NIH is to announce their interest in the application of basic research through the SBIR Program Announcements. This approach allows the sponsoring agency to maintain control over the project, but includes the private sector in the research process.

The FDA and DOE methods for encouraging the transfer of scientific knowledge from basic to applied phases may be peculiar to the sponsoring agency. The NIH approach of using the SBIR program, however, may be replicated by other Federal agencies.

(4) Evaluation Of The Research Applications

Most research applications for Federal funding are carefully reviewed by panels of experts. Grant applications are generally submitted to a multi-tiered review process; the first review panel judges the proposal's scientific merit, and the second (and possibly third) panel evaluates

it for concept and technical merit. The initial review is generally conducted by scientific review groups, established generally along lines of discipline or disease area. Members of these groups are primarily non-Federal scientists. The subsequent review(s) is/are usually conducted by a national advisory council or board. These councils/boards are composed of outstanding scientists and lay community leaders with demonstrated interest in the health program areas of the agency.

The FDA uses a different application review approach. Rather than rely on study sections or senior staff, the FDA uses external consultants or "field reviewers" as evaluators. At least three "field reviewers" are chosen from the FDA list of some 300 scientists representing 35 specialties to review each set of applications received in response to an announcement. This protocol, the FDA reports, also stimulates rare disease research, because the reviewers often are prompted to become applicants themselves at a later date.

C. EVALUATION OF THE EFFECTIVENESS OF RESEARCH

Evaluation of the effectiveness of research is part of the recompetition process at the NIH. In the case of DoD, periodic project monitoring is conducted by DoD senior staff. At the USAID, project assessments are routinely made according to the evaluation schedule laid out in the original application. The assessments are conducted by evaluation teams comprised of USAID personnel and external experts selected by the USAID funding office. At NIDA, project evaluations are conducted on an annual basis by the Project Officer and continuation of funding is contingent on the results of the review, which examines such things as accomplishments, thus far, and future directions of the research plan.

Outcome evaluations are conducted by NIDRR at the completion of the project. This evaluation consists of a technical peer review by a panel of experts, and a second review by the professional program staff of the appropriate office. This two-tiered review judges the overall merit of the project, and is in no way tied to the refunding process.

The effectiveness of the research program as a whole, is evaluated by all the agencies. These agencies conduct assessments on the quality, progress, and accomplishments of research grants and contracts and provide recommendations for restructuring policies related to program funding and management. The recent evaluation of the NIMH Preventive Intervention Research Center, for example, provided a recommendation for the institution of annual structured site visits to improve the quality of projects and reduce the possibilities of problems

interfering with research.

D. ACCOMPLISHMENTS OF RESEARCH ON RARE DISEASES

All but four agencies reported achieving major accomplishments in the rare disease field in FY 1987. The accomplishments are varied and relate to each agency's research orientation, such as the USAID's development of an oral rehydration solution to be used in less developed countries, and NIDA's development of a drug to replace methadone.

In an effort to compare the agencies' accomplishments, a matrix was developed to illustrate the several categories of accomplishments achieved. This matrix displays contributions made by each agency, categorizing them by research orientation. Table 4 illustrates that the most varied accomplishments were reported by the FDA, which by virtue of its mission promotes the development of safe and effective products for the diagnosis or treatment of rare diseases.

No attempt was made to rank the importance of these accomplishments. One could not judge, for example, whether NICHD's reported progress in understanding 28 rare diseases is more important than DOE's synthesis of a boron compound, identifying synchrotron light sources, and developing the use of proton beams. The weighing of accomplishments requires more than a mere tally of disease-specific discoveries. A more revealing measure would involve several years of patient tracking to determine such things as: number of people benefiting from the technologies, or number of deaths prevented by virtue of a study's findings.

Agencies obligating small proportions of their research budget to rare disease research (1 or 2 percent of their total research obligation) reported the fewest number of accomplishments. Clearly, there is a range in the commitment agencies make to the study of rare diseases, and this commitment can generally be translated into reportable accomplishments and progress.

E. BARRIERS TO RESEARCH

Ten agencies reported problems that interfere with conducting research on rare diseases (see Table 5). The most pressing research barrier was the problem of identifying and locating human subjects. By the very definition of rare diseases, few persons are afflicted. And, according to some respondents, even fewer people are willing to participate in research projects, especially those involving placebo control trials. The NIH's assurance of ancillary care to research subjects is a step in addressing part of the problem. This perception differs somewhat from the results generated in the

TABLE 4

FEDERAL AGENCY ACCOMPLISHMENTS IN RARE DISEASE RESEARCH BY DISEASE, TECHNOLOGY, AND DRUG/PRODUCT FOCI: FY 1987

AGENCY	FOCI		
	Disease	Technology	Drug/Product
Outside of DHHS			
. USDA			
. DoD	Conducted research on malaria		Examined the use of calicum channel blocker drugs for conducting research on malaria and an adenovirus vaccine for use in treating hepatitis B
. ED			
. DOE		Synthesized and tested a boron compound for use in boron neutron capture therapy of glioblastoma multiforme; identified synchrotron light sources that will be tested for use in angiography; and used proton beams to treat arterio-venous malformations	
. USAID		Applied biotechnology to diagnose typhoid fever, diarrheal diseases, malaria, and TB; developed nonreusable needles and syringes; and developed and tested new oral rehydration solution to affect diarrheal fluid loses	Developed prototype vaccine against malaria; completed field trials of new pertussis vaccine and developed new vaccine against typhoid fever
. VA			
DHHS (excluding NIH)			
. HRSA			
Hansen's Center		Developed in vitro measures of metabolism of M. leprae and identified macrolides as active in M. leprae	
OMCH			
. CDC	Conducted research on malaria, poliomyelitis, plague, Kawasaki syndrome, and rabies		

TABLE 4 (CONT'D)

AGENCY	FOCI		
	Disease	Technology	Drug/Product
DHHS (excluding NIH) (cont.)			
. ADAMHA			
NIDA			Tested a depot preparation of the drug naltrexone and reviewed studies of the potential carcinogenicity of LAAM
NIMH	Conducted research in pervasive developmental disorders, depression (adults and children), childhood psychopathology, and obsessive-compulsive disorder		Developed two drugs for various types of social phobias
. FDA			
OPD	Developed new techniques for preventing bacterial meningitis and atypical pneumonia	Investigated potential usefulness of products derived from genetic engineering and monoclonal antibodies in treatment of viral diseases, developed specific skin and serological tests for use in diagnosis of TB and related mycobacterial infections, and studied the role of mycoplasma and ureaplasma infections in human diseases	Conducted studies on: immune serum globulin products; quality control of hepitis B vaccine and hepatitis B immune globulin; whole cell and acellular vaccines for pertussis; bioavailability and pharmokinetics of four products for infantile seizure disorders; therapies for pneumococcus, pertussis, rubella, and meningococcus; a polysacchride vaccine; and developed technologies for the assessment of endotoxins
DHHS (NIH)			
. DRS			
. FIC			
. NCI	Conducted research on bladder, prostate, and rectal cancers	Conducted radiotherapy clinical trials and biological response modifiers clinical trials	
. NINCDS	Conducted research on juvenile myoclonic epilepsy, Gaucher's disease, laryngeal papillomatosis, William's syndrome, profound hearing loss, hydrocephaly, metachromatic leukodystrophy, neurofibromatosis Duchenne muscular dystrophy, myasthenia gravis, Creutzfeldt-Jacob disease, and Huntington's disease		

TABLE 4 (CONT'D)

AGENCY	FOCI		
	Disease	Technology	Drug/Product
DHHS (NIH) cont.			
. NIDDK	Conducted research on: enzyme replacement therapy for rare inherited metabolic disorders, rare disorders of fatty acid oxidation, sphingolipidoses, prenatal diagnosis of ornithine transcarbamylase deficiency; hereditary amyloidosis; biotinidase deficiency; Lesch-Nyhan syndrome; methylmalonic acidemia; Zellweger syndrome; cystic fibrosis; parathyroid adenoma; primary biliary cirrhosis; cystine kidney stones; polycystic kidney disease; and hemochromatosis		
. NHLBI	Conducted research on heart and vascular diseases (hereditary cardiomyopathies and myocarditis, forms of hyperlipidemia, and Kawasaki disease), lung diseases (neonatal respiratory distress syndrome, idiopathic pulmonary fibrosis, familial emphysema, cystic fibrosis, sarcoidosis, apneas, and primary pulmonary hypertension) and blood diseases (sickle cell disease, Cooley's anemia, hemophilia, thrombotic thrombocytopenic purpura, and pheochromocytoma)		
. NIAID	Conducted research on AIDS, juvenile recurrent respiratory papillomatosis, neonatal herpes, congenital cytomegalovirus infections, hepatitis A, pertussis, haemophilus influenzae type b, group B streptococci, neisseria meningitides, rickettsial disease, cryptococcal meningitis, coccidioidomycosis, candidiasis, schistosomiasis, leishmaniasis, malaria, and chronic granulomatous diseases of childhood		
. NICHD	Conducted research on adrenal insufficiency and Cushing's syndrome, central precocious puberty, cervical dystocia, and congenital adrenal hyperplasia,		

TABLE 4 (CONT'D)

AGENCY	FOCI		
	Disease	Technology	Drug/Product
DHHS (NIH) (cont.)			
. NICHD (cont.)	cystinosis, fetal alcohol syndrome, fibrodysplasia ossificans progressiva, glycogen storage disease (Type I), homocystinuria, hyperprolactinemia, hypogonadotropic hypogonadism, hypopituitary dwarfism, immune deficiency syndromes, mucopolysaccahride storage diseases (Hurler, Hunter, and Sanfilippo syndromes), Nelson's syndrome, osteogenesis imperfecta, maternal phenylketonuria, renal Fanconi syndrome, respiratory distress syndrome, salla disease, sudden infant death syndrome, urea cycle enzymopathies, immunologic infertility, amenorrhea, and premature ovarian failure		
. NIGMS	Conducted research on Hermansky-Pudlak syndrome and mitochondrial diseases	Maintained the Human Genetic Mutant Cell Repository	
. NEI	Conducted research on retinopathy of prematurity, retinoblastoma, retinitis pigmentosa, macular corneal dystrophy, secondary glaucomas, and motor neuro-opthalmic disorders		
. NIA			
. DRR	Provided support for research on: Duchenne-like muscular dystrophy, X-linked severe combined immunodeficiency, alpha mannosidosis, Wilson's disease, multiple sclerosis, short stature, sickle cell anemia, neurogenetic diseases, amyloidosis, Kawasaki syndrome, Werdnig-Hoffman disease, porphyrias, hereditary hemochromatosis, infant apnea and sudden infant death syndrome, group b Beta-hemolytic streptococcal disease, X-linked lymphoproliferation syndrome, and Wilms' tumor		

TABLE 4 (CONT'D)

AGENCY	FOCI		
	Disease	Technology	Drug/Product
DHHS (NIH) (cont.)			
. NIDR	Examined the following genetic and congenital disorders: ectodermal dysplasia, osteogenesis imperfecta, neurofibromatosis, precocious puberty, and nevoid basal cell carcinoma		
. NIAMS	Conducted research on epidermolysis bullosa, pemphigus, osteogenesis imperfecta, Duchenne's muscular dystrophy, Lyme disease, polymyositis, arthritis in children, scleroderma, Sjogren's syndrome, and Reiter's syndrome		
. NCNR	Conducted research related to malignant melonomas and congenital cardiovascular malformations	Conducted research on chemotactic receptor loss during renal dialysis	
. Clinical Center	Conducted research on osteogenesis imperfecta		Developed and evaluated a bracing system to permit children with osteogenesis imperfecta to ambulate

TABLE 5

BARRIERS TO RESEARCH ON RARE DISEASES

AGENCY	BARRIERS			
	Lack of Patients	Lack of Staff	Outdated Equipment	Other
Outside of DHHS				
USDA				
DoD	o			
DE				
DOE	o			
USAID				
VA			o	o[1]
DHHS (excluding NIH)				
HRSA				
Hansen's Center				
OMCH				
CDC				
ADAMHA				
NIDA				o[2]
NIMH				o[3]
FDA				
OPD	o			o[4]

TABLE 5 (CONT'D)

AGENCY	BARRIERS			
	Lack of Patients	Lack of Staff	Outdated Equipment	Other
DHHS (NIH)				
DRS				
FIC				
NCI	o			
NINCDS		o		
NIDDK	o			o[2,3]
NHLBI				
NIAID				o[5]
NICHD				
NIGMS				
NEI				
NIA				
DRR				o[6]
NIDR	o			
NIAMS	o			
NCNR				
Clinical Center				

[1] In less developed countries the population is often illiterate and/or malnourished.

[2] Pharmaceutical firms are reluctant to market products.

[3] Shortage of investigators.

[4] Obtaining raw materials and obtaining field reviewers.

[5] Industrial sponsors are not willing to assume liability risks during clinical trials.

[6] Inadequate biomedical research equipment.

patient survey. The patient study indicated 68% of the patients were willing to participate in investigational trials.

The FDA indicated that their application review process was problematic because of the paucity of rare disease experts available as reviewers. These field reviewers are the most qualified persons to assess the quality of research proposals, and they are adept at screening out those proposals that are unfeasible, impractical, or lack merit. Unfortunately, these specialists are few in number and often difficult to locate. Should the FDA modify its application review policy to resemble that of other agencies (i.e., in-house review) it runs the risk of destroying a seemingly effective application review process. However, the study sections or the continued emphasis on clinical research at FDA should maintain the progress recognized in its grant program.

