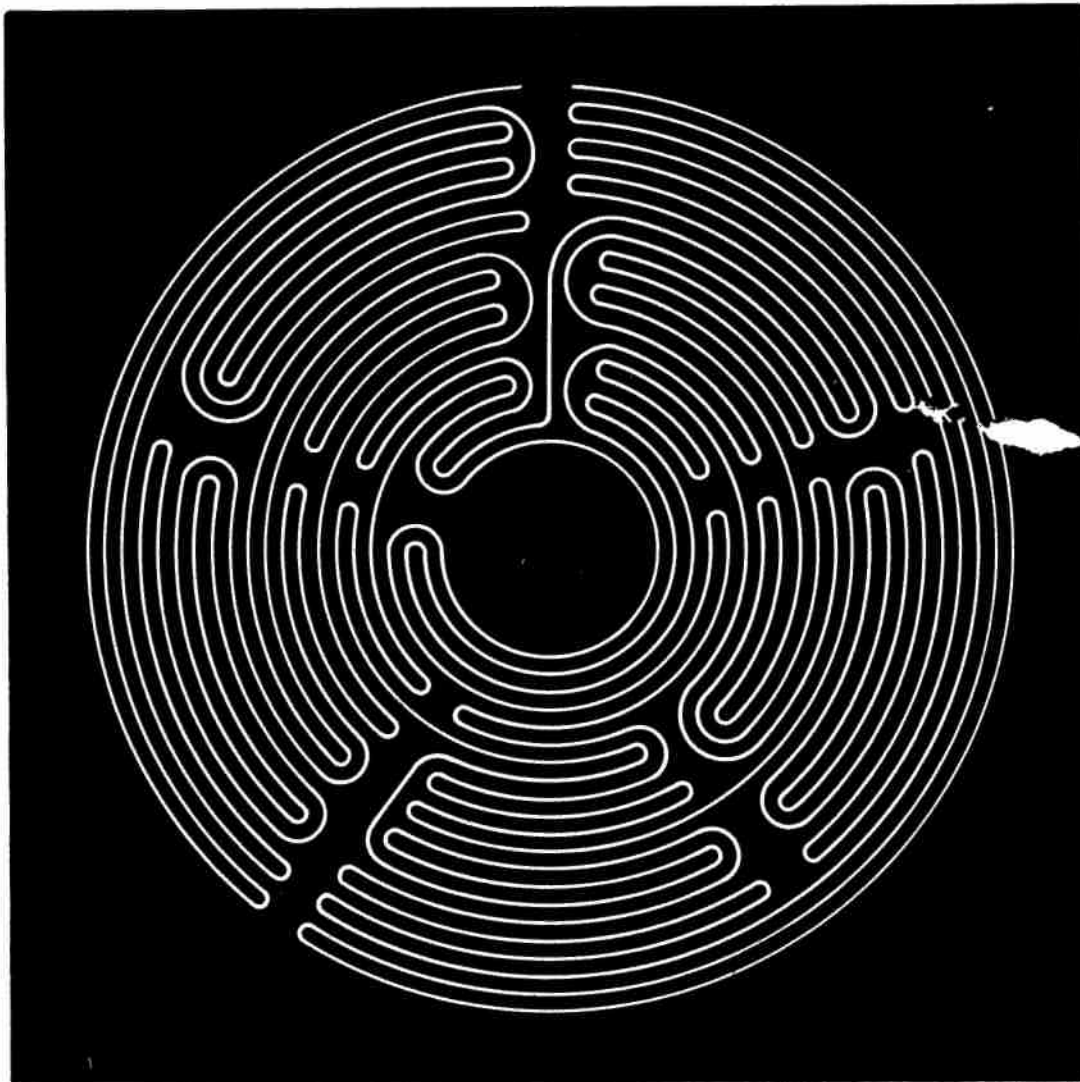


# REPORT OF THE NATIONAL COMMISSION ON ORPHAN DISEASES

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Office of the Assistant Secretary for Health  
February 1989



DEPARTMENT OF HEALTH & HUMAN SERVICES  
NATIONAL COMMISSION ON ORPHAN DISEASES

Public Health Service

5600 Fishers Lane, Room 1-20, Park Bldg., 301-443-6156

Rockville MD 20857

February 27, 1989

The Honorable Louis W. Sullivan  
Secretary  
Department of Health and Human Services  
Washington, D.C. 20201

Dear Mr. Secretary:

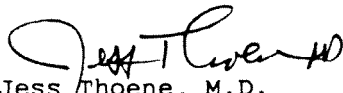
In accordance with Section 4(n) of the Orphan Drug Amendments of 1985 (Pub.L. 99-91), as amended, we respectfully transmit the final report of the National Commission on Orphan Diseases.


For millions of Americans who suffer from one of the over 5,000 rare diseases, the prognosis for good health is very uncertain. For most of these disorders, there is no effective treatment, and even simple basic knowledge about the cause, frequency, prognosis and heritability is unknown.

The Commission has heard hours of testimony from patients, their relatives, physicians, investigators, members of private foundations, officers of the appropriate Federal agencies and representatives of pharmaceutical companies. What was learned was both encouraging and frustrating: there are many resources which can help rare disease patients, but there is no effective mechanism to provide for appropriate and timely use of these facilities and services. In other areas, resources need to be developed and coordinated to meet the unique needs of this population. This report details what the needs are and makes suggestions for their alleviation. While significant costs will be attached to some of the recommendations, many others will involve minimal costs. The relief of human suffering will be enormous.

We hope that the report will provide guidance as you address these issues in the coming months. It has been a privilege for us to serve on this important Commission.

Respectfully submitted,

  
Jess Thoene, M.D.  
Chair  
National Commission  
on Orphan Diseases

  
Glenna M. Crooks, Ph.D.  
Vice Chair  
National Commission  
on Orphan Diseases



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February 27, 1989

The Honorable Dan Quayle  
President of the Senate  
Washington, D.C. 20510

Dear Mr. President:

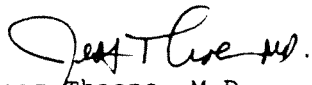
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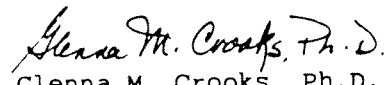
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February 27, 1989

The Honorable Jim Wright  
Speaker of the House of Representatives  
Washington, D.C. 20515

Dear Mr. Speaker:

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## PROLOGUE

Hidden among the many strident voices clamoring to be heard by Congress and to receive a share of our national resources is the persistent murmur of those left outside the current health care system. Lacking adequate health insurance, a correct diagnosis, and any real hope of effective therapy, persons with rare diseases are truly medically disenfranchised. Yet, with the creation of the National Commission on Orphan Diseases, Congress opened a channel through which these voices could be heard. Their story is compelling: forced to fend for themselves, they must often become expert on their own condition to educate their health care providers about the existence of the rare disease, its prognosis, and any available therapy. They must become expert in dealing with Federal agencies, since no central directory to all relevant programs exists. They must independently discover clinical trials of drugs potentially useful in their condition. For the ten to twenty million Americans of all ethnic groups and every

socio-economic level who suffer from a rare disorder, the story the Commission heard was the same—no one knows, and no one cares.