Another barrier reported by respondents was the difficulty in working with industry. NIDA, for example, reports that pharmaceutical firms are less than eager to market drugs targeted for drug abusers, fearing that such an investment would adversely affect their firm's marketing image. NIDA finds that its research endeavors are frequently "placed on hold" until an obliging manufacturer is located. NIAID's experience with the industry has also been strained, because pharmaceutical firms are hesitant to participate in clinical trials if they must assume the liability risks during a product's development. These problems with industry translate into lost scientific opportunities, because of the time required to resolve them. The shortage of investigators was also cited by two organizations as a barrier to research on rare diseases.

F. COORDINATION OF TECHNOLOGY AND INFORMATION TRANSFER

All agencies engaging in rare disease activities have mechanisms for communicating with various Department of Health and Human Services (DHHS) agencies involved in this area. Communication links are established through participation in DHHS advisory councils or committees and through representation on the DHHS Orphan Products Board. Agencies engaged in product development activities (e.g., NIDA, OPD, NCI, and the NINCDS often work cooperatively with independent pharmaceutical companies, the Pharmaceutical Manufacturers Association and the FDA. Institutes within the NIH have developed close working relationships with the faculties of leading universities and with voluntary associations.

G. MECHANISMS USED TO TRANSFER INFORMATION AND TECHNOLOGY

The dissemination of research findings to the public, the research community, and funding agencies is vital to the progress

of rare disease research. Several mechanisms are used by Federal agencies to reach this end, including: the funding of clearinghouses and information centers; the preparation of papers; the support of conferences, workshops, and symposia; and the establishment of communication links with other agencies and interested organizations.

(1) Methods Used To Transfer Information To The Public

The public--people with rare diseases and their families, often want to learn as much as possible about a given disease, such as the cause, cure, prognosis, and ongoing research. Others seek the identity of institutes, associations, or hospital centers that can lend support.

The Federal Government supports four clearinghouses to provide information about rare diseases to the public. The National Rehabilitation Information Center (NARIC), funded by the NIDRR, responds to telephone, on-line, mail, or walk-in queries about treatments and therapeutic devices to assist the handicapped. The clearinghouses supported by USAID and NIAMS provide the public with documents describing agency programs and activities.

Only one clearinghouse, the National Information Center for Orphan Drugs and Rare Diseases (NICODARD), funded by the FDA and operated under contract to the Office of Disease Prevention and Health Promotion, was set up to provide information about a variety of rare disorders. Due to recent budget cutbacks, however, NICODARD now provides only nominal service. FDA expects to rectify this by increasing funding for FY 1989. With more money and with more publicity about its existence and services, NICODARD has the potential to meet the informational needs of the public, physicians, and researchers.

All the NIH Institutes, FDA, CDC, and the NIMH have information offices to answer public inquiries. For example, the NIAID informs the public about several infectious disorders of interest to the Institute. The DRR maintains the Research Resources Information Center (RRIC) that regularly prepares publications highlighting research activities supported by DRR's five multidisciplinary programs.

Additional materials for public use are occasionally available through the agencies themselves. The Hansen's Disease Center, publishes The Star to provide continuous information on the status of research on leprosy. The NINCDS prepares Fact Sheets that summarize the available information on specific neurological or communicative disorders. In addition, the NICHD has a publication

available to parents who wish to learn about cystinosis.

Unfortunately, Federal information services cannot begin to meet the public's needs. Consequently, the public must seek out support groups, privately sponsored clearinghouses, and disease-oriented associations for additional help. This provides the public with a "patchwork quilt" of services and places the burden of finding the additional help on ailing individuals. Those individuals who are not creative in their search for assistance, or too weak to network through the patchwork system, remain uninformed.

(2) Methods Used To Transfer Information To Professionals

Scientists, physicians and researchers have many resources available to them to keep them informed of research findings and scientific progress. All but 11 agencies report that agency staff or grantees frequently prepare articles summarizing their research for scientific publications. The publications frequently have a wide readership and they are often available to foreign audiences. Conferences, workshops, and symposia sponsored by NIH institutes serve a similar end, bringing leaders of the various research specialties together to discuss research findings and future needs.

Methods to transfer information adopted by individual institutes include the clearinghouses and the Physician's Data Query (PDQ) developed by NCI. The PDQ is a computer database that allows subscribing physicians to search the database for cancer treatments and treatment facilities across the country. The information received by the physician has a direct impact on the public and may serve to direct a patient's care and treatment.

The NIGMS Human Genetic Mutant Cell Repository provides a valuable resource for investigators studying genetic disorders. The Repository collects and distributes cell lines from patients and families with a wide variety of diseases, including many that are rare.

(3) Dissemination Of Information To Other Funding Agencies

Federal agencies keep each other informed about research developments and research findings through an elaborate system of agency-to-agency collaboration. The most common form of collaboration used by DHHS agencies is intradepartmental. The various NIH institute staff interact when participating on coordinating committees, grant review committee panels, and advisory boards. The institutes also collaborate with the private sector through their individual

memberships in professional societies, participation on advisory boards of lay organizations, and their seating on advisory boards of pharmaceutical firms. Unlike other institutes, the NIGMS engages in extensive extradepartmental collaborations, working closely with the NSF and the DOE in areas of common interest.

Collaboration on an extradepartmental basis is more common in agencies outside of DHHS. The DoD, for example, sends representatives to most interagency councils and participates on DHHS advisory councils and committees. Similarly, the Department of Education's NIDRR is active in the Interagency Committee on Handicapped Research and the National Council on the Handicapped. Such collaboration allows communication between departments, produces synergistic developments in the field of research, and serves to eliminate duplication of effort. Policies to promote increased Federal support of extradepartmental communication could serve to accelerate the research process and enhance the possibility of providing diagnostic techniques, treatments, and therapies for the many rare disorders that collectively affect a large proportion of the population.

APPENDIX A

GLOSSARY

GLOSSARY

ARS--Agricultural Research Service (USDA)

ADAMHA--Alcohol, Drug Abuse, and Mental Health Administration

B/I/D--Bureaus, Institutes, and Divisions (NIH)

CDC--Centers for Disease Control

CLINICAL CENTER--Warren Grant Magnuson Clinical Center (NIH)

CRISP--Computer Retrieval of Information of Scientific Projects

DHHS--Department of Health and Human Services

DoD--Department of Defense

DOE--Department of Energy

DRR--Division of Research Resources (NIH)

DRS--Division of Research Services (NIH)

ED--Department of Education

FDA--Food and Drug Administration

FIC--Fogarty International Center (NIH)

FIRST--First Independent Research Support and Transition Award

FY--Fiscal Year

GCRC--General Clinical Research Centers

HANSEN'S DISEASE CENTER--Gillis W. Long Hansen's Disease Center

HRSA--Health Resources and Services Administration

ICHR--Interagency Committee on Handicapped Research

IRG--Initial Review Group

IND--Investigational New Drug

LDC--Less Developed Country

MARC--Minority Access to Research Career Program

MERIT--Method to Extend Research In Time

MMWR--Morbidity and Mortality Weekly Report (published by CDC)

MSTP--Medical Scientist Training Program

MTF--Medical Treatment Facility (DoD)

NARIC--National Rehabilitation Information Clearinghouse

NASA--National Aeronautics and Space Administration

NCI--National Cancer Institute (NIH)

NCNR--National Center for Nursing Research (NIH)

NDA--New Drug Application

NEI--National Eye Institute (NIH)

NHLBI--National Heart, Lung, and Blood Institute

NIA--National Institute on Aging (NIH)

NIAID--National Institute of Allergy and Infectious Diseases (NIH)

NIAMS--National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH)

NICODARD--National Information Center for Orphan Drugs and Rare Diseases

NIDA--National Institute on Drug Abuse (ADAMHA)

NIDDK--National Institute of Diabetes and Digestive and Kidney Diseases (NIH)

NIDR--National Institute of Dental Research (NIH)

NIGMS--National Institute of General Medical Sciences (NIH)

NIH--National Institutes of Health

NIMH--National Institute of Mental Health (ADAMHA)

NICHD--National Institute of Child Health and Human Development (NIH)

NINCDS--National Institute of Neurological and Communicative Disorders and Stroke (NIH)

NORD--National Organization for Rare Disorders

NRSA--National Research Service Award

NTIS--National Technical Information Service

OMCH--Office of Maternal and Child Health (HRSA)

OOPD--Office of Orphan Products Development (FDA)

PDQ--Physician's Data Query

PHS--Public Health Service

PMA--Pharmaceutical Manufacturers Association

RFA--Request for Applications

RFP--Request for Proposals

RSDA--Research Scientist Development Award

RRTC--Rehabilitation Research and Training Center (Department of Education)

SBIR--Small Business Innovation Research Program

USAID--United States Agency for International Development

USDA--United States Department of Agriculture

VA--Veterans Administration

APPENDIX B

LIST OF RESPONDING AGENCIES

LIST OF AGENCY/INSTITUTE CONTACTS

Department/Agency	Contact Person	Telephone Number
DEPARTMENTS OTHER THAN HHS		
Department of Agriculture	Dr. Alex B. Thierman	(301) 344-2774
Department of Agriculture	Dr. Jane F. Robens	(301) 344-3381
Department of Defense	Capt. David Uddin, USN	(202) 695-7117
Department of Education	Dr. Paul Thomas	(202) 732-1194
Department of Energy	Dr. James S. Robertson	(301) 353-5355
OFFICES WITHIN HHS		
Centers for Disease Control	Dr. Mary Guinan	(404) 329-3707
Health Resources and Services Administration	Dr. Robert C. Hastings	(504) 642-4704
OTHER GOVERNMENT AGENCIES		
Agency for International Development	Dr. Kenneth J. Bart	(202) 235-8926
National Aeronautics and Space Administration	Dr. Marshall S. Levine (Mr. Dan Woodard)	(202) 453-2660
Veterans Administration	Mr. Ted Lorei	(202) 233-2618

LIST OF AGENCY/INSTITUTE CONTACTS
(continued)

Department/Agency	Contact Person	Telephone Number
NATIONAL INSTITUTES OF HEALTH		
Division of Research Services	Dr. Henry S. Eden	(301) 496-5771
Fogarty International Center	Dr. Coralie Farlee	(301) 496-1491
National Cancer Institute	Dr. Robert E. Wittes	(301) 496-6138
Natl. Institute of Neurological and Communicative Disorders and Stroke	Dr. F. Jack Brinley, Jr.	(301) 496-6541
National Institute of Diabetes and Digestive and Kidney Diseases	Dr. Benjamin T. Burton	(301) 496-4955
National Heart, Lung, and Blood Institute	Dr. Peter Frommer	(301) 496-1078
National Institute of Allergy and Infectious Diseases	Dr. Catherine A. Laughlin	(301) 496-7051
National Institute of Child Health and Human Development	Dr. Duane Alexander	(301) 496-3454
National Institute of Environmental Health Sciences	Dr. Dorothy Canter	(301) 496-3511
National Institute of General Medical Sciences	Dr. Christine K. Carrico	(301) 496-7707
National Eye Institute	Mr. Julian Morris	(301) 496-4308
National Institute on Aging	Dr. Miriam Kelty	(301) 496-9322
Division of Research Resources	Dr. John A. Biesler	(301) 496-6743
National Institute of Dental Research	Dr. James P. Carlos	(301) 496-7032
Warren Grant Magnuson Clinical Center	Dr. John L. Decker	(301) 496-4114
ALCOHOL, DRUG ABUSE AND MENTAL HEALTH ADMINISTRATION	Dr. Charles R. Schuster	(301) 443-6480
FOOD AND DRUG ADMINISTRATION	Dr. Marlene E. Haffner	(301) 443-4903

APPENDIX C

QUESTIONNAIRE

NATIONAL COMMISSION ON ORPHAN DISEASES

Survey of Biomedical and Behavioral Research Activities Relating to Orphan (Rare) Diseases at Federal Agencies

FY 1987

Agency/Institute: _____

Questionnaire Completed By: _____

Phone Number: _____

NATIONAL COMMISSION ON ORPHAN DISEASES

Survey of Biomedical and Behavioral Research Activities Relating to Orphan (Rare) Diseases at Federal Agencies

The National Commission on Orphan Diseases (NCOD), established by Presidential Order in 1985, is charged with:

- Assessing the status of biomedical research on and information transfer of rare diseases in the Federal and private sectors.

- Reporting to the Secretary of Health and Human Services and to Congress with recommendations and a long-range plan on rare disease research and information dissemination activities. (See Attachment A)

The attached survey is an important part of the Commission's preparation for the report. It was developed by NCOD in cooperation with responding agencies. NCOD has contracted with Macro Systems, Inc., to collect and analyze the data provided by the several respondents. All responding agencies will receive a copy of the draft analysis for review and comment.

Thank you for your assistance and cooperation on this important survey.

II. GENERAL POLICIES ENCOURAGING RESEARCH ON RARE DISEASES

2. Please, briefly outline your review processes for:
   (a) extramural, biomedical and behavioral grant applications and contract proposals,
   (b) intramural or in-house biomedical and behavioral research projects, and
   (c) the impact of these processes in the intra- and extramural environments on rare disease research.

3. Please, describe:
   (a) ways in which your organization stimulates research in general [e.g. (but not limited to), requests for applications (RFAs), program announcements, requests for proposals (RFPs), etc.],
   (b) whether this applies to research on rare diseases, and
   (c) (if it does not apply to rare diseases at this time) how it could apply).

4. Please, describe ways in which your organization:
   (a) stimulates biomedical and behavioral research <u>training</u> in general,
   (b) whether this applies to research on rare diseases, and
   (c) (if it does not apply to rare diseases at this time) how it could apply.

5. Please, describe ways in which your organization:
   (a) stimulates <u>clinical</u> research in general [e.g. (but not limited to), General Clinical Research Centers, intramural research hospitals or clinics, etc.],
   (b) whether this applies to research on rare diseases, and
   (c) (if it does not apply to rare diseases at this time) how it could apply.

6. If you have evaluated the effectiveness of research grants and contracts, please:
   (a) describe how you have done this, and
   (b) briefly outline your findings.

7. Please, list and briefly describe existing programs to:
   (a) ensure longer term support for researchers [e.g., the Method to Extend Research in Time (MERIT) award at NIH], and
   (b) encourage research to move from basic applications into clinical and applied phases (e.g., RFPs or RFAs).

8. For intramural research only, please identify existing policies or mechanisms that could be used to facilitate clinical research on rare diseases.

III. ACCOMPLISHMENTS, OPPORTUNITIES, AND PROBLEMS WITH RESEARCH RELATING TO RARE DISEASES

9. Please, highlight recent accomplishments in research concerned with rare diseases (FY 1987 and 1988) and identify scientific opportunities for additional research.

10. Please, identify any problems that have been encountered or that you foresee in the development and implementation of basic or clinical research concerned with rare diseases and wnether these problems differ from research on common diseases.

11. Please, identify potential treatments or products (if any) that appear to have useful applications in the prevention, diagnosis, and treatment of rare diseases but have not moved forward.

12. If you provide direct patient services (e.g., in hospitals or outpatient services not supported through contracts or grants), please briefly describe ancillary services during the hospital stay and after discharge with emphasis on services that are specifically applicable to patients with rare diseases. (Such services may include offering support group meetings or referrals, transfer of patient records to primary physician, follow-up visits with researcher physician, and assistance with locating other experimental treatments.)

IV. FUNDING OF RESEARCH RELATING TO RARE DISEASES

13. Please, list for FY 1987:
    (a) actual obligations (by program including direct and indirect costs) extramural and intramural research relating to rare diseases including research training, and
    (b) your organization's total obligations for all extramural and intramural research activities including research training.

    (Please note, for institutes at the NIH utilizing computerized data retrieval, a preliminary CRISP listing of research projects is attached to assist in the identification of rare disease research projects. Additions and deletions can be made directly on the printout. For agencies not utilizing computerized data retrieval, estimates for each program are acceptable, and should be noted as "Est." A brief description of the method of estimation should be included if actuals are not available.)

V. COOPERATION WITH THE FEDERAL AND PRIVATE SECTORS, AND TRANSFER OF INFORMATION AND TECHNOLOGY

14. Please, describe how you coordinate your research activities within the Federal sector (e.g., other divisions in your agency, other institutes, or other departments) and with the private sector (e.g., voluntary organizations, universities/medical schools, foundations, or the pharmaceutical industry) with particular reference to research on rare diseases.

15. Please, list clearinghouses, information centers, and educational efforts that involve rare diseases or have potential for rare diseases, and that you supported in FY 1987 in Attachment C.

16. Please, describe ways in which you stimulate the transfer of technology to effect the development of innovative treatments for rare and common diseases (e.g., cooperative ventures or contracts with the private sector, workshops, consensus or other conferences, seminars, publications, etc.).

ATTACHMENT C

EDUCATION AND TECHNOLOGY/INFORMATION TRANSFER ACTIVITIES

Activity	Target Audience	Type of Activity: Education (check)	Type of Activity: Information Transfer (check)	Source of Support: In-House (check)	Source of Support: Extramural (check)	Actual or Estimated Obligation
Clearinghouses* (provide title)						
1. _____						
2. _____						
3. _____						
Information Centers*						
Workshops						
Conferences						
Public Education						
Publications (please identify date of last printing or revision)						
Other (please describe):						
1. _____						
2. _____						
3. _____						
4. _____						

* Please attach most recent report of activities and return with the completed survey form.

ANALYSIS OF THE RARE DISEASE-RELATED ACTIVITIES OF PHARMACEUTICAL MANUFACTURERS

TABLE OF CONTENTS

LIST OF TABLES

I. INTRODUCTION

In 1987, the U.S. pharmaceutical industry spent nearly $6.8 billion for health related research and development activities. In 1986, approximately 15 percent of pharmaceutical sales was reinvested in research activities.

Drug development is a very long and complex process. The pharmaceutical industry reports that it takes almost 10 years and costs over $100 million to bring a new product to market. The cost is due to extensive research conducted during the discovery and development phases of drug development. During the discovery phase, chemical, biological, and toxicological studies must be conducted. During the developmental phase, pharmacologic and pharmacokinetic studies are conducted, as well as additional toxicological studies. The last part of the development phase includes introduction of the product into humans in clinical trials. This part of the development phase can frequently take up to six years.

The drug development process is a concerted effort between the pharmaceutical industry, the Federal government, and research investigators. The Federal government is involved, for the most part, through the Food and Drug Administration (FDA) and the National Institutes of Health (NIH). The FDA regulates the safety and efficacy of drug products, and the NIH often provides funds for basic and clinical biomedical research. These funds are provided to investigators who are frequently located at medical schools throughout the country.

This report presents the results of a pilot study of 37 pharmaceutical manufacturers that support rare disease research and orphan drug development. It describes the activities of these firms that are related to the development of drug products for rare diseases. The study was conducted between April 1988 and January 1989 by the Pharmaceutical Manufacturers Association, the Association of Biotechnology Companies, the Generic Pharmaceutical Industry Association, and the Orphan Developers Coalition. A description of the methodology used is given in Section II.

II. METHODOLOGY/SAMPLE CHARACTERISTICS

The pilot study described below was conducted by the Pharmaceutical Manufacturers Association (PMA) in conjunction with the Association of Biotechnology Companies (ABC), the Generic Pharmaceutical Industry Association (GPIA), and the

Orphan Developers Coalition (ODC). The questionnaire (Appendix A) was developed by the PMA, in conjunction with the National Commission on Orphan Diseases and was provided to the ABC, GPIA, and ODC. The questionnaire was mailed to members of the four associations. Summaries of the responses were provided to the National Commission on Orphan Diseases.

The PMA represents approximately 100 research based pharmaceutical firms that discover, develop, and produce prescription drugs and biological products in the United States. The ABC has 240 members, a substantial portion (about 75 percent) of which are not pharmaceutical manufacturers. The GPIA has 20 members that are pharmaceutical manufacturers. The ODC consists of 8 pharmaceutical companies, all involved in orphan drug development.

Twenty-one PMA members responded to the survey. Four firms reported that they are not engaged in orphan drug research. This report includes the activities reported by the remaining 17 PMA members. In addition, 11 members of the ABC, 3 members of the GPIA, and six members of the ODC completed the survey. The total number of respondents was 37.

The findings described below are those of a pilot study, and do not necessarily generalize to all pharmaceutical manufacturers engaged in rare disease research or orphan drug development activities. In the strictest sense, the findings can only be used to describe the 37 participating firms. The responses do, however, reflect the activities of a wide variety of firms, from small start-up companies to large multinational firms.

III. KEY FINDINGS

o The 37 manufacturers surveyed have 37 approved orphan products on the market. They also have an additional 81 orphan products under investigation.

o Eighteen firms reported that they have spent $190 million on their investigational orphan products. Fifteen firms anticipate that they will spend an additional $95.4 million to bring their investigational products to market. Potential sales volume for products under investigation range from $0.5 to $50 million per year.

o The sum of the total research and development budgets of six respondents was $35 million. Two firms reported a budget of about $1.0 million, 3 indicated their budgets were between $3.0

and $9.0 million, and one reported a budget of $15 million.
o Four pharmaceutical firms with small research and development budgets reported that they spend from 80 to 100 percent of their research and development budgets on orphan drugs. Two other firms, also with small research and development budgets, indicated that they spend 12 and 35 percent.

o Thirty-four of the companies surveyed agreed that the most powerful incentive for orphan drug development is exclusive approval rights.

o Twelve of the firms surveyed suggested that faster FDA review or more flexible safety requirements could be the most powerful incentive in future orphan drug development.

o The respondents most frequently suggested that coordination between the public and private sectors could be improved by providing for a central, public source of information on orphan drugs and diseases.

IV. MARKETED PRODUCTS

As indicated above, it is no small task to bring a drug product to market. Many firms are unable to make the financial commitment when little or no return on investment costs can be expected for a product. This is frequently the case for drugs for rare diseases.

Despite the low financial return, the 37 respondents have 37 approved orphan products on the market (Table 1). Sales volume information for 1987 was reported for only 5 products. Two products had a sales volume of less than $.5 million, two had less than $1 million and one had more than $10 million.

TABLE 1

Marketed Products

Q 1a: Please list those marketed drugs with approved indications (on or off patent) to treat both orphan and common diseases. What was the sales volume for orphan indications in FY 1987?

	Marketed Orphan Drugs
ABC	1
GPIA	0
ODC	7
PMA	29

V. INVESTIGATIONAL PRODUCTS

The goal of rare disease research and orphan drug development is to continuously introduce new products to the market to meet the needs of patients with rare diseases. In order to meet this goal, the responding firms indicated that they have 81 orphan products under investigation.

Eighteen firms reported that they have already spent a total of $190 million on their investigational orphan products. Fifteen firms anticipate that they will spend an additional $95.4 million in development costs on their products.

Estimated sales volume for products under investigation range from $0.5 to $50 million. Seven firms estimated that the total anticipated sales volume for 12 of their investigational products would range from $151 to $166 million per year.

TABLE 2

Investigational Products

Q 1b: Please list those investigational drug products either under active investigation towards an NDA or available for the treatment of an orphan disease but not actively pursuing an NDA. Include any products that are supplied to physicians for compassionate or treatment purposes including current and projected future development costs. What is the potential sales volume for these orphan indications?

	Inves. Products	Costs	Future Costs	Potential Sales volume million/year
ABC	22	NR	NR	NR
GPIA	5	$1.5 (4)	$17.1 (4)	$13.5 - $25.5 (3)
ODC	11	$24.7 (7)	$15.8 (7)	$137 - $140 (9)
PMA	43	$164	$62.5	

NR - Not Reported
(N)- Number of Products

VI. FUNDING OF RESEARCH AND DEVELOPMENT

The pharmaceutical industry is a major sponsor of health related research and development. Twelve of the 17 PMA firms reported that they spent a total of $51.6 million on orphan drug research and development in FY 1987 (Table 3). Two of the firms indicated that they had difficulty separating their orphan drug research and development costs, and that their actual expenditures exceed those reported.

Four ODC members reported a combined research and development budget of $23.3 million. The individual budgets were $0.8, $1.0, $6.5, and $15 million. Five ODC firms indicated the percent of their research and development budget spent on orphan drugs. One firm reported that it spends 12 percent, another spends 80 percent, and three spend 95 or 100 percent.

Two GPIA firms reported a combined research and development budget of $12 million. The individual budgets were $3.3 and $8.5 million. Two firms reported the percent of their research and development budget spent on orphan drugs. One firm reported 5 percent and the other 35 percent.

The separation of research and development costs by rare and common diseases is very difficult. For instance, many drugs are used for both rare and prevalent diseases. The rare disease indication may not become apparent until late in the development process or even after the drug is marketed. Thus, figures reported herein should be considered in light of these difficulties.

TABLE 3

Funding of Research and Development

Q 2a: What is the total amount of your company's budget spent for pharmaceutical research and development?

Q 2b: How much is devoted to orphan drug research and development?

	Combined Budgets (million)	Amount Devoted to Orphan Drugs
ABC	NR	NR
GPIA	$11.8 (2)	5%, 35%
ODC	$23.3 (4)	12%, 80%, 95%, 100%, 100%
PMA	NR	$51.6 (12)

NR - Not Reported
(N)- Number of Firms

VII. INCENTIVES FOR ORPHAN PRODUCTS DEVELOPMENT

The Orphan Drug Act provides incentives for the development of orphan products. These include assistance in the development of research protocols, tax credits for costs of clinical studies,

and exclusive approval privileges for orphan products. The survey asked about the usefulness of these incentives and the need for additional incentives to stimulate further orphan products develoment.

Almost all of the companies (34) responding to the survey listed exclusive marketing rights as the most powerful incentive for stimulating research on orphan diseases (Table 4). The eleven ABC firms ranked tax benefits and protocol assistance as the second and third-ranked inducements, respectively. In addition, eighteen and thirteen member firms of the ODC, GPIA, or PMA listed tax incentives and protocol assistance, respectively, as helpful in stimulating research on orphan diseases.