Documenting the nature and extent of the problem was easy for the Commission; proposing realistic solutions was much more difficult. Every branch of government involved in health care, including NIH, ADAMHA, FDA, HCFA, and the Congress must join with the pharmaceutical industry and academia to focus resources on the problem of lack of knowledge about and lack of treatment for rare diseases. To do less is to condemn those affected by these disorders to remain outside the health care system.

Jess G. Thoene, M.D.  
Chair, National Commission on  
Orphan Diseases

# ACKNOWLEDGEMENTS

The National Commission on Orphan Diseases was established to assess the activities of the private and public sector in connection with the various aspects of rare diseases. These include basic and clinical research, the need for and dissemination of information to the public and health professionals, availability of health insurance and reimbursement for patients with rare diseases, as well as the discovery and development of orphan products for rare diseases. The National Commission on Orphan Diseases considered the needs of patients, physicians, researchers, the pharmaceutical industry, voluntary organizations, private foundations and the Federal agencies associated with all rare diseases. In this report, the Commission presents Congress and the Administration a blueprint to guide the country's policies regarding rare diseases into the 21st Century. It is a privilege to present the needs of these patients to the public. The Commission looks forward to the implementation of the recommendations in this report.

Many individuals and organizations assisted the Commission. We are unable to mention all who assisted, but there are many persons who deserve a special thanks:

Dr. Robert E. Windom, Assistant Secretary for Health, Department of Health and Human Services, for his support and attention at the time of the formation of the Commission and during its deliberations;

Mr. Wilford Forbush, Deputy Assistant Secretary for Health Operations, for providing administrative support and facilitating the Commission's activities;

Dr. Jay Moskowitz, Associate Director for Science Policy and Legislation, and Dr. Jerome Green, Director, Division of Research Grants at the National Institutes of Health, for their assistance in retrieving and reviewing information and data from the Bureaus, Institutes, and Divisions of NIH.

A special thank you is given to the principal editor, Blair Burns Potter who wove the results of the surveys, written and oral testimony, and recommendations of the Commission into this final report. Also a note of thanks to Dr. Tom Truss who shared his writing and editing talents with the Commission.

Several individuals assisted the Commission in the design and analysis of the numerous surveys conducted by the Commission. The conscientious efforts of Dr. Louis A. Morris, Dr. Arthur Kirsch and Dr. John L. Swasy are particularly recognized. The Commission also appreciates the cooperation of the many patients, physicians, investiga-

tors and representatives of government agencies, voluntary rare disease organizations, foundations, and pharmaceutical manufacturers who provided essential information for the surveys and discussions conducted by the Commission.

Several organizations conducted or sponsored surveys and transmitted the results to the Commission. Their enthusiasm and willingness to assist the Commission's data gathering efforts deserves special thanks. These organizations and their representatives follow:

American Medical Association—Dr. Lorayn Olson and Dr. Paul D. Frenzen

Chilton Research Services—Dr. David B. Lambert, Gwen Miller, and Lorie McCafferty

Hamilton, Fredericks, and Schneider—Pat Junkins and James Gill

Macro Systems, Inc.—Dr. Jean Cohen

The National Organization for Rare Diseases—Abbey Meyers

The Rockefeller University—Dr. D. Martin Carter

The Pharmaceutical Manufacturers Association—Dr. Lawrence Weaver, Dr. George Goldstein, and Gerald J. Mossinghoff

The Generic Pharmaceutical Industry—Dee Fensterer

The Orphan Developers Coalition—John Presutti

The Association of Biotechnology Companies—Jeffrey N. Gibbs

The Commission gratefully acknowledges the efforts and contributions of the Commission's staff including Dr. Mary Custer, Henrietta Hyatt-Knorr, Beatrice Anderson, and Carol Lewis. A special mention of thanks to Paris Pacchione, Donna Young, Frank Teets, and the Electronic Phototypesetting Section (Printing Management) for assistance in preparing the report for publication. In addition, the computer support staff provided by Management Systems Applications, Inc., in particular, Frank Newman and Bill Kibby, minimized down time and kept the computer system working through many deadlines.

Stephen C. Graft, Pharm.D.  
Executive Director

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Management Systems Applications, Inc.  
National Organization for Rare Disorders, Inc.



# EXECUTIVE SUMMARY

*Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual laws of nature by careful investigation of cases of rarer forms of diseases. For it has been found in almost all things that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way.*

—William Harvey, 1657

Between 10 million to 20 million Americans suffer from one of the approximately 5,000 known rare diseases. Most of these rare diseases are also orphan diseases: they have no parent organization, investigator, or agency dedicated to research on the prevention, diagnosis, or treatment of their victims. The costs of rare diseases, in monetary and human terms, are enormous. Patients and their families struggle with disabling, painful, sometimes disfiguring illness and suffer loss of educational and employment opportunities, family life, and physical and mental abilities.

Responding to recurrent problems in rare disease research and product development and to voluntary organizations' pleas for action, Congress established the National Commission on Orphan Diseases in August 1985.

## The Commission and Its Activities

The Commission conducted numerous public meetings, hearings, interviews, work group meetings, round-table discussions, and surveys of patients, physicians, researchers, Federal agencies, voluntary organizations, private foundations, and the pharmaceutical industry.

At its meetings the Commission discussed the needs of patients; drug development and approval; the National Center for Toxicological Research; the activities of the Office of Orphan Products Development at FDA; the extramural and intramural research programs of NIH, FDA, ADAMHA, and CDC; Medicare and Medicaid; health insurance coverage; and other programs and issues.

The Commission learned that little is known about most rare diseases and that too few investigators are studying

them. Rare diseases can be extremely difficult to identify and manage, requiring years of searching for a diagnosis, referral, and treatment. Considerable effort is required to find the speech or physical therapy, special education, medical foods, or prosthetic devices needed by patients. Frequently these needs are not covered by insurance. Often patients are denied appropriate services because the services are tied to lists of specific diagnoses or categories of disease, which do not include many rare diseases or conditions.

## Survey Results

### Patients and Families:

- Patients and families have difficulty obtaining information about new treatments, research advances, appropriate voluntary support groups, and the location of treatment centers for their disease or condition.
- A majority of patients and families are willing to use investigational drugs but find it difficult to locate information on research projects in which they could participate.
- Forty-two percent of the 801 patients surveyed said their illness prevents them from working or attending school, and 43 percent said their illness constitutes an extreme financial burden on their family.

### Physicians:

- Forty-two percent of the 270 physicians surveyed need, but are unable to find for their patients, printed information about their illness.
- Only 27 percent of the 150 physicians surveyed who had not used an investigational product reported that they

had ever considered using such a product. If the illness was lifethreatening, 92 percent would prescribe an investigational drug.