In response to the need for additional incentives, 12 firms suggested that modifications in FDA's review process would be the one most powerful incentive for stimulating future orphan products development. Seven of these firms wanted a faster FDA review for orphan products. Five wanted greater flexibility in FDA's safety or regulatory requirements, such as a reduction in the requirements for long-term toxicity studies, greater use of foreign data and more consideration for the size of rare disease populations.

Because many firms did not prioritize their suggestions for additional incentives, all of the suggested incentives were classified into the general categories in Table 5. Among all the responses, more flexibility in regulatory requirements or modified safety requirements was cited 20 times. In general, firms requesting modifications in safety requirements desired a reduction in toxicological data requirements. A more expedited or faster FDA review was listed 14 times. In addition, extension of the present tax credits, in particular to preclinical studies, and more grants for the development of orphan products were each suggested nine times.

TABLE 4

Incentives for Orphan Drug Development

Q 3a: Which of the incentives in the current orphan drug law have been helpful in stimulating orphan disease research? (e.g., exclusive marketing rights, protocol assistance, tax incentives) List in order of priority from high to low.

	PMA	GPIA	ABC	ODC
Exclusive Marketing	15	3	ranked first	5
Tax incentives	13	2	ranked second	3
Protocol assistance	8	2	ranked third	3
Federal/Private grants	3			1
Priority FDA review		1		1

TABLE 5

Suggestions for Additional Incentives

Q 3b: In addition to the current incentives provided by the Orphan Drug Act, what other incentives would be helpful in stimulating further research of orphan diseases and development of orphan drugs?

	PMA	ODC	ABC	GPIA	Total
More Flexible Regulatory/ Safety Requirements	8	4	5	3	20
Fast FDA Review	8	1	5		14
More Tax Incentives	6	1		2	9
More Grants	2	4	3		9
Extension of Exclusivity	3	2			5

VIII. COORDINATION OF RESEARCH AND DEVELOPMENT

As indicated above, drug development is a concerted effort between the public (Federal) sector and private entities, including the pharmaceutical industry, voluntary organizations and foundations. The respondents offered many suggestions for improving coordination between the private and public sectors.

The most frequent class of suggestions (10 cites) focused on information needs and a central, public source of information on orphan drugs and diseases. Firms indicated that they needed more information, including directories of expert clinicians and sources of funding and better databases for identifying and quantifying orphan diseases and populations. Furthermore, they suggested that this type of information should be dispensed by a central, public office.

The second most frequent class of suggestions (8 cites) focused on changes in current FDA procedures and requirements. Firms suggested that FDA should assume a more proactive and cooperative role when dealing with manufacturers. They requested clearly defined study requirements from FDA, more familiarity with orphan products by FDA reviewers, more authority for FDA's Office of Orphan Products Development, and an expedited review process for orphan drugs.

Coordination With the Private Sector

When asked to describe how they coordinate their rare disease activities with the private sector, the respondents indicated that they coordinate research activities most frequently with universities and medical schools (11 cites). They support research at these institutions by developing protocols, providing drug products, and funding grants for clinical studies. A smaller number of firms (4 cites) indicated that they coordinate research and development activities with voluntary organizations. None of the firms reported any interaction with foundations.

The firms surveyed indicated that they are involved in a variety of activities with the private sector (Table 6). A majority of the firms reported that they co-fund clinical research with the private sector. Almost as many firms conduct or sponsor scientific meetings and are involved in compassionate use protocols.

Coordination With the Public Sector

Responses from the PMA and GPIA indicate that member firms coordinate their orphan diseases activities with the public sector through meetings. The responding firms also reported that they specifically interact with the FDA and NIH. No other government agencies were specifically named. The ABC noted that there has been little coordination between its members and the public sector over orphan disease research and development. The ODC did not include information on coordination activities with the public sector in its summary of results.

A majority of the responding firms indicated that they interact with government agencies by either receiving assistance or providing assistance with the development of study protocols (Table 7). They also interact with the public sector through compassionate use protocols, by providing steady supplies of investigational products, co-funding clinical research, and conducting scientific meetings.

TABLE 6

Activities With Private Sector

Q 4c: Are you involved in any of the following activities with the private sector?

Co-fund clinical research	19
Conduct or sponsor scientific meetings	17
Compassionate use protocols	16
Assistance in developing study protocols	13
Contractual agreements for drug development programs	12
Educational programs/meetings for health professionals	11
Guarantee availability of products for investigational uses	11
Co-fund basic research	10
Educational programs for patients/families	8

TABLE 7

Activities With Public Sector

Q 4e: Are you involved in any of the following activities with the public sector?

	GPIA	ODC	PMA	Total
Co-fund clinical research		2	7	9
Co-fund basic research			3	3
Assistance in developing study protocols	1	5	9	15
Conduct or sponsor scientific meetings			8	8
Contractual agreements for drug development programs			3	3
Guarantee availability of products for investigational purposes		2	7	9
Compassionate use protocols		2	9	11

IX. INFORMATION DISSEMINATION

A major aspect of drug development is the dissemination of research results to physicians, voluntary organizations, patients, the general public and other researchers. Manufacturers were asked if they use any special procedures to disseminate the results of research on rare diseases. Responding firms reported that they most often used meetings, symposia, and seminars (18 cites) to disseminate research results. In addition, they also use the published literature (10 cites) and the news media (4 cites).

In order to determine whether to increase the financial resources devoted to rare diseases, a manufacturer must consider a multitude of data from various sources. Manufacturers were

asked what type of information from researchers, physicians, voluntary organizations, and patients would be useful in making such a determination. Responding member firms of the PMA and GPIA stated that they needed general medical information or demographic data on rare diseases (5 cites), safety data from clinical experience or controlled studies (3 cites), and information on the needs of patients (3 cites) in order to determine whether to expand their orphan disease related activities. The ABC and ODC did not indicate what type of information would be helpful when making such a decision.

APPENDIX A

PHARMACEUTICAL MANUFACTURERS ASSOCIATION SURVEY OF ORPHAN DISEASE RESEARCH
AND ORPHAN DRUG DEVELOPMENT ACTIVITIES

I. Orphan Disease Research and Orphan Drug Development Activities - Marketed and Investigational Drugs

A. Please list those marketed drugs with approved indications (on or off patent) to treat both orphan and common diseases. What was the sales volume for orphan indications in FY '87? If sales volume is not available by indication, please provide aggregate sales and so indicate.

	Indication for use		Sales Volume FY '87*	
Drug Product	Common Diseases	Orphan Diseases	Common Diseases	Orphan Diseases

(Alternate) Describe in narrative form your company's involvement in orphan drug research and development, highlighting your activities in FY 1987. (A response to this alternative will be helpful, even though you have answered A. above.) IF YOU WISH TO EXPAND ON THIS RESPONSE, PLEASE USE A SEPARATE PAGE.

B. Please state the total amount spent by your company on orphan drug research and development in FY 1987.**

$ _____

* FY'87 sales volume and estimated sales volume for investigational drug products will be provided by PMA to NCOD in the form of ranges and averages without identification to particular products.

** Drug development costs and amounts spent on R&D will be aggregated and provided to NCOD as an industry total.

C. Please list those investigational drug products either under active investigation towards an NDA or available for the treatment of an orphan disease but not actively pursuing an NDA. Include any products that are supplied to physicians for compassionate or treatment purposes. Indicate aggregate previous and projected future development costs for all products listed. What would you estimate will be the sales volume for the orphan indications shown for each drug?

Investigational*** Drug Product	Proposed Indication for Use	Status: Active Investigation (NDA Planned)	Status: Treatment or Compassionate (No NDA Planned)	Drug Development Costs**: Amount Previously Funded	Drug Development Costs**: Projected Future Costs	Estimated* Sales Volume
				(Aggregate)		

D. Please list any potential orphan drug that your company would be interested in possibly making available to other organizations for development and/or distribution.

II. Incentives for orphan disease research and orphan drug development.

A. Which of the incentives in the current orphan drug law have been helpful in stimulating orphan disease research? (e.g., exclusive marketing rights, protocol assistance, tax incentives) List in order of priority from high to low.

* FY'87 sales volume and estimated sales volume for investigational drug products will be provided by PMA to NCOD in the form of ranges and averages without identification to particular products.

** Drug development costs and all amounts spent on R&D will be aggregated and provide to NCOD as an industry total.

*** If you do not want the name of a particular investigational product to be provided to NCOD, please indicate "confidential".

D. Are you involved in any of the following activities with the private sector with respect to orphan drugs?

ORGANIZATION	YES	NO
1. CO-FUND BASIC RESEARCH	____	____
2. CO-FUND CLINICAL RESEARCH	____	____
3. ASSISTANCE IN DEVELOPING STUDY PROTOCOLS	____	____
4. EDUCATIONAL PROGRAMS FOR PATIENTS/FAMILIES	____	____
5. EDUCATIONAL PROGRAMS/MEETINGS FOR HEALTH PROFESSIONALS	____	____
6. CONDUCT OR SPONSOR SCIENTIFIC MEETINGS	____	____
7. CONTRACTUAL AGREEMENTS FOR DRUG DEVELOPMENT PROGRAMS	____	____
8. GUARANTEE AVAILABILITY OF PRODUCTS FOR INVESTIGATIONAL USES	____	____
9. COMPASSIONATE USE PROTOCOLS	____	____

IF YOU WOULD LIKE TO EXPAND ON THIS RESPONSE, PLEASE USE A SEPARATE PAGE.

E. Briefly describe how you coordinate your orphan disease research and orphan drug development activities with the public sector, e.g., NIH, FDA, CDC, VA OR OTHERS.

_____

_____

_____

F. Are you involved in any of the following activities with the public sector with respect to orphan drugs?

AGENCY/DEPARTMENT/OFFICE	Yes	No
1. CO-FUND CLINICAL RESEARCH	____	____
2. CO-FUND BASIC RESEARCH	____	____
3. ASSISTANCE IN DEVELOPING STUDY PROTOCOLS	____	____
4. CONDUCT OR SPONSOR SCIENTIFIC MEETINGS	____	____
5. CONTRACTUAL AGREEMENTS FOR DURG DEVEOPMENT PROGRAMS	____	____
6. GUARANTEE AVAILABILITY OF PRODUCTS FOR INVESTIGATIONAL PURPOSES	____	____
7. COMPASSIONATE USE PROTOCOLS	____	____

IF YOU WOULD LIKE TO EXPAND ON THIS RESPONSE, PLEASE USE A SEPARATE PAGE.

B. In addition to the current incentives provided by the orphan drug act, what other incentives would be helpful in stimulating further research of orphan diseases and development of orphan drugs? List in order of priority from high to low.

_____

_____

_____

III. Coordination of orphan disease research and orphan drug development activities with the private and federal sectors.

A. Recognizing that research is expensive and personnel intensive, how could the research and development activities and funding efforts be better coordinated between the private and public sectors with respect to orphan drugs and diseases?

_____

_____

_____

B. Briefly describe how you coordinate your orphan disease research and orphan drug development activities with the private sector; e.g., voluntary organizations, private foundations, and universities/medical schools.

_____

_____

_____

C. List all activities relating to orphan drugs and diseases that you have undertaken, other than those directly related to R&D.

_____

_____

_____

IV. Information Dissemination Activities

A. What special procedures do you use to disseminate information resulting from research to the rare disease specific organizations? Researchers? Physicians? Patients? And the general public?

_____

_____

_____

B. What type of information form these groups would be useful to you in determining whether to expand personnel or financial resources for rare disease research or orphan drug development program?

_____

_____

_____

SURVEY OF
VOLUNTARY RARE DISEASE ORGANIZATIONS

TABLE OF CONTENTS

LIST OF TABLES

I. INTRODUCTION

Rare disease voluntary organizations serve the many needs of their constituency, namely patients with rare diseases and their families. For many patients these private, non-profit organizations are the sole source of support and information about their disease. Voluntary organizations tend to focus on one or several related diseases or disease group. Voluntary organizations, through their membership are dedicated to educating patients, their families, physicians, and the general public. Voluntary organizations range from small, grass-root support groups formed by patients, local organizations, to local chapters of relatively large, national organizations. Often, they are stretched to or beyond their limits of financial and personal resources in their service to their members and the general public. Most rely on fund-raising efforts from varying sources and donations from the patients and their families and friends to fund their activities.

This report summarizes the results of a study of rare disease voluntary organizations conducted in 1988 by the National Organization for Rare Disorders (NORD) and presented the findings to the National Commission on Orphan Diseases for inclusion in its deliberations. The survey was to determine the activities of voluntary organizations, the types of support services provided, and the priorities, cooperative efforts, and needs of the organizations.

The survey questionnaire was sent by NORD to 217 organizations. 113 completed the questionnaires at a response rate of 52 percent. The questionnaire is shown in the appendix. Descriptions of the methodology, sample characteristics, and findings follow below in chapters II, III, and IV.

II. METHODOLOGY AND SAMPLE CHARACTERISTICS

The mailing list for the survey was constructed from two mailing lists of relevant voluntary organizations maintained by NORD and the Commission. These lists were thought to represent the most active national rare disease voluntary groups. Duplicate listings for organizations were eliminated. The composite list from the mailing lists contained 217 organizations. NORD contacted the organization and requested completion of the questionnaire.

122 organizations replied and 92 completed the questionnaires. Follow-up telephone calls resulted in another 21 responses, yielding a total sample size of 113.

For each question, frequency distribution, percent of responses, cumulative percent, as well as mean and median were computed. If the question was open ended, replies were recorded verbatim. Additionally, select responses were summarized by "age

of organization" and by "size of budget", and subgroup responses were compared.

AIDS groups or organizations with a very broad-based focus such as diabetes) and organizations that were not U.S. based were excluded. Representativeness based on the original lists are difficult to assess. However, the Commission concluded that the organizations that responded constitute the most active national voluntary organizations on rare diseases and that the information provided is not only pertinent but also confirmed by testimony at the public hearings of the Commission.

The sample organizations were stratified by several organizational features: By age of organization as three years or younger, four year to 17 years, and eighteen years or older. They were also stratified by the size of their budget as small, medium, and large.

In terms of several descriptive characteristics, the voluntary organizations in this sample are quite varied. The number of rare disease voluntary organizations has increased dramatically in the last decade. Fifty percent of the responding organizations are seven years old or younger. Two in three of the organizations have been established in the last ten years. Only 20 percent are 17 years or older.

Dues paying membership also varies considerably. Some voluntary organizations do not have dues paying members. Approximately one-third of the sample have no dues paying members. Of those organization that have dues paying membership, 50 percent have 800 or fewer dues paying members. The top 20 percent have 4,000 or more dues paying members.

Fifty percent of the organizations have mailing lists of fewer than 2,100 people. Mailing lists may include not only members, but other interested persons as well including family members of patients, physicians, researchers, and select members of the general public. The largest 20 percent of voluntary organizations have 13,000 or more people on their mailing lists.

Budgets also vary greatly for the voluntary organizations. Fifty percent of the organizations have annual budgets of less than $50,000 per year. Those organizations that represent the top 20 percent based on membership have budgets of $500,000 or more. One organization in the sample has a budget of $115 million which is 2 and 1/2 times that of the next largest organization.

A wide variety of rare diseases and disorders (hereafter simply referred to as diseases) are addressed by the organizations in the sample. Over 100 different diseases are represented in the organizations that responded to the survey.

III. KEY FINDINGS

Key findings of the survey revealed that

- One-half of the voluntary organizations focusing on rare diseases are 7 years old or younger; have fewer than 150 dues paying members; have mailing lists of fewer than 2100 people and/or organizations; and have budgets of $50,000 or less.

- Reliable estimates of disease prevalence and incidence do not exist. One quarter of the organizations could not provide prevalence estimates and one-half (55 percent) percent) could not report incidence estimates.

- The four organizational activities most frequently rated as "very important" were educational in nature - providing educational materials for patients (81 percent), newsletters (68 percent), educational programs for patients and families (62 percent), and educational materials for health professionals (61 percent).

- One-half of the annual budget of the average voluntary organization four years old or younger is allocated to newsletters, educational programs for patients and families, and telephone hotlines.

- For voluntary organizations older that ten years, forty percent of their annual budget is allocated for educational programs for patients and families, and biomedical research.

- Research grants for biomedical researchers were provided by 44 percent of the organizations. These grants ranged from $10,000 to $53,000.

- Seventy-two percent of the grant awarding organizations indicated that researchers who received seed money from them subsequently received grant money from other organizations including the federal government.

- Thirty-one organizations coordinated or cofunded educational or research projects with universities. Nineteen did so with foundations, 18 with the federal government, 16 with the pharmaceutical industry, and 15 with other voluntary organizations.

A detailed discussion of the findings follows below.

IV. DISCUSSION OF FINDINGS

KNOWLEDGE ABOUT PREVALENCE AND INCIDENCE OF RARE DISEASES

When questions concerning disease prevalence and incidence and attendant costs for the care of a patient were asked, estimates could only be given with difficulty. In fact, over a quarter of the organizations did not report prevalence, and 55 percent did not report incidence of the disease or condition. Responses that were provided must be viewed as broad estimates. This paucity of information supports the Commission's finding that prevalence and incidence data do not exist and that estimates are very general and probably mostly inaccurate.

ESTIMATED COSTS FOR TREATMENT AND AVAILABILITY OF TREATMENT CENTERS

Estimates for the cost of caring for a patient with a rare disease vary widely since the expense depends upon the severity and specific complications of the disease. About half the respondents did not provide a range in cost. For those that did, the median value for the minimum cost per year was $3,000 and the median value for the highest cost was $33,000.

The number of specialized research or treatment centers available for patients also varies considerably. One half of the organizations indicated that one or more specialized research or treatment centers existed for their disease. The median number of centers for all respondents was 8. For the other half of rare diseases relevant treatment centers do not exist at all.

SOURCES OF FUNDS, AND ALLOCATION TO ACTIVITIES

Fund raising and membership contributions are the most frequently mentioned sources of funds for 72 percent of the organizations. Contributions received from corporations were indicated by 50 percent of the groups. However, organized fundraising and corporate funding are more characteristic of voluntary organizations with fairly large annual budgets (Table 1). For those organizations with the smallest budgets, membership contributions are the most frequently cited source of funds.

The four activities most frequently ranked as "very important" are educational in nature - providing educational materials for patients (81 percent), newsletters (68 percent), educational programs for patients and families (62 percent), and educational materials for health professionals (61 percent). Less frequently mentioned as a "very important" for the organization are rehabilitation (5 percent), psychological research (9 percent), clinical trials (11 percent) and lobbying (19 percent)(Table 2). Biomedical research, clinical trials and

TABLE 1. SOURCES OF FUNDS

Question: Where does your funding come from?

Source	Times Mentioned	Percent of Vol. Organizations
Membership Contributions	83	73.5
Fundraising	82	72.5
Corporate Giving	57	50.4
Federal Funds	8	7.1
User Fees	5	4.4

Interpretation: 57 of the 113 organization (50.4 percent) indicated that corporate giving was a source of funds.

TABLE 2. IMPORTANT ORGANIZATIONAL ACTIVITIES

Question: Which of your organization's activities do you consider to be very important?

Activity	Times Mentioned	Percent of Vol. Organizations
Materials on Diseases for Patients	90	79.6
Newsletter	76	67.3
Educational Programs for patients/families	69	61.1
Educational Materials for Health Professionals	68	60.2
Support Group Activity	64	56.6
Referral of Patients	48	42.5
Annual Meeting	44	38.9
Biomedical Research	43	38.1
Telephone Hotline	38	33.6
Referral Source for Researchers	25	22.1
Advocacy	21	18.6
Scientific Meetings	20	17.7
Educational Programs for Health Professionals	19	16.8
Clinical Trials	13	11.5
Psychiatric Research	10	8.8
Rehabilitation/Training	6	5.3
Other	12	10.6

Interpretation: 69 of the 113 organization (61.1 percent) rated this activity as very important.

sponsorship of scientific meetings are rated as important only by the oldest organizations and those with large budgets. Organizations were asked to describe their budget allocations. It appeared that the categories provided in the questionnaire were either not adequately describing their expenditures or such data were not readily available.

Based on those who provided the data, it appears that the most important activity for voluntary organizations 4 years or younger is providing educational materials for patients, as 14 of the 15 organizations reported allocations for this activity. Newsletters (12 of 15 organizations) and educational materials for health professionals (11 of 15 organizations) were also frequently mentioned activities. In terms of estimated dollar expenditures, newsletters, educational programs for patients and families and telephone hotlines were the three largest expenditures, together accounting for about 50 percent of the average budget of an organization that is between one and four years old.

For voluntary organizations that are 5 to 10 years old, it appears that the most frequently funded activities are newsletters (23 of the 24 reporting), educational materials for patients (20 of 24 organizations), and educational programs for health professionals (19 of 24 organizations). In terms of estimated average yearly expenditures, the three largest dollar activities were seed money for biomedical research ($20,300), educational materials for patients ($20,000), and educational programs for health professionals ($14,300). These three accounted for 53 percent of the average budget of a voluntary organization ages 5 to 10.

For organizations 11 years or older, the most frequently funded activities are educational programs (19 of the 24 reporting), educational materials for patients (19 of 24), educational materials for health professionals and newsletters (17 of 24), and biomedical research (16 of 24). In terms of estimated average yearly expenditures, the two largest dollar activities were biomedical research ($840,000) and educational programs for patients and families ($1,378,000). These account for 40 percent of the average budget of a voluntary organization 11 years or older.

SERVICES

The nature of direct patient support services, maintenance of information files/registries, and advocacy/lobbying activities was also examined. Patient/family discussion groups, peer counseling, and referral to physicians were common services for about 80 percent of the organizations. Referral to physicians

was mentioned by 80 percent; peer counseling was mentioned by 79 percent; referral to ancillary services by 57 percent; and patient care support by 12 percent (Table 3).

Patient/family discussion groups were more frequent among mature organizations (89 percent offered the service) than among young organizations (65 percent offered the service). For a peer counseling service, the trend was just the opposite (69 percent for older versus 92 percent for younger organizations). Referral to ancillary services was more common among mature organizations (75 percent) than among the young (40 percent).

National files/registries of some sort are reported by 80 of the 113 organizations. Of these, national files regarding disease information were common (present in 85 percent of these organizations). Of the 113 organizations, 9.7 percent maintained biological tissue bank files, 31 percent maintained patient files and 39 percent maintained a physician/research file. Forty-one of the 113 organizations have some type of computerized files or registries.

When asked to describe their advocacy activities, the most frequently mentioned activities were: membership in another organization such as NORD; testifying or attending hearings; letter and telephone calls; and contacts with representatives in government.

SEED MONEY FOR BIOMEDICAL RESEARCHERS

Research grants were provided by 44 percent of the organizations. The most frequent number of grants awarded each year is one (by 14 groups) and 50 percent of those offering grants award 3 or less per year. One organization awards 700 grants per year. Forty-six of the organizations reported that the priority placed on funding research has increased over the last five years, while 25 percent reported that the priority remained the same (Table 4).

The two major purposes of the grant programs were to provide independent grant support and to provide seed money for research ideas (Table 5). On average, the size of grants awarded ranged from about $10,000 to about $53,000.

Seventy-two percent of the grant awarding organizations indicated that researchers who received seed money from them, subsequently received grant money from the federal government. The next two frequently mentioned sources of subsequent funding were foundations (reported by 32 percent of the organizations providing seed money) and other voluntary organizations (reported by 26 percent) (Table 6).

TABLE 3. PATIENT SUPPORT SERVICES

Question: What kind of direct patient support services does your organization provide?

Kind of Service	Times Mentioned	Percent of Vol. Organizations
Referral to Physicians	90	79.6
Peer Counseling	89	78.8
Patient/Family Discussion Group	86	76.1
Referral to Ancillary Services	64	56.6
Patient Care Support	13	11.5
Other	23	20.4

Interpretation: 86 of the 113 organization (76.1 percent) provide this service.

TABLE 4. PRIORITY OF RESEARCH GRANTS

Question: Over the last five years, has the priority your organization places on research grants (a) remained the same (b) increased or (c) decreased?

Priority	Times Mentioned	Percent of Vol. Organizations
Increased	52	46.0
Remained the same	29	25.7
Decreased	3	2.7
No response	29	25.7

Interpretation: 29 of the organization who have a research grants program (25.7 percent) responded that the priority placed on the research grant program has remained the same.

TABLE 5. PURPOSES OF RESEARCH GRANT PROGRAM

Question: What is the major purpose of your research grant program?

Purpose	Times Mentioned	Percent of Vol. Organizations
Seed Money/Research Ideas	35	31.0
Provide Independent Grant Support	33	29.2
Provide Funds to Defray Costs for Patients	8	7.1
Provide Matching Funds	2	1.8

Interpretation: 33 of the 113 organization (29.2 percent) have providing independent grant support in mind for their granting program.

TABLE 6. SUBSEQUENT GRANT MONEY FOR SPONSORED RESEARCHERS

Question: Have any of the researchers who received seed money from you subsequently obtained grants from other organizations to continue this research?

Organization	Times Mentioned	Percent of Vol. Organizations
Federal Government	33	29.2
Foundations	15	13.3
Other Voluntary Organizations	12	10.6
Private Industry	11	9.7
State/Local Government	5	4.4
Other/Don't Know	11	9.7

Interpretation: 12 of the 113 organization (10.6 percent) have researchers who received subsequent funding from other voluntary organizations.

Thirty-one percent of the sample indicated that they provide funds to stimulate the entry of scientists and physicians into biomedical research. When asked how the number of scientists and physicians entering rare disease research might be increased, respondents frequently mentioned the following issues:

- more funding and facilities;
- better education;
- more publicity and awareness;
- increased professional recognition, prestige and training grants; and,
- attempt to relate rare disease research to important scientific and intellectual issues.

For the question of "What barriers prevent or slow down successful research?", respondents frequently mentioned limited funding and financial rewards for researchers, low interest and awareness by the public, lack of availability of sufficient numbers of subjects, perceived limited professional prestige of researchers in the field, and limited media attention for rare diseases.

COOPERATIVE EFFORTS

Educational or research projects were coordinated or cofunded with the federal government by 18 of the organizations. Sixteen organizations coordinated or cofunded projects with the pharmaceutical industry; 19 did so with foundations; 31 with universities and 15 voluntary organizations with other voluntary organizations.

In cases where several voluntary organization exist for the same disease or group of diseases, 86 percent indicated that they shared information with each other, 24 percent indicated they cosponsored meetings, and 15 percent indicated they cofunded projects.