- Nearly 48 percent of the responding physicians reported that they would be very hesitant and an additional 40 percent reported they would be somewhat hesitant to use an investigational product if information about the product was limited.

#### **Investigators:**

- A majority of the 604 investigators of both rare and common diseases surveyed believe that it is harder to get funding for basic or clinical research on rare diseases than for similar research on common diseases.
- Respondents agreed that lack of funds for research is the single greatest barrier to the discovery of treatments for rare diseases.
- Limited availability of patients for clinical studies is a major problem for rare disease investigators.

#### **Federal Agencies:**

- The Federal sector plays the largest role in rare disease research funding, but it does so through general rather than rare disease-specific research programs. Most agencies do not have special mechanisms to stimulate research on rare diseases.
- The only specific funding mechanism for the development of treatments for rare diseases is the FDA's Office of Orphan Products Development. Currently this program funds \$5 million a year in research—about \$1 thousand per rare disease per year.

#### **Private Foundations:**

- Twelve of the 106 foundations surveyed fund rare disease-related projects, at a level of \$1.59 million (or 1.3 percent) of their total budgets. Forty-five have policies that preclude the funding of grants on specific rare diseases.

#### **Voluntary Organizations:**

- The 113 responding organizations identified their most important activities as preparing and providing educational materials and programs for patients and health professionals.
- Sixty-two percent of organizations maintain files and registries of patients, investigators, or physicians.
- Forty-four percent of the organizations provide research grants, and 29 percent provide seed money to encourage scientists and physicians, many of whom eventually obtain Federal research funds. Twenty-five percent of these organizations were unable to provide an estimate of the prevalence of the rare disease or condition with which they are concerned.

#### **Pharmaceutical Manufacturers:**

- Since the passage of the Orphan Drug Act in 1983, 257 products have received the orphan drug designation and 33 designated orphan products have been approved for marketing.
- Manufacturers reported that the most important incentive in the act is the exclusive marketing provision.
- Firms report spending \$54.6 million on rare disease research and development in 1987; they plan to spend \$95.4 million in the future on development of 81 orphan products under investigation and 37 marketed products. An additional \$190.3 million in research and development costs had been allocated to the 118 approved and investigational products for rare diseases. Many of the firms surveyed do not differentiate rare disease research from common disease research. Thus it is not possible to determine the exact financial resources devoted to rare disease research.

#### **The Need for Information**

The Commission found overwhelming evidence of patients' difficulty in obtaining timely and accurate diagnoses of and information about their rare diseases. Physicians are often unfamiliar with the vague and confusing symptoms of rare diseases. Almost one-third of the patients surveyed indicated it took from one to five years to obtain a diagnosis, and one in seven went undiagnosed for six years or more. Only half of the respondents report receiving a diagnosis less than one year after first visiting a doctor.

Once diagnosed, most patients with rare diseases and their families seek information from their physicians. They want to know how to cope with the physical manifestations of their illness; what services are available to offer medical, emotional, and financial support and comfort; and what approved therapies or experimental treatments may be available. Often, such information does not exist.

#### **Sources of Information**

For many patients and their families, voluntary organizations are their sole source of support and information. Most voluntary organizations are private, not-for-profit groups and provide most, if not all, of their services at no charge. Often, they are stretched to or beyond the limits of their financial and personal resources. The Commission views voluntary organizations as a national resource and is concerned that millions of Americans with rare diseases have no voluntary organizations to provide them assistance. Voluntary organizations with common research and education interests should be encouraged to form alliances to enhance the use of their scarce dollars, and public policies should support their efforts.

The greatest volume of information about rare diseases is generated, directly or indirectly, by the Federal government. Materials designed for distribution to the public include fact sheets, booklets, and research reports, which, even when adapted for the public, may be difficult for patients and their families to understand. Dissemination of information to the general public is not usually a program priority and is constrained by limitations on printing. In agencies that have a budget for information dissemination, rare diseases must compete for funds with common diseases and with preventive education programs for healthy people.

The Commission recognizes the need to support patients in their search for information and to assist physicians in providing it. An active and fully funded central source of information on rare diseases is needed to facilitate access to information and to coordinate existing information systems and services in the public and private sectors.

### **Financing Patient Care**

Most health insurance is obtained as group insurance through employers; however, persons with rare diseases are often uninsurable because third-party payers lack information about their disease or will not insure pre-existing conditions. Those who do have insurance often find it inadequate, expensive, or difficult to obtain. Medical costs for a patient with a rare disease can range from \$9,500 to \$115,000 per year.

Seven percent of the patients surveyed reported inadequate health insurance; another 9 percent indicated they had no health insurance at all. Thus, several million persons in the United States with a rare disease may have inadequate or no insurance. This number is likely to grow as more restrictive cost-cutting measures are adopted and more definitive diagnostic techniques become available and widely used.

The Commission believes that everyone in the United States must have access to affordable health care. Federal and state governments and insurance carriers should develop plans to provide health and life insurance coverage or make it accessible at an affordable cost.

Federal and state governments should require all group health plans to provide coverage for patients with pre-existing rare diseases. The insurance industry should develop minimum standards of coverage for small firms and make "extended group" coverage available by enrolling employees of many small firms in one group policy.

Currently, some insured patients may not be reimbursed for care. For example, insurance companies generally do not cover experimental treatments, even when available evidence indicates the treatment is effective and will lower overall medical costs. Differences exist in coverage of new

technologies and treatments among companies and among contracts issued by the same company. Insured patients also may face high out-of-pocket expenses for premiums, deductibles, and coinsurance; in addition, they must pay for services and supplies not covered by their policy.

Insurers, including the Federal government, should cover treatments and services associated with investigational protocols approved by a local institutional review board as well as unapproved treatments of rare diseases considered standard care.

Coverage should be expanded to provide uniform reimbursement for appropriate and necessary ancillary services, such as physical, speech, and respiratory therapies, dental care, and genetic testing and counseling, which are commonly required by persons with rare diseases.

Insurers should also provide reimbursement for marketed drugs and devices not approved for orphan indications, for medical foods which are medically indicated to prevent severe impairment or death, and over-the-counter products used in the appropriate treatment of rare diseases.

### **Biomedical Research**

The greatest barrier to prevention or diagnosis and treatment of rare diseases is lack of knowledge about them. The key to developing this knowledge is attracting and retaining investigators.

Many students avoid a career in research because they have misconceptions about it, because they lack incentives to do it, or because they had little exposure to it in undergraduate and medical school. Emphasis on rare disease research by the NIH would signal young investigators that research opportunities exist. Workshops and symposia have proved effective in attracting new and experienced investigators and in stimulating new research hypotheses.

Stable funding would be an important inducement for investigators to enter and remain in the rare disease research field. Investigators should be able to expect continued support after their training is completed.