APPENDIX A: Questionnaire

Dear Friend,

We would like to ask you a number of questions about the work of voluntary organizations. It is important to us that you respond to every question; if a question does not apply, please enter N/A. If more than one answer is relevant, please check all that apply. Please note that when the questionnaire refers to a rare disease, individual rare diseases and conditions are included as well as groups of rare diseases or conditions.

INTRODUCTION

1. How many years has your organization been in existence?
   _____years

2. (a) How many dues paying members does your organization have? _____
   (b) How large is your mailing list?_____

3. What is the approximate annual budget of your organization?
   $_____

4. Where does your funding come from?

(a)	Corporate giving	[ ]
(b)	Fund raising	[ ]
(c)	Federal funds	[ ]
(d)	Membership contributions	[ ]
(e)	User fees	[ ]
(f)	Other_____	[ ]

5. What disease does your organization focus on?
   _____

6. (a) How many people have this disease in the U.S.A. at any given time (prevalence)?_____
   (b) How many new cases of this disease occur in the U.S.A. each year (incidence)?_____

7. What is the estimated range of cost per year to care for a patient with this disease (excluding lost earnings)? From $_____ to $_____

8. How many specialized research or treatment centers are there for this disease? _____
   (a) How many of these provide treatment?_____
   (b) How many of these conduct research?_____

9. Which Federal agencies support research or educational activities focusing on this disease?
   _____
   _____

10. Are there other voluntary organizations that focus on the same disease?
[ ] yes [ ] no

11. If yes, how do you coordinate efforts with these organizations?
Co-sponsor meetings [ ]
Co-fund projects [ ]
Share information [ ]
Other _____
_____
_____

SERVICES AND ACTIVITIES

12. Which of your organization's activities are
(a) A major focus of your organization, (please, rank them as 1 - Very Important
2 - Important
3 - Less Important)
(b) What is the percentage of your organization's current annual budget?

Activity	Major Focus (1, 2, or 3)	Percent of Budget
(a) Educational programs for patients/families	[ ]	[ ]
(b) Educational materials about disease for patients	[ ]	[ ]
(c) Educational materials for health professionals	[ ]	[ ]
(d) Newsletter	[ ]	[ ]
(e) Patient/family support groups	[ ]	[ ]
(f) Referral source for patients	[ ]	[ ]
(g) Rehabilitation/training for patients	[ ]	[ ]
(h) Telephone hotline	[ ]	[ ]
(i) Conduct national and/ or annual meetings	[ ]	[ ]
(j) Educational programs for health professionals	[ ]	[ ]
(k) Fund basic biomedical research	[ ]	[ ]
(l) Fund psychosocial research	[ ]	[ ]
(m) Fund patient-oriented clinical trials	[ ]	[ ]
(n) Referral source for researchers	[ ]	[ ]
(o) Conduct scientific meetings	[ ]	[ ]
(p) Advocacy (lobbying) efforts	[ ]	[ ]
(q) Other _____	[ ]	[ ]

13. What kind of direct patient support services does your organization provide?

(a) Patient/family discussion groups [ ]
(b) Peer counseling (support for new patients/families by experienced patients/families) [ ]
(c) Referral to physicians [ ]
(d) Referral to ancillary services including social services, financial assistance, etc. [ ]
(e) Direct patient care support including help with medical expenses, devices (wheel chairs, respiratory assist devices, artificial limbs, etc.) [ ]
(f) Other _____ [ ]

14. Does your organization maintain or financially support any of the following files/registries? Please identify whether they are national or State/local in scope, and whether they are computerized.

Type of File	National	State/ Local	Compu-terized
(a) Information on disease	[ ]	[ ]	[ ]
(b) Physician/researcher registry	[ ]	[ ]	[ ]
(c) Patient registry for scientific use	[ ]	[ ]	[ ]
(d) Biological (tissue) bank	[ ]	[ ]	[ ]
(e) Other _____	[ ]	[ ]	[ ]

15. Please describe briefly
(a) The kind of advocacy/lobbying activities your organization undertakes,
(b) Resulting achievements, and
(c) Difficulties encountered.

_____
_____
_____

RESEARCH GRANTS

16. Over the last five years, has the priority your organization places on research grants
(a) Remained the same [ ]
(b) Increased [ ]
(c) Decreased [ ]

17. How many research grants does your organization award on the average per year? _____

18. What is the range of funding for individual research grants?
From $_____ to $_____.

19. What is the major purpose of your research grant program?
(a) Provide independent grant support [ ]
(b) Provide matching funds for grants from other agencies [ ]
(c) Provide seed money for research ideas [ ]
(d) Provide funds for costs incurred by patients participating in research studies (e.g., travel expenses, cost of experimental drugs, etc.) [ ]
(e) Other _____ [ ]

20. How effective has your research program been in achieving its purposes and how do you evaluate its effectiveness?_____
_____
_____
_____
_____
_____

21. Have any of the researchers who received seed money from you subsequently obtained grants from other organizations to continue this research?
(a) Other voluntaries [ ]
(b) Federal government [ ]
(c) State/local government [ ]
(c) Private industry [ ]
(d) Foundations [ ]
(e) Other _____ [ ]
(f) Don't know [ ]

22. What type of process do you use to award research grants?
(a) Peer review by Standing Committee [ ]
(b) Peer review by outside expert panel [ ]
(c) Recommendation of Board of Directors [ ]
(d) Other_____ [ ]

23. Do you fund any programs or grants that stimulate the entry of scientists and physicians into biomedical research?
[ ] yes [ ] no

24. If yes, please describe.
_____
_____

25. How can the number of scientists and physicians entering rare disease research be increased?

26. What are the barriers that prevent or slow down successful research on rare diseases?

27. If you do not fund research grants, what policies or circumstances directly prevent your organization from doing so?

COOPERATIVE ACTIVITIES

28. How many research or education projects do you coordinate or co-fund with the

(a)	Federal government	[ ]
(b)	Pharmaceutical industry	[ ]
(c)	Foundations	[ ]
(d)	Universities or academic institutions	[ ]
(e)	Other voluntary organizations	[ ]
(f)	Other _____	[ ]

29. What Federal programs have been helpful in facilitating cooperative ventures between Federal agencies and voluntary organizations?

30. What else could the Federal government do to increase cooperation between Federal agencies and voluntary organizations?

(If you need additional space, please attach separate sheet of paper).

31. Please complete the following:

Name and Address of Voluntary Organization _____

_____

Name of Person Completing Questionnaire _____

_____

Telephone Number _____

Thank you very much for your assistance. The National Organization for Rare Disorders appreciates your help in this information gathering effort. Since we will present findings from this survey to the National Commission on Orphan Diseases, is there something that the Commission might be able to do to assist you in your important work?

_____

_____

_____

_____

_____

_____

APPENDIX B: Voluntary Organizations

Helpful correspondence was received from the following organizations:

The Meniere's Network
National Hydrocephalus Foundation
United Parkinson Foundation
Parkinson's Disease Foundation, Inc.
4P-Parent Contact Group
Ehlers Danlos National Foundation
Dystrophic Epidermolysis Bullosa Research Association (DEBRA) of America
Acoustic Neuroma Association
National Multiple Sclerosis Society
National Ataxia Foundation
Guillain-Barre Syndrome Support Group International
National Alopecia Areata Foundation
National MPS Society Inc.
Osteogenesis Imperfecta Foundation, Inc.
Williams Syndrome Association
American Foundation for AIDS Research
American Kidney Fund
National Foundation for Ectodermal Dysplasias
Histiocytosis-X Association of America, Inc.
Lupus Foundation of America, Inc.
Benign Essential Blepharospasm Research Foundation
Maple Syrup Urine Disease Support Group
The Sturge-Weber Foundation
National Retinitis Pigmentosa Foundation
National Organization for Rare Disorders (NORD)
Little People of America, Inc.
National Gaucher Foundation
Foundation for Ichthyosis & Related Skin Types
Lowe's Syndrome Association Inc.
National Spasmodic Torticollis
Immune Deficiency Foundation
Aplastic Anemia Foundation of America
California Neurofibromatosis Network, Inc.
National Marfan Foundation
United Leukodystrophy Foundation, Inc.
Fanconi's Anemia Support Group
Wilson's Disease Association
Interstitial Cystitis Association of America, Inc.
PKU Foundation
National Addison's Disease Foundation
American Tinnitus Association
Dysautonomia Foundation, Inc.
American Narcolepsy Association
United Scleroderma Foundation, Inc.
Osteogenesis Imperfecta/N.C.A. Inc.
National Vitiligo Foundation, Inc.
Prader-Willi Syndrome Association

Association for Glycogen Storage Disease
Dystonia Medical Research Foundation
PLS Newsletter
Parent to Parent of Miami
National Psoriasis Foundation
Reflex Sympathetic Dystrophy Association (RSDSA)
Paralyzed Veterans of America
Mucopolysachiridosis (MPS) Foundation
American Porphyria Foundation
The Amyotrophic Lateral Sclerosis (ALS) Association
National Congenital Port Wine Stain Foundation
American Diabetes Association
National Spinal Cord Injury Association
American Liver Foundation
PHP Self-Help Clearinghouse
National Foundation for Peroneal Muscular Atrophy
Scleroderma Federation
Sjogren's Syndrome Foundation, Inc.
American Leprosy Foundation
Spastic Dysphonia Support Group
The Dizziness and Balance Disorders Association of American
Ohio Chronic Epstein-Barr Virus Syndrome Association
Narcolepsy Network, Inc.
March of Dimes Birth Defects Foundation
Klippel-Trenaunay Support Group
National Ataxia Foundation
Orofacial Guild
Chronic Epstein-Barr Virus (CEBV) Syndrome Support Group
Neurological Sciences Center
Malignant Hyperthermia Association of the U.S.
Arthritis Foundation
APA Hotline
The Neurofibromatosis Association Inc. (Massachusetts Chapter)
National Neurofibromatosis Foundation
Parent to Parent VA
Hemochromatosis Research Foundation, Inc.
Jaw Joints & Allied Musculo-Skeletal Disorders
Family Survival Project
Neurofibromatosis Foundation
Paget's Disease Foundation
Newton-Wellesley Parkinson Support Group
Chronic Granulomatous Disease Association
CFSS-Chronic Fatigue Syndrome
Myasthenia Gravis Foundation
Narcolepsy and Cataplexy Foundation of America
National Foundation for Facial Reconstruction
The Association for Children with Down Syndrome, Inc.
Parents Project
National Center for Youth with Disabilities
Community Information and Referral Service
Familial Polyposis Registry
Canadian Neurological Coalition

Charcot-Marie Tooth Disease/Peroneal Muscular Atrophy/
International Association, Inc.
Allergy Information Association
Genetics Unlimited
Parent-To-Parent of GA.
The Self-Help Clearinghouse
Del Oro Regional Resource Center
Association for Brain Tumor Research
People Services to the Disabled, Inc.
Infants and Toddlers Program
Hereditary Haemorrhagia Telangiectasia
Retinitis Pigmentosa (RP) Foundation Fighting Blindness
The Michael Fund - International Foundation
for Genetic Research
The New York Blood Center
The Devereux Foundation
Infant Development Program
International Rett Syndrome Association, Inc.
Friedreich's Ataxia Group in America, Inc.
Tourette Syndrome Association
Tuberous Sclerosis Association of Illinois
National Tuberous Sclerosis Association
Families of SMA
National Lyme Borreliosis Foundation
Tuner Syndrome Support Group
Alabama Society for Sleep Disorders
Epilepsy Foundation of America
Leukemia Society of America
Research Trust for Metabolic Diseases
Iron Overload Diseases Association Inc.
MPS Research Funding Center, Inc.
CDLS Foundation, Inc.
Cystinosis Foundation, Inc.
National Craniofacial Foundation
Turner's Syndrome Society

ANALYSIS OF THE RARE DISEASE-RELATED ACTIVITIES OF FOUNDATIONS

PREPARED FOR:

NATIONAL COMMISSION ON ORPHAN DISEASES

TABLE OF CONTENTS

LIST OF TABLES

I. INTRODUCTION

Health related activities, including research, research training and patient services, are sponsored by a variety of sources. The pharmaceutical industry and the Federal government, primarily through the National Institutes of Health, are the major sponsors of such activities. Private foundations and voluntary organizations are also important sources of grants for these activities.

Foundations provide different types of grants for various health related activities. Some grants, referred to as "seed" grants, fund the development of preliminary data or establish pilot projects. Other grants augment funds provided by the Federal government, the pharmaceutical industry, voluntary organizations, and other foundations.

This report presents the results of a pilot study of 106 foundations that actively support health related activities. The study was conducted by D. Martin Carter, M.D., Ph.D., under the auspices of the Rockefeller University, New York, NY. The study was conducted between March and August of 1988. Section II describes the methodology used in the survey. Data analysis was provided by John Swasy, Ph.D., of American University, Washington, D.C. Major findings of the study are summarized in Section II. Appendix A contains the survey questionnaire and cover letter. Appendix B is a list of cooperating foundations.

This study was undertaken to determine the extent to which foundations support research or services that are related to rare diseases. The study is intended to augment available information about specific activities sponsored by foundation grants. Such information is limited, and when distributed, is usually contained in brief summaries in annual reports. In addition, because most foundations have a narrow focus either by design or policy, many of the foundations that fund health related grants may be precluded from providing grants for activities related to specific rare diseases.