Experienced investigators who avoid research on rare diseases because they believe that it is less likely to be funded or that the funding is less stable than funding for other research should be assured by the NIH that this is not the case. Investigators who believe that basic research is more likely to be funded than clinical or applied research or that more emphasis on research funding is needed, should join the Commission in promoting additional funds for all research.

Because of both investigators' concerns about peer review and its importance in funding research, the Commission examined the effects of peer review on the fund

ing of rare disease research. It found the review process to be generally equitable in reviewing grant applications and making awards. Nonetheless, the Commission directed several recommendations toward the peer review process.

Federal agencies should heighten their awareness of rare diseases and should declare research and other activities related to rare diseases to be of high priority. They should ensure that rare disease experts are included in grant reviews and that they are allowed to vote. Patients with rare diseases or their representatives and families should be included on advisory councils.

### **Funding of Research on Rare Diseases**

Increased funding of all biomedical research and training is essential if advances are to be made in preventing rare diseases and treating patients. In many instances, an advance in research on a common disease can have a direct bearing on research on a rare disease and vice versa.

Responses to the Commission's surveys indicate that in FY 1987, the Federal government spent \$1.3 billion on rare disease research, foundations spent \$1.6 million, and the pharmaceutical industry spent \$51.6 million on both research and development of orphan products. Of the \$1.3 billion spent by the Federal government, over half was spent on approximately 200 rare forms of cancer, leaving only \$640 million for the remaining 4,800 known rare diseases. The majority (63%) of research funds is spent on basic research. The Commission concludes, therefore, that overall funding for rare disease research is inadequate.

Some of the most important clinical studies in the United States occur in Clinical Research Centers (CRCs). No other research resource addresses the needs of rare disease patients and investigators as directly as they do. Federal funding of CRCs should be increased. Criteria used in evaluating centers should emphasize rare disease and orphan drug research programs conducted in the past or proposed for the future.

### **Epidemiological Studies**

Accurate information about the incidence and prevalence of a rare disease, as well as the geographical distribution of patients, can be extremely important, both for the investigator who proposes a project and the reviewers who evaluate it. The Commission recommends that the National Center for Health Statistics determine the prevalence of rare diseases.

### **Scientific and Technical Registries**

Registries of scientific and technical data have been shown to stimulate research on rare diseases and improve patients' access to treatment. The Federal government should provide appropriate funding to establish new and maintain existing registries. Voluntary organizations,

patients, physicians, and researchers should assist in their development.

### **Product Discovery, Development, and Availability**

More products are needed to treat persons with rare diseases; however, there are numerous barriers to the discovery and development of such products. These barriers include difficulty in developing an appropriate study protocol; insufficient flexibility in the regulatory process, (especially regarding the number of patients needed for clinical trials); delays in review; weak economic incentives for development; and lack of commercial sponsors.

Current law gives the pharmaceutical industry a number of economic incentives for developing orphan products. Testimony and survey results indicate that, although these incentives have been effective, industry activity would be enhanced by increasing existing incentives and developing incentives for medical foods and devices. Biotechnology products should receive intellectual property protection not currently provided by existing legislation.

The FDA with its regulatory responsibility plays a crucial role in the orphan products development process. To enhance this process, FDA can take several actions. To speed up the review process, all designated orphan products should be classified as a 1A product. FDA should conduct an educational program for product review personnel to highlight problems unique to the development of products for rare diseases.

FDA should institute a program to encourage sponsors to add rare disease indications to the labeling of marketed products and encourages sponsors of drugs approved in other countries to seek FDA approval of those drugs and to participate in FDA's treatment IND program.

The FDA and the pharmaceutical industry should help academic investigators locate sponsors for promising orphan products and gain access to reference of existing Drug Master Files for investigational products. FDA could also serve as an intermediary to assist investigators gain access to new chemical compounds developed by private industry and Federal agencies.

Frequently, failure to meet the stringent pre-marketing testing requirements prevents further development of orphan products. To overcome this barrier, the National Center for Toxicological Research should conduct the required toxicological studies of orphan products when the sponsor is unable to do so.

### **Liability**

Concerns about potential liability may deter pharmaceutical companies, device companies, and practicing physicians from studying and treating persons with rare diseases.

In a number of instances, concerns about liability have led to significant delays in product development and increased liability insurance costs. Congress should consider special relief in instances where concerns about liability pose insurmountable obstacles to progress on rare diseases.

The Commission is sensitive to liability as it affects research and treatment generally and is concerned that persons with rare diseases not be adversely affected. Forums seeking general solutions to the issue of liability should pay special attention to the implications of those solutions for rare diseases. Congress and state legislatures should resolve product and professional liability issues promptly.

### **The Product Approval Process**

Congress should expedite the regulatory review process by providing appropriate additional funds to the FDA to increase the number of review and support personnel.

Some pharmaceutical companies that are active in discovery and development of orphan products are limited in their resources and experience with the investigational and new drug application process. The FDA should continue to assist clinical investigators and firms involved with the development of products for rare diseases. If implemented, FDA should waive user fees, where appropriate, for sponsors of orphan products seeking investigational or new drug status for those products.

### **Technology Transfer**

Federal agencies should be directed to make available as soon as possible intellectual property developed by Federal employees. This can be done by utilizing the provisions of the Federal Technology Transfer Act. Scientists are encouraged to participate in programs that provide incentives for the development of products for rare diseases, and Federal employees are encouraged to develop cooperative agreements with the private sector to stimulate the transfer of new research developments to the marketplace.

### **The Need to Coordinate Research and Development Efforts**

The Commission found that many of the barriers to progress in research and treatment are caused not only by the lack of funding, but also by the lack of coordination of and access to existing resources. Open communication and close cooperation among Federal agencies, voluntary organizations, foundations, societies for health professionals, and health-related industries should be encouraged in all aspects of rare disease research, orphan product development, information dissemination, and reimbursement procedures.

Federal agencies and the private sector should notify clinical investigators in rare diseases of FDA's protocol assistance service through appropriate statements on grant applications. Investigators should make certain their clinical study protocols meet FDA requirements for adequate and well-controlled therapeutic trials of orphan products. The FDA, NIH, and ADAMHA should ensure that when rare disease-related grants cannot be funded by one agency they are forwarded to the others for consideration.

There are at present several groups that coordinate research and development efforts, among them, the Office of Orphan Products Development in FDA, the Orphan Products Board in the Office of the Assistant Secretary for Health, the Commission on Drugs for Rare Diseases of the Pharmaceutical Manufacturers Association, the Institute for Orphan Drugs of the Generic Pharmaceutical Industry Association, the Orphan Developers Coalition, and the Association of Biotechnology Companies. Investigators should be made aware that these organizations have services to assist in coordinating research efforts and finding sponsors for orphan products. The Commission believes that many problems surrounding rare disease research could be resolved by better coordination between these groups.