II. METHODOLOGY/SAMPLE CHARACTERISTICS

The list of potential respondents was constructed in consultation with the Foundation Center, Washington, D.C. Specifically, the following 1987 publications of the Foundation Center were examined to identify those foundations actively funding health related grants:

- Grants for Medical and Professional Health Education,
- Grants for Public Health,

- Grants for Hospitals and Medical Programs, and
- Medical Research & Advancement.

Approximately 400 foundations were identified. A judgement was made to survey only those foundations most active in funding health related grants. Foundations providing $100,000 or more in grant support were deemed most active and, therefore candidates for the sample. Two-hundred seventy-six (276) foundations met this criteria. In addition, the Howard Hughes Medical Institute was included even though it is technically not a foundation. The questionnaire (Appendix A) was mailed to these 277 foundations.

Sixty-seven foundations returned a completed questionnaire. Another 59 replied by written letter. A variety of reasons for not completing the questionnaire were given. Thirty-eight foundations indicated that they do not support biomedical research in general, or biomedical research on rare diseases. Thirteen returned a grant application form, apparently treating the questionnaire as a request for funds. Five stated that they did not have the time or staff skills to complete the questionnaire.

Of the original 277 potential respondents, 62 rank among the 100 largest foundations in the U.S. Twelve of these had completed the questionnaire. Follow-up telephone contact was attempted with the remaining 50. Telephone interviews were conducted with 36 of the 50, resulting in an 82 percent response rate for the potential respondents ranked among the 100 largest foundations.

The total number of respondents was 106 which corresponds to an overall response rate of 38 percent. The average annual budget for the respondents is $20.2 million. Their budgets range from a low of $512,000 to a high of $252 million. The respondents' priorities cover a wide range of social issues.

A second assessment of the extent and nature of rare disease related research supported by foundations was obtained by examining the grant titles listed by the Foundation Center in Medical Research and Advancement (1987). This publication lists 1002 grants funded by 175 foundations with a total value of $156,229,863. While not comprehensive, this list can be used as a barometer of foundation grants in the area of medical research.

The findings described below are those of a pilot study, and do not necessarily generalize to all foundations supporting health related activities. In the strictest sense, the findings can only be used to describe the 106 participating foundations.

III. KEY FINDINGS

o Of the foundations surveyed, 43 (41 %) fund biomedical research; they devote, on average, 17.5 percent of their budgets ($3 million per year) to such grants.

o The foundations that fund biomedical research grants indicate that the major purpose of these grants is to provide independent grant support and seed money for research ideas.

o Of the foundations surveyed, one-third (32 %) fund patient services grants; they devote, on average 22 percent of their budgets ($3.3 million per year) to such grants.

o One in ten (11 %) of the foundations surveyed fund grants related to rare diseases. Combined they spend about $1.6 million per year. This expenditure represents 1.3 percent of their annual budgets.

o Of the foundations surveyed, 45 (42 %) report that policy restrictions prevent them from funding grants related to specific diseases.

o One-in-thirty (3.8 %) of the 1002 grants listed in the Foundation Center's 1987 publication, Medical Research and Advancement, are related to rare diseases. These grants represent support totalling $4.3 million or 2.8 percent of the total dollars spent on grants listed in this publication.

IV. ESTABLISHING PRIORITIES

A board of trustees or similar body establishes the funding priorities of most (81%) of the foundations surveyed (Table 1). The priorities of the remainder of the foundations are set by the president (15%), the staff (9.8%), or some other entity (9.8%). Only 1 percent reported that their priorities were established by medical or scientific advisors.

TABLE 1

Responsibility for Establishing Funding Priorities

Q2: Who has the primary responsibility for establishing the funding priorities of your foundation?

	Count*	PCT of Base**
President	15	15.0%
Board of Trustees	83	81.0
Staff	10	9.8
Medical or Scientific Advisors	1	1.0
Other	10	9.8
No Response	4	

* Because of multiple responses, total count exceeds the number of foundations answering this question.

** The number of foundations answering this question (base) equals 102

V. TYPES OF GRANTS FUNDED

Forty three (51%) of the 85 foundations answering this question fund biomedical research grants (Table 2). Thirty six foundations (42%) fund training grants, thirty four (40%) fund grants for patient services, and twenty nine (34%) fund other types of grants. Sixteen of the 43 foundations that fund biomedical research grants also fund patient services grants.

TABLE 2

Types of Grants Funded

Q3: What types of grants does your foundation fund?

	Count*	PCT of Base**
Biomedical Research	43	51%
Patient Services	34	40
Training	36	42
Other	29	34
No Response	21	

* Because of multiple responses, total count exceeds the number of foundations answering this question.

** The number of foundations answering this question (base) equals 85.

VI. CO-FUNDING GRANTS

Of the sixty-one foundations that fund biomedical research grants and/or patient services grants, 44 (72%) reported that they co-fund these types of grants (Table 3) with other agencies. An almost equal number of foundations indicated that they co-fund grants with universities or academic institutions (30), other foundations (28), and voluntary organizations (24). Fourteen foundations reported co-funding grants with the Federal government, while only 6 (14%) co-fund grants with the pharmaceutical industry.

TABLE 3

Co-Funding Grants

Q4: Do you co-fund biomedical research projects or patient services with:

	Count*	PCT of Base**
Federal Government	14	32%
Universities or Academic Institutions	30	68
Pharmaceutical Industry	6	14
Voluntary Organizations	24	55
Other Foundations	28	64
Other	4	9
No Response	17	

* Because of multiple responses, total count exceeds the number of foundations answering this question.

** The number of foundations answering this question (base) equals 44.

VII. PURPOSE OF BIOMEDICAL RESEARCH GRANTS

The foundations that fund biomedical research grants indicated that the major purpose of their grants is to provide independent grant support (60%) and to provide seed money (48%) for research ideas (Table 4).

TABLE 4

Purpose of Biomedical Research Grants

Q5: What is the major purpose of your biomedical research grant program?

	Count*	PCT of Base**
Provide Seed Money for Research Ideas	19	48%
Provide Independent Grant Support	24	60
Match Funds for Grants From Other Agencies	2	5
Other	10	25
Patient's Expenses to Participate in Research	1	3
No Response	3	

* Because of multiple responses, total count exceeds the number of foundations answering this question.

** The number of foundations answering this question (base) equals 40.

VIII. AWARDING BIOMEDICAL RESEARCH GRANTS

Foundations that fund biomedical research grants use peer review most frequently (53%) as the basis for awarding biomedical research grants (Table 5). Peer review by an ad hoc committee is used by 11 foundations (28%) and peer review by a standing committee is used by 10 foundations (25%). Recommendation of a board of directors or similar body is used by 18 foundations (45%). Fourteen foundations (35%) use other processes as the basis of awarding biomedical research grants.

TABLE 5

Awarding Biomedical Research Grants

Q6: What type of process does your foundation use to award biomedical research grants?

	Count*	PCT of Base**
Peer Review by Standing Committee	10	25%
Recommendation of Board of Directors	18	45
Peer Review by Ad Hoc Committee	11	28
Other	14	35
No Response	3	

* Because of multiple responses, total count exceeds the number of foundations answering this question.

** The number of foundations answering this question (base) equals 40.

IX. MEASURING THE EFFECTIVENESS OF BIOMEDICAL RESEARCH GRANTS

The foundations that fund biomedical research use a variety of factors to measure the effectiveness of these grants. The most frequently mentioned (69%) factor is comments by scientific peers (Table 6). Nineteen foundations (54%) rely on positive findings and seventeen (49%) use the number of publications resulting from the research.

TABLE 6

Measuring the Effectiveness of Biomedical Research Grants

Q7: What criteria are used to measure the effectiveness of biomedical research grants funded by your foundation?

	Count*	PCT of Base**
Comments by Scientific Peers	24	69%
Number of Publications Resulting from Research	17	49
Positive Findings	16	54
Prestige of Journal Publishing Results	12	34
Other	8	23
No Response	8	

* Because of multiple responses, total count exceeds the number of foundations answering this question.

** The number of foundations answering this question (base) equals 35.

X. BUDGET SIZE AND ALLOCATION TO RESEARCH AND PATIENT SERVICES

The average annual budget for the foundations in this sample (106) is $20.2 million. The budgets range from a low of $512,000 to a high of $252 million (Table 7). Forty three (41%) of the foundations fund biomedical research grants. They fund an average of 15 grants per year, ranging in size from $1000 to $13.5 million. On average, these foundations devote 17.5 percent of their budgets to such grants.

Thirty four (32%) of the 106 foundations fund grants for patient services. They fund an average of 21 grants per year, ranging in size from $1000 to $3 million. On average, these foundations devote 22% of their budgets to such grants.

XI. RARE DISEASE RELATED ACTIVITIES

Twelve of the 106 foundations (11%) fund grants related to rare diseases (Table 7). Grants related to rare diseases are most frequently for basic biomedical research (80%) and patient-oriented research (40%) (Table 8). In addition a smaller number of grants are for education (20%), patient care (20%), and rehabilitation (20%).

Eight of the 12 foundations spend less than 1 percent of their budget for such grants, while one foundation reported that all of its biomedical research grants are related to a specific rare disease. On average, the twelve foundations spend about $1.6 million or 1.3 percent of their budgets on grants related to rare diseases.

Seven foundations (7%) reported that they fund grants that stimulate the entry of scientists and physicians into biomedical research on rare diseases (Table 9). Twenty-three of the remaining foundations indicated that their current priorities would permit support for such grants.

Forty five foundations (48%) report policies or circumstances that prevent them from funding grants on specific rare diseases or rare diseases in general, while ten (11%) indicated no restrictions for such funding (Table 10). Restrictions cited by some foundations included the following--"it falls outside our area of interest, except serendipitously," "fund major pediatric health concerns only," "not permitted by foundation's charter," "we fund various biomedical disciplines, not specific diseases."

Table 7

Budget Size and Allocation to Biomedical Research
Patient Services, and Rare Disease Related Activities

		Mean	Median	Minimum	Maximum	# of Responses
Q8:	What is Your Foundation's Total Annual Budget? (000)	$20,221	10,000	512	252,000	95
Q9a:	What percentage of your foundation's annual budget is devoted to biomedical research grants?	19.8%*	9	1	100	39
	In terms of estimated dollar expenditures, biomedical research grants represent about 17.5% of the total budgets of the responding foundation which fund biomedical research grants.					
Q9b:	How many biomedical research grants did your foundation award last year?	15.2	6	1	130	35
Q9c:	What is the range in dollars of the biomedical research grants funded by your organization last year?					
	[lowest]: ($000)	138.5	27.0	1	2,500	34
	[highest]: ($000)	803.7	166	9	13,500	33
Q10a:	What percentage of your foundation's annual budget is devoted to grants for patient services?	16.6%	10	1	76	29
	In terms of estimated dollar expenditures, patient service grants represent about 22.1% of the total budgets of the responding foundation which fund patient service grants.					
Q10b:	How many grants for patient services did your foundation award last year?	21.1	12.5	1	101	22
Q10c:	What is the range in dollars of the grants for patient services funded by your organization last year?					
	[lowest]: ($000)	23.4	7	1	130	27
	[highest]: ($000)	394.8	100	5	3,000	27
Q13:	What percentage of your annual budget do you estimate is spent on rare disease related activities?	3.5	1	1	20	12
	In terms of estimated dollar expenditures, rare disease related activities represent about 1.3% of the total budgets of the 12 foundations funding rare disease related activities.					

* This figure, 19.8%, is the average of the percentages of budget reported by 39 foundations. Note that this average does not 'weight' their percentage response by the size of the responding foundation's budget. When estimated dollar expenditures are totalled for the 39, the biomedical research expenditures represent 17.5% of the total budgets for the 39 foundations.

TABLE 8

Rare Disease Related Grants

Q11: What types of grants did your foundation fund in 1987 or 1988 that were directly related to a rare (orphan) disease(s)?

	Count*	PCT of Base**
Rehabilitation	2	20%
Basic Biomedical Research	8	80
Psychosocial	0	0
Clinical (Patient Oriented) Research	4	40
Patient Care	2	20
Policy	1	10
Education	2	20
Other	2	20
No Response	2	

* Because of multiple responses, total count exceeds the number of foundations answering this question.

** The number of foundations answering this question (base) equals 10.

TABLE 9

Stimulating the Entry of Researchers
into Rare Disease Related Research

Q14: Do you fund grants that stimulate the entry of scientists and physicians into biomedical research on rare disease?

7 (7%)	Yes	99 (93%)	No

Q15: If no, do your current foundation priorities permit programs that attempt to stimulate the entry of researchers into rare disease related research?

23 (23%)	Yes	76 (77%)	No

TABLE 10

Policies Regarding Rare Disease Related Research

Q12: (For those foundations not funding rare disease related grants ...) "What policies or circumstances prevent your foundation from funding grants on specific rare disease or rare disease in general?

10 (11%)	"None"
45 (48%)	"Can't for some reason"
39 (41%)	Blank/NA

XII. REVIEW OF THE FOUNDATION CENTER'S PUBLICATION-- MEDICAL RESEARCH AND ADVANCEMENT

Another estimate of the extent of foundation support for biomedical research on rare diseases was obtained from an examination of the grant titles listed in the Foundation Center's publication Medical Research and Advancement (1987). This publication lists 1002 grants with a total value of $156,229,863 funded by 175 foundations. It covers grants to hospitals, medical colleges, and other medical institutions or associations for scholarships, fellowships, equipment, building construction, research, rehabilitative medicine, and general program needs. While not comprehensive, this list of grants is probably the best available barometer of foundation grants in these subject areas.