### **Conclusion**

The Commission believes that rare disease research and product development would be enhanced by adequate funding and greater coordination. Information of all kinds, for patients and their families, physicians, researchers, insurers, and the public, is lacking or poorly disseminated. The financial burden of a rare disease or condition can reduce a family to poverty, particularly when insurance coverage is not available. In short, *the needs of patients with rare diseases are not being adequately met.*

### **The Need for an Advocate**

The Commission believes that progress in these areas must be made—and made quickly. If this is to be done, then patients and the persons most closely associated with them—family, physicians, investigators, and voluntary organizations—need an advocate in the Federal government. Congress should establish a Central Office of Orphan and Rare Diseases (COORD) in the Office of the Assistant Secretary for Health. The office should have an advisory council composed of Federal and non-Federal scientists, health professionals, representatives of voluntary organizations, and representatives of the pharmaceutical and insurance industries. The council would be responsible for an annual report to Congress highlighting progress and needs in rare disease research and orphan products development.

COORD would provide the strong central coordinating function under a broad mandate to deal with the complex issues of research funding, insurance practices, the interests and needs of pharmaceutical manufacturers and voluntary organizations, and the delivery of treatment by physicians and clinical investigators. The Commission believes that COORD, with its wide-ranging responsibilities as advocate, coordinator, and educator is needed to implement the recommendations presented in its report.

Specifically, COORD would:

- Foster the implementation of the recommendations of the National Commission on Orphan Diseases, especially access to health care and insurance,
- Respond to new needs and issues as they arise, including proposals for legislation and regulations with implications for persons with rare diseases,
- Collect, develop, and disseminate information on rare diseases,
- Promote a "Year of Rare Diseases" to educate the public,
- Subsume the current responsibilities of the Orphan Products Board, and
- Report to Congress on Federal activities related to rare diseases.

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## **PART I**

### **INTRODUCTION**

*“We all share equally in the risk of having a child with a genetic disease. Therefore, all of us ought to share in providing effective treatment to the unfortunate children affected by them.”*

*A Physician Who Treats Patients With Rare Diseases*

## Chapter 1

### THE COMMISSION AND ITS ACTIVITIES

The term “orphan diseases” is used to describe a staggering array of rare diseases and conditions with few common characteristics. Some of these diseases are hereditary, some are not. Some are present at birth, others do not appear until adulthood. Some are communicable, some are not. Some are treatable, others are not. Some are rare in the United States but endemic in developing countries.

What these diseases do have in common is their orphan status—that is, most of them have no parent organization, investigator, or company dedicated to research on prevention, diagnosis, or treatment of their victims. A rare disease or condition is defined in the Orphan Drug Act as one that affects fewer than 200,000 persons in the United States or that affects more than 200,000 persons in the United States and for which there is no reasonable expectation that the costs of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.<sup>1</sup> The terms “orphan” and “rare” are used interchangeably in this report. “Rare” better describes the Commission’s concerns, however, because even if a parent is available to advocate, do research on, or develop drugs for a disease, a special focus will always be needed to meet patients’ needs. This report does not include research on the Human Immunodeficiency Virus, the virus related to the Acquired Immunodeficiency Syndrome (AIDS).

Anyone can be affected— orphan diseases do not confine themselves to “other” people or “other” families. Millions of Americans suffer from one of the approximately 5,000 known rare diseases. Some of them, such as Huntington’s disease, muscular dystrophy, sickle cell disease, and multiple sclerosis, are familiar to most people. Others, such as osteogenesis imperfecta, autism, or reflex sympathetic dystrophy, are not.

The costs of rare diseases, in both monetary and human terms, are enormous. The medical expenses of a person with cystic fibrosis, for example, range from \$10,500 to over \$100,000 per year, depending on the severity of the

disease and the frequency of hospitalizations. In addition, a person with a rare disease can account for millions of dollars in special education costs, Social Security disability benefits, housing assistance, and lost tax revenues.

The human costs are even higher. Patients and their families must struggle with disabling and sometimes disfiguring illness and suffer loss of educational and employment opportunities, human potential, family life, and physical and mental abilities. Not just the patient, but every member of the family is affected.

The outlook is not altogether bleak, however. Patients and their families are organizing into groups to support each other. Investigators are pursuing research on rare diseases, and industry is developing new products. Progress is being made, but it is slow—often unnecessarily so.

Responding to recurrent problems impeding rare disease research and product development and to voluntary organizations’ pleas for action, Congress established the National Commission on Orphan Diseases in August 1985. (See Appendix A for the enabling legislation and list of Commission members and Appendix B for the charter creating the Commission.) The Commission met for the first time in January of 1987.

### THE PURPOSE OF THE COMMISSION

#### *CHARGES*

The Commission was charged with assessing the status of research on rare diseases, the dissemination of information about rare diseases to all communities in need of such information, and the problems pertaining to rare diseases in general. Specifically, the Commission was charged with assessing the activities of the National Institutes of Health (NIH), the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), the Food and Drug Administration (FDA), public agencies, and private entities in four areas:

- Basic research conducted on rare diseases;
- The use in research on rare diseases of knowledge developed in other research;
- Applied and clinical research on the prevention, diagnosis, and treatment of rare diseases; and
- The dissemination to the public, health care professionals, investigators, and drug and medical device

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This report does not include research on the Human Immunodeficiency Virus, the virus related to the Acquired Immunodeficiency Syndrome (AIDS).

manufacturers of knowledge developed in research on rare and other diseases that can be used in the prevention, diagnosis, and treatment of rare diseases.

In assessing the research activities of the NIH, ADAMHA, and FDA, the Commission was asked to review:

- The appropriateness of the priorities currently set on research on rare diseases;
- The relative effectiveness of grants and contracts used to fund research on rare diseases;
- The appropriateness of specific requirements for applicants seeking funds for research on rare diseases, taking into consideration the reasonable ability of applicants to meet such requirements;
- The adequacy of the scientific basis for such research, including the adequacy of the facilities and resources used and the appropriateness of the scientific training of the personnel;
- The effectiveness of activities undertaken to encourage research;
- The organization of the peer review process for granting research funds, to determine if it could be made more effective for reviewing proposals for research on rare diseases;
- The effectiveness of the coordination of research activities among Federal agencies and private entities; and
- The effectiveness of activities undertaken to ensure that knowledge developed in research on non-rare diseases is used in research on rare diseases.

## **THE COMPOSITION OF THE COMMISSION**

The Commission was composed of individuals who have a rare disease themselves or whose family members have a rare disease, health professionals experienced in research on and treatment of rare diseases, scientists conducting research on rare diseases, representatives of voluntary organizations, and senior scientists or administrators from selected Federal agencies.

## **THE STUDIES OF THE COMMISSION**

The Commission conducted 11 public meetings and 4 public hearings, as well as interviews, work group meetings, round-table discussions, and telephone surveys of patients, physicians, and investigators. Written questionnaires were submitted to Federal agencies. The American Medical Association (AMA) assisted the Commission by conducting a survey of practicing physicians. Individual members of the Commission or their organizations sponsored surveys of voluntary organizations and private foundations. The Pharmaceutical Manufacturers Association,

the Generic Pharmaceutical Industry Association, the Orphan Developers Coalition and the Association of Biotechnology Companies surveyed member companies to determine their experiences with rare disease research.

At its various meetings the Commission discussed with special interest the following subjects:

- The drug approval process at FDA,
- The extramural and intramural programs of NIH,
- Rare disease research activities of the FDA, NIH, ADAMHA, the Centers for Disease Control (CDC), and the Orphan Products Board,
- Medicare, Medicaid, and health insurance,
- The Small Business Innovation Research program,
- Activities of foundations and voluntary health agencies, and
- The National Center for Toxicological Research.

In addition, the Commission heard presentations on the implementation of the Orphan Drug Act, activities of the National Library of Medicine, activities of the Office of Medical Applications of Research, the General Clinical Research Centers, and the AMA's Health Policy Agenda for the American People: Special Applications to Rare Diseases.

## **HEARINGS**

The Commission held four hearings between June 1987 and February 1988 in order to obtain testimony from members of the public concerned about rare diseases. The hearings were announced in the *Federal Register* and were held in San Francisco, California, on July 16-17, 1987; Washington, D.C., on September 17-18, 1987; Chicago, Illinois, on November 5-6, 1987; and Dallas, Texas, on February 4-5, 1988. In addition to the announcements, over 2,000 investigators, health care providers, and members of voluntary organizations were invited to attend and participate in these hearings.

Approximately 230 persons attended the meetings; 100 made oral presentations, and 21 persons who were unable to attend submitted written testimony. Of these 121 persons, 42 represented rare disease voluntary organizations, 26 were patients with rare diseases, 33 were health care professionals (both clinicians and investigators), 3 were medical students, 15 were parents or family representatives, and 2 were from the pharmaceutical industry.

Testimony focused on four general areas of concern:

- Information needs,
- Research and research training needs,
- Health care needs, and
- Professional education needs.

The Commission was impressed by the range of concerns expressed by these individuals and is especially grateful

to the patients, some of whom endured considerable pain and physical hardship in order to testify. From the patients the Commission learned that rare diseases can be extremely difficult to identify and manage, requiring years of searching for a diagnosis and referral to appropriate sources of help. Persons with complex, baffling symptoms are often misdiagnosed: frequently, they are viewed as having psychiatric disorders or are stigmatized because of their disease. Patients exhibit extraordinary courage as they face degenerative disorders; increasing physical barriers at home, at work, and in transportation; and poverty from high medical care costs. Many also face early death.

In the parents of children with rare diseases, the Commission saw anguish. These parents described their realization that something was wrong with their child; their search, often in vain and at great expense, for a diagnosis, referral, and treatment; and their efforts to find the speech or physical therapy, special education, medical foods, or prosthetic devices their child needed. Frequently these needs were not covered by insurance; sometimes parents' insurance policies were canceled. Whatever their situation, the lives of these families were changed radically.

The Commission also heard from volunteers—those patients, primary caregivers, spouses, or parents who, having survived the ordeal of learning about the disorder and how to cope with it, work to help others. It learned how volunteers work to improve public awareness of and medical and support services for rare diseases, raise funds for research, organize support groups, publish and distribute educational pamphlets and newsletters, and maintain lists for referrals. The individuals who undertake these activities, often at great personal, financial and emotional expense, are to be commended for their efforts.

Some of the investigators who testified before the Commission said they had received sufficient funding to develop orphan products; many others, however, were concerned that Federal budget cuts will prevent work on promising ongoing projects. These investigators fear that scientists will seek "safe" funding in common diseases and that there are few incentives for persons considering a research career in rare diseases. Despite considerable difficulty, several persistent investigators have succeeded in bringing the products of their research to the marketplace. The Commission commends these investigators but recognizes that most academic scientists do not have the resources to pursue the development of a new drug without encouragement from the FDA, extensive support services and financing.

## ***SURVEYS***

The Commission developed and conducted its surveys in conjunction with the National Center for Health Statistics, the Department of Survey Design and Analysis of the AMA, and the consulting firms of Hamilton, Frederick,

and Schneiders, Inc., Chilton Research Services, Inc. and Macro Systems Inc. Seven groups were surveyed: patients, physicians, investigators, Federal agencies, private foundations, voluntary organizations, and pharmaceutical manufacturers.

### **Patients**

In June and July 1988, the Commission obtained a list of persons who had inquired about rare diseases at the National Organization for Rare Disorders (NORD) and surveyed by telephone 801 randomly selected patients or their caregivers (representing an 89 percent response rate). The Commission asked questions about:

- The ramifications of coping with a rare disease, including effects on and quality of life,
- The kind of information needed by patients and their families to better understand the disease,
- The nature and sources of information on rare disease research that have been most helpful to patients and their families,
- The importance of voluntary support groups in helping patients cope with their disease,
- The willingness of patients to take an investigational drug when approved effective drugs are not available,
- The willingness of patients to participate in research studies,
- The accessibility of treatments, and
- Barriers to diagnosis and treatment of rare diseases.

The following are key findings from the patient survey:

- Sixty-eight percent of respondents indicated a willingness to use an investigational drug; 12 percent had actually done so.
- Forty-two percent reported that their illness prevents them from working or attending school; an additional 32 percent who are able to work said the amount or type of work they could do was limited because of their illness.
- Forty-three percent said their illness caused an extreme financial burden on the family.
- Nine percent of patients had no health insurance and an additional 7 percent have insurance that does not cover their illness.
- Physician specialists (42 percent) and family physicians (19 percent) were the two primary sources of information for patients.
- A majority of respondents found it difficult to locate information on
  - ☆ research projects they could participate in (76 percent),
  - ☆ new treatments (74 percent),
  - ☆ research advances (73 percent),
  - ☆ the existence of appropriate voluntary support groups (68 percent),
  - ☆ written, easy-to-understand information about their illness (61 percent), and
  - ☆ the location of treatment centers (57 percent).

These statistics are likely to be even more dramatic for the many patients and their families who have not been in touch with NORD or other voluntary organizations.

### Physicians

The survey of physicians was conducted for the Commission by the AMA in June and July 1988. Physicians who spend 25 percent or more of their professional time in direct patient care (343,856 physicians) were included in the study population, and a stratified random sample of 440 physicians was selected for the survey. Of these physicians, 316 were interviewed and 270 completed the survey, yielding a response rate of 85.4 percent. The survey was designed to provide data about:

- The sources of information used to diagnose and treat patients with rare diseases,
- The willingness of physicians to prescribe investigational drugs and devices,
- Attitudes toward possible actions to support research on rare diseases,
- Suggestions for improving the dissemination of information about rare diseases,
- Barriers to diagnosis, treatment, and prevention of rare diseases, and
- The importance of voluntary support organizations to patients with rare diseases.