Examination of the grant titles listed in Medical Research and Advancement indicated that 38 (4 %) of the 1002 grants are related to rare diseases. These grants represent a total expenditure of $4.3 million or 2.8 percent of the $156 million in grants listed in Publication 32. The grants were funded by 25 (14%) of the 175 foundations listed in the publication. One foundation provided 9 of the 38 grants related to rare diseases and alone accounted for 48 percent of the total dollars provided for such grants.

APPENDIX A

COVER LETTER AND QUESTIONNAIRE

Dear :

I am writing to request your assistance in the efforts of the National Commission on Orphan (Rare) Diseases to gather information on foundation activities related to orphan (rare) diseases. As chairman of the Task Force on Foundation Activities, I have volunteered to collect this information through the resources of the Rockefeller University. The Task Force will forward the results to the Commission when completed.

Thus far, a small amount of information regarding foundation activities has been gathered at four public hearings held by the Commission between July 1987 and February 1988. The enclosed questions are designed to augment this information. Because your foundation has an expressed interest in the public health, I believe that your response to the enclosed questions will greatly assist the Task Force and ultimately the Commission in its information gathering efforts.

The National Commission on Orphan (Rare) Diseases has been charged by Congress to collect this information to:

(a) assess the status of biomedical research and information transfer related to rare diseases, both in the Federal and private sectors, and

(b) submit a report to the Secretary of the Department of Health and Human Services and to Congress containing recommendations and a long range plan for such research and information dissemination activities.

A copy of the Commission's charter and the current membership are enclosed. If you have any questions regarding the Commission or its activities, please contact Dr. Stephen C. Groft, Executive Director of the Commission at 301-443-6156. If you have any questions regarding this specific information gathering activity, please call Dr. Mary Custer at the same number.

Thank you for your assistance in this important endeavor. Your cooperation and submittal of your response by May 15 are greatly appreciated.

Sincerely yours,

D. Martin Carter, M.D., Ph.D.
Professor, Rockefeller University
Chairman, Task Force on Foundations
National Commission on Orphan Diseases

INSTRUCTIONS

Please respond to all questions. If a question is unanswerable, please write "unknown" in the space after the box marked Other. If a question does not apply, please write "NA" in the space after the box marked Other. If more than one response is applicable, please check all that apply.

If you have any questions, please call Dr. Mary Custer at 301-443-6156. Completed forms should be returned by May 15 to:

D. Martin Carter, M.D., Ph.D.
Chairman
Task Force on Foundation Activities
The Rockefeller University
1230 York Ave.
New York, NY 10021-6399

Thank you.

Definition of Orphan (Rare) Diseases

For purposes of this study, the term orphan (rare) disease denotes any disease which:

(A) Affects fewer than 200,000 persons in the U.S., or

(B) Affects 200,000 or more persons and for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease will be recovered from sales in the U.S.; the term includes diseases rare in the U.S. but common elsewhere.

For examples of specific rare diseases please refer to list on reverse side.

NOTE: Do NOT include information on AIDS even though it falls under the above definition.

Random Selection of Rare Diseases*

Acoustic Neuroma
Addison's Disease
Alopecia Areata
Amyotrophic Lateral Sclerosis
Aplastic Anemia
Ataxia
Autism

Behcet's Syndrome
Blepharospasm

Charcot Marie Tooth Disease
Congenital Port Wine Stain
Cornelia DeLange Syndrome
Cystinosis

Dwarfism
Dysautonomia
Dystonia
Dystrophic Epidermolysis Bullosa

Ectodermal Dysplasia
Ehlers-Danlos Syndrome

Fragile X Syndrome

Galactosemia
Gaucher's Disease
Gluten Intolerance
Glycogen Storage Disease
Guillain-Barre Syndrome

Hemochromatosis
Hemophilia
Histiocytosis-X
Huntington's Disease

Joseph Disease

Leprosy
Leukodystrophy
Lowe's Syndrome
Lupus Erythematosus

Malignant Hyperthermia
Maple Syrup Urine Disease
Marfan Syndrome
Mucopolysaccharidosis
Multiple Sclerosis
Myasthenia Gravis
Myoclonus

Narcolepsy
Neurofibromatosis

Osteogenesis Imperfecta

Paget's Disease
Parkinson's Disease
Porphyria
Prader-Willi Syndrome
Pseudoxanthoma Elasticum

Reflex Sympathetic Dystrophy
Retinitis Pigmentosa
Rett Syndrome

Sarcoidosis
Scleroderma
Sickle Cell Anemia
Sjogren's Syndrome
Spasmodic Torticollis
Spina Bifida

Tay Sachs Disease
Tourette Syndrome
Tuberous Sclerosis
Turner's Syndrome

Uveitis

Vitiligo

Wilson's Disease

*This list includes only a very small number of the estimated 5,000-6,000 rare diseases in the U.S.

FOUNDATION ACTIVITIES

1. Please list the major areas of focus or priorities of your foundation.

_____

_____

_____

_____

2. Who has the primary responsibility for establishing the funding priorities of your foundation?

___ a. President
___ b. Board of Trustees
___ c. Staff
___ d. Medical or Scientific Advisors
___ e. Other (Please specify) _____

3. What types of grants does your foundation fund?

___ a. Biomedical Research
___ b. Patient Services
___ c. Training
___ d. Other (Please specify) _____

4. Do you co-fund biomedical research projects or patient services with

___ a. The Federal government?
___ b. Universities or academic institutions?
___ c. The pharmaceutical industry?
___ d. Voluntary organizations?
___ e. Other Foundations?
___ f. Other (Please specify) _____

5. What is the major purpose of your biomedical research grant program?

___ a. Provide Seed Money for Research Ideas
___ b. Provide Independent Grant Support
___ c. Match Funds for Grants from Other Agencies
___ d. Other (Please Specify) _____
___ e. Provide Funds for Costs Incurred by Patients Participating in Research Studies, such as Travel Expenses, Cost of Experimental Drugs, etc.

6. What type of process does your foundation use to award biomedical research grants?

___ a. Peer Review by Standing Committee
___ b. Recommendation of Board of Directors or Similar Body
___ c. Peer Review by Ad Hoc Committee
___ d. Other (Please specify) _____

7. What criteria are used to measure the effectiveness of biomedical research grants funded by your foundation?

___ a. Comments by Scientific Peers
___ b. Number of Publications Resulting from Research
___ c. Positive Findings
___ d. Prestige of Journal Publishing Results
___ e. Other (Please specify) _____

8. What is your foundation's total annual budget? $_____

9. a. What percentage of your foundation's annual budget is devoted to biomedical research grants? _____

b. How many biomedical research grants did your foundation award last year? _____

c. What is the range in dollars of the biomedical research grants funded by your organization last year? (Lowest to highest) $_____ to $_____

10. a. What percentage of your foundation's annual budget is devoted to grants for patient services? _____

b. How many grants for patient services did your foundation award last year? _____

c. What is the range in dollars of the grants for patient services funded by your organization last year? (Lowest to highest) $_____ to $_____

11. What types of grants did your foundation fund in 1987 or 1988 that were directly related to a rare (orphan) disease(s)? (See attached list for examples of rare [orphan] diseases).

___ a. Rehabilitation
___ b. Basic Biomedical Research
___ c. Psychosocial
___ d. Clinical (Patient Oriented) Research
___ e. Patient Care
___ f. Policy
___ g. Education
___ h. Other (please specify) _____
___ i. Did not Fund Grants Related to Rare Diseases

12. If not, what policies or circumstances prevent your foundation from funding grants on specific rare diseases or rare diseases in general?

_____

13. What percentage of your annual budget do you estimate is spent on rare disease related activities? _____

14. Do you fund grants that stimulate the entry of scientists and physicians into biomedical research on rare diseases?

___ Yes
___ No

15. If no, do your current foundation priorities permit programs that attempt to stimulate the entry of researchers into rare disease related research?

___ Yes
___ No

16. *Would a representative of your foundation be able to participate in a meeting of the National Commission on Orphan Diseases on June 9-10, 1988 in Washington, D.C. to discuss these issues more fully?*

___ *Yes*
___ *No*

If so, please provide us with the name, address, and telephone number of this representative.

Name _____ *Telephone number* _____

Address _____ *Name of Foundation* _____

_____

APPENDIX B

LIST OF COOPERATING FOUNDATIONS

The helpful cooperation of the following foundations is acknowledged:

Aetna Life & Casualty Foundation, Inc.
Alcoa Foundation
George I Alden Trust
Primerica Foundation
Amoco Foundation
The Annenberg Fund, Inc.
ARCO Foundation
The Vincent Astor Foundation
AT&T Foundation
Mary Reynolds Babcock
Borg-Warner Foundation, Inc.
The Boston Foundation, Inc.
Otto Bremer Foundation
The Brown Foundation, Inc.
The Burroughs Wellcome Fund
Edyth Bush Charitable Foundation, Inc.
The Bush Foundation
California Community Foundation
Carnegie Corporation of New York
Amon G. Carter Foundation
The Champlin Foundation
The Chicago Community Trust
The Greater Cincinnati Foundation
The Edna McConnell Clark Foundation
Robert Sterling Clark Foundation, Inc.
The Cleveland Foundation
The Commonwealth Fund
Corning Glass Works Foundation
C.S. Fund
The Charles A Dana Foundation, Inc.
The Herbert H. and Grace A. Dow Foundation

The Duke Endowment
Jessie Ball duPont Religious,
Charitable and Education Fund
The Educational Foundation of America
Exxon Education Foundation
Leland Fikes Foundation, Inc
First Bank System Foundation
The Ford Foundation
The Frost Foundation, Ltd.
The B.C. Gamble and P.W. Skogmo Foundation
Gannett Foundation, Inc.
General Electric Foundation
General Mills Foundation
General Motors Foundation, Inc.
General Service Foundation
Morris Goldseker Foundation of Maryland, Inc.
William T. Grant Foundation
The Greenwall Foundation
The George Gund Foundation
Ittleson Foundation, Inc.
The John A. Hartford Foundation, Inc.
The Hearst Foundation, Inc.
The William and Flora Hewlett Foundation
The Howard and Bush Foundation, Inc.
Stewart W. & Willma C. Hoyt Foundation
Hudson-Webber Foundation
Howard Hughes Medical Institute
The Hyde and Watson Foundation
The Indianapolis Foundation
The International Foundation
The James Irvine Foundation
The J.M. Foundation
Johnson Controls Foundation
The Robert Wood Johnson Foundation

Walter S. Johnson Foundation
Daisy Marquis Jones Foundation
W. Alton Jones Foundation, Inc.
The Joyce Foundation
The Henry J. Kaiser Family Foundation
The J.M. Kaplan Fund, Inc.
W.K. Kellogg Foundation
Peter Kiewit Foundation
Knight Foundation
Koret Foundation
The Kresge Foundation
Joan B. Kroc Foundation
Levi Strauss Foundation
The J.E. and L.E. Mabee Foundation, Inc.
John D. and Catherine T. MacArthur Foundation
Lucille P. Markey Charitable Trust
James S. McDonnell Foundation
McInerny Foundation
The McKnight Foundation
Meadows Foundation, Inc.
The Medical Trust
The Andrew W. Mellon Foundation
Richard King Mellon Foundation
Joyce Mertz-Gilmore Foundation
Metropolitan Life Foundation
Morgan Guaranty Trust Co. of NY
Charles Stewart Mott Foundation
Mountain Bell Foundation
M.J. Murdock Charitable Trust
The Pew Charitable Trusts
New York Foundation
The Samuel Roberts Noble Foundation, Inc.
Northwest Area Foundation
Jessie Smith Noyes Foundation, Inc.

Ordean Foundation
The David and Lucile Packard Foundation
Elsa U. Pardee Foundation
Gustavus and Louise Pfeiffer Research
The Pfizer Foundation, Inc.
The Piton Foundation
The Proctor & Gamble Fund
The Prudential Foundation
Public Welfare Foundation, Inc.
The Retirement Research Foundation
Charles H. Revson Foundation, Inc.
The Christopher Reynolds Foundation, Inc.
Kate B. Reynolds Charitable Trust
Z. Smith Reynolds Foundation, Inc.
Fannie E. Rippel Foundation
Rockefeller Family Fund, Inc.
The Rockefeller Foundation
The Winthrop Rockefeller Foundation
Helena Rubinstein Foundation, Inc.
The San Francisco Foundation
Schering-Plough Foundation, Inc.
Security Pacific Foundation
Shell Companies Foundation, Inc.
Siebert Lutheran Foundation, Inc.
L.J. Skaggs and Mary C. Skaggs
The Skillman Foundation
W.W. Smith Charitable Trust
Anne Burnett and Charles D. Tandy Foundation
The Teagle Foundation, Inc.
Thrasher Research Fund
Turrell Fund
Union Pacific Foundation
USX Foundation, Inc.
Virginia Environmental Endowment

The William K. Warren Foundation
Weingart Foundation
Westinghouse Electric Fund
The Whitaker Foundation
Woods Charitable Fund, Inc.