The following are key findings from the physician survey:

- Forty-two percent of physicians say they need, but are unable to find, printed information to give to patients concerning their illness.
- Thirty-nine percent report having prescribed investigational drugs or devices; of that number, 92 percent would do so again. Only 27 percent of the 150 physicians surveyed who had not prescribed investigational drugs reported that they had never considered prescribing such a product. However, if the illness was life threatening, 92 percent would prescribe an investigational product.
- Ninety-one percent of physicians agreed that limiting the legal liability for doctors who prescribe investigational products would help support research on rare diseases.
- Forty-eight percent need more information and would be very hesitant and an additional 40 percent would be somewhat hesitant to prescribe an investigational drug or device; 26 percent indicated concern for the patient's safety and possible side effects as deterrents.
- Pharmaceutical companies were the most frequently cited source of information by physicians in diagnosing or treating rare disease patients.

### Investigators

In July and August 1988, the Commission surveyed a sample of 659 investigators selected from 12,632 who had

applied to six NIH institutes for grants. The 604 respondents, representing a 91.7 percent response rate, included 303 investigators into rare diseases and 301 into common diseases. Of the respondents, 67 percent were Ph.D.'s and 34 percent were M.D.'s. The investigators were questioned about:

- Factors that were instrumental in stimulating their interest in rare disease research,
- The availability and accessibility of funds for disease-specific research,
- Sources of information about funding and respondents' persistence in learning about them,
- Respondents' experiences with coordination between public and private funding sources,
- Respondents' experiences with private and public grant review processes,
- Barriers (both intramural and extramural) to conducting disease-specific research, especially in the area of rare diseases, and
- Barriers to obtaining funding for disease-specific research.

The following are key findings from the survey of investigators:

- Both rare and common disease investigators agree that it is easier to get funding for basic and clinical research on common diseases than for basic and clinical research on rare diseases.
- Thirty-seven percent of respondents identified lack of research funds as the single greatest barrier to the discovery of treatments for rare diseases.
- Availability of patients appears to be a bigger problem for rare disease investigators than for common disease investigators.
- Both groups gave the government funding process (that is, peer review) a higher rating than the processes private institutions use when judging proposals for research projects on the basis of scientific merit.
- Sixty-five percent of rare and 85 percent of common disease investigators would turn first to the Federal government for funding of basic research; however, only 42 percent of rare and 61 percent of common disease investigators would turn first to the government for funding of a clinical study. Twenty-two percent of the rare disease investigators would go to voluntary rare disease organizations for funding of a clinical study.

### Federal Agencies

In January 1988, Federal agencies were surveyed to identify the type and extent of their involvement in biomedical and behavioral research relating to orphan diseases. The Commission identified 31 Federal agencies likely to support projects related to orphan disease research. These included 24 institutes or agencies located in:

- National Institutes of Health,

- Alcohol, Drug Abuse, and Mental Health Administration,
- Centers for Disease Control,
- Food and Drug Administration, and
- Health Resources and Services Administration (HRSA),

and 7 Federal departments or agencies outside the Public Health Service:

- Veterans Administration,
- Department of Defense,
- Department of Education,
- National Aeronautics and Space Administration,
- Department of Energy,
- United States Department of Agriculture, and
- United States Agency for International Development.

Twenty-eight of the 31 agencies responded to the survey, which focused on the following:

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

The following are key findings from the survey of Federal agencies:

- The Federal sector funds the largest portion of rare disease research. In fiscal year (FY) 1987, \$1.3 billion was obligated to rare disease research, \$1.15 billion of that amount by NIH; more than 50 percent (\$662 million) of all Federal funds spent on rare disease research was spent on research on rare forms of cancer (these figures exclude funds designated for AIDS research).
- Few agencies are rare disease-specific; most do not have special mechanisms to stimulate research on rare diseases. Successful recompetition for grants is the main mechanism for stable, long-term funding of research.
- Those organizations involved in product development report active cooperation with the private sector, including manufacturers, voluntary organizations, and academia.
- Nine clearinghouses or information centers were reported to disseminate information both to the public and to health professionals. Only one of these, the National Information Center for Orphan Drugs and Rare Diseases (NICODARD), funded by FDA, is rare disease-specific; the others provide information on rare diseases in the context of their normal operations.

## Private Foundations

The Foundation Center in Washington, D.C., assisted in identifying 277 foundations supporting health-related activities at a level of \$100,000 or more per year. The 106 foundations responding to the survey (reflecting a 38 percent rate of response) were asked questions about:

- the types of grants they funded,
- peer review mechanisms,
- their priorities, and
- restrictions on the grants they award.

The Commission also sought another estimate of the extent and nature of rare disease-related medical research funded by foundations by examining grant titles listed in the 1987 *Medical Research and Advancement*, published by the Foundation Center. This publication lists 1,002 grants, totaling over \$156 million, from 175 foundations to hospitals, medical colleges, and other medical institutions and associations for scholarships and fellowships, equipment, building construction, research, rehabilitative medicine, and general program needs.

The following are key findings from the survey of foundations:

- Forty-five reported policies that prevent the funding of grants on specific rare diseases.
- Seven indicated they fund grants that stimulate the entry of scientists and physicians into biomedical research on rare diseases.
- Twelve reported funding rare disease-related grants; 1.3 percent (\$1.6 million) of the total budget of these 12 foundations is devoted to rare disease research.
- Thirty-eight of the 1,002 grants reported in *Medical Research and Advancement* are considered rare disease-related; these grants represent 2.8 percent of the total \$156 million in medical research grants.
- Twenty-five of the 175 foundations listed in *Medical Research and Advancement* supported medical research grants on rare diseases.

## Voluntary Organizations

The National Organization for Rare Disorders conducted a survey for the Commission 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 to 217 organizations listed by NORD and the Commission; 113 organizations responded (a rate of 52 percent).

The following are key findings from the survey of voluntary organizations:

- 25 percent of the organizations were unable to provide an estimate of the prevalence of the rare

disease or condition in question because epidemiological data do not exist.

- About half reported that medical costs for a patient with a rare disease ranged from \$9,500 to \$115,000 per year, the other 50 percent did not report any costs.
- Fund raising and membership contributions are the main sources of funds for 72 percent; 50 percent received some corporate contributions as well.
- Their most important activities are
  - ☆ educational materials for patients (81 percent),
  - ☆ newsletters (68 percent),
  - ☆ educational programs for patients (62 percent), and
  - ☆ educational material for health care professionals (61 percent).
- National files and registries of various types are maintained by many of the organizations: 31 percent maintain a patient file; 39 percent maintain a physician or investigator file; and 10 percent support biological repositories, such as tissue, blood, or brain samples.
- Research grants were supported by 44 percent of the organizations; half of these organizations awarded 3 or more per year.
- Twenty-nine percent provide seed money to stimulate scientists and physicians to enter into research on their disease; 72 percent of these reported that investigators eventually obtained Federal funding.
- Eighteen organizations reported coordination or cofunding of educational or research projects with the Federal government, 16 with the pharmaceutical industry, 19 with foundations, 31 with universities, and 15 with other voluntary organizations focusing on the same disease or condition.

### Pharmaceutical Manufacturers

The Pharmaceutical Manufacturers Association (PMA), in conjunction with the Commission staff, developed a questionnaire to collect information on the following:

- Extent of rare disease research and orphan product development activities related to marketed and investigational products,
- Utilization of existing incentives for orphan product development,
- Need for additional incentives to stimulate research on rare diseases,
- Extent of coordination of rare disease research and orphan product development activities with the private and Federal sectors, and
- Information dissemination activities.

The questionnaire was sent to member firms of the PMA, the Association of Biotechnology Companies, the Generic Pharmaceutical Industry Association, and the Orphan Developers Coalition. Responses were received

from 17 member firms of the PMA, 6 member firms of the Orphan Developers Coalition, 3 member firms of the GPIA, and 11 member firms of the Association of Biotechnology Companies.

The following are key findings from the survey of pharmaceutical manufacturers:

- The right to exclusive marketing is considered the most important incentive of the Orphan Drug Act.
- Thirty-seven marketed products were identified; six additional marketed products had New Drug Applications (NDAs) pending before the FDA.
- Eighty-one products are under investigation.
- Over \$54 million was spent on orphan product research and development in 1987.
- Development costs for products identified in the survey totaled \$190.3 million.
- Anticipated future expenditures for investigational products were \$95.4 million.
- Extensive coordination of product development activities with public and private sectors was reported.

### THE REPORT OF THE COMMISSION

The Commission's report is based on the testimony and presentations it heard and on data from its surveys and questionnaires. This volume summarizes the Commission's findings and groups them into the broad areas of patients' needs, research, product discovery and development, and conclusion. Details of the studies are provided in a companion volume. The Commission's recommendations are presented in appropriate places throughout the report and are grouped together in Appendix C.

Many of the Commission's findings give cause for concern. Information of all kinds, for patients and their families, physicians, investigators, insurers, and the public, is lacking or poorly disseminated. The financial burden of a rare disease or condition can reduce a family to poverty, particularly when insurance coverage is not available. Rare disease research and product development are largely uncoordinated and underfunded. In short, *the Commission found that the needs of patients are not being adequately met*. It recommends the establishment of a Central Office of Orphan and Rare Diseases (COORD) to help address these needs.

At the same time, the Commission was heartened by the efforts of many of the individuals and organizations it encountered. While there is at present no way to eliminate the suffering that patients with rare diseases and their families must undergo, the Commission believes that society can do a great deal to alleviate that suffering. Its report is grounded in that belief.

## Chapter 2

### HISTORICAL PERSPECTIVE

The word "orphan" was first used in medicine in connection with the use of drugs in infants and children. In an attempt to protect the public from untested and unsafe drug products, Congress passed the Food, Drug, and Cosmetic Act of 1938 requiring manufacturers to provide evidence of product safety and to include warnings on labels. The Kefauver-Harris amendments in 1962 required that all drug products be effective. This legislation, combined with ethical concerns about testing drugs on infants and children, resulted in a population for whom few drugs were available—a population that Shirkey described in 1968 as "therapeutic orphans."<sup>2</sup>

Subsequently, Provost described "homeless" drugs as substances or drugs, such as shelf chemicals, intended for chemical, laboratory, or manufacturing purposes and not approved for human consumption.<sup>3</sup> Many of these chemicals were used in clinical practice, however, and were demonstrated to be efficacious. Because of their small target populations or inability to be patented, as well as the costs of meeting FDA requirements, these drugs did not appear profitable enough to warrant commercial interest. Althuis defined orphan drugs as agents that have potential benefit for the treatment of diseases but no commercial sponsors.<sup>4</sup> Asbury and Stolley expanded the definition to include drugs for use in diseases rare in the United States but endemic to developing countries, for example, parasitic and infectious diseases.<sup>5</sup> The concept of orphan diseases was a logical extension of the concept of orphan drugs.

### LEGISLATIVE ACTION

Congress began considering bills to enhance orphan drug development in 1978. By 1981, none had been passed, but congressional interest in the problem was building. In that year, the House Subcommittee on Health and the Environment surveyed independent investigators, the pharmaceutical industry, and Federal agencies in an effort to identify orphan drugs. Of the 134 products identified, 34 were marketed and 100 were under development—10 by the pharmaceutical industry and 90 by the Federal government or university investigators. The study also identified numerous barriers to the development of orphan drugs and suggested that certain aspects of research in general were impeding progress in understanding rare diseases and developing drugs.

A number of these barriers were removed by the Orphan Drug Act (P.L. 97-414) signed into law January 4, 1983. This act and its subsequent amendments were intended to facilitate the development and availability of drugs and biologics of little commercial value (orphan drugs) for rare diseases or conditions. The act included the following major provisions:

- Written protocol assistance from the FDA for the study of drugs to be used for rare diseases or conditions;
- "Orphan" designations for drugs and biological products for rare diseases or conditions, the term "rare disease or condition" being defined as any disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from domestic sales;
- Seven-year exclusive marketing privileges for designated unpatentable orphan drugs and biologics;
- Encouragement for sponsors of orphan drugs to develop and distribute investigational new drugs for treatment purposes under open protocols so that such drugs will be available to patients as early as possible (this was intended to make investigational drugs available to patients who could not participate in controlled clinical trials);
- An Orphan Products Board to coordinate Federal efforts in orphan product development and to submit an annual report on orphan drug activities to Congress;
- Tax credits equivalent to 50 percent of the costs incurred in conducting clinical trials on orphan drugs (this represents a significant tax advantage over previous laws, which simply allowed a deduction for these costs); and
- Authorization of up to \$4 million per year for three years to fund grants and contracts for clinical studies of orphan drugs.

The Health Promotion and Disease Prevention Amendments of 1984 (P.L. 98-551) redefined a rare disease or condition as one that affects fewer than 200,000 persons in the United States or that affects more than 200,000 persons in the United States but for which there is no reasonable expectation that the costs of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.<sup>6</sup>



The Orphan Drug Amendments of 1985 (P.L. 99-91) established the National Commission on Orphan Diseases and included the following provisions: <sup>7</sup>

- Extension of the exclusive marketing rights provision of the Orphan Drug Act to include patented and patentable products;
- Extension of the grants and contracts authority through 1988;
- Permission to fund grants and contracts for preclinical testing, including animal studies; and
- Extension of provisions of the Orphan Drug Act to include antibiotics.

The 1986 Tax Reform Act extended the tax credit of 50 cents on every dollar spent on rare disease research until 1990.<sup>8</sup> The Orphan Drug Amendments of 1988 (P.L. 100-290) revised the Food, Drug, and Cosmetic Act as it related to orphan drugs <sup>9</sup> and:

- Required requests for orphan drug designation to be made before submission of an application for product approval, certification, or licensing;
- Required sponsors of approved, designated orphan drugs to notify the Department of Health and Human Services (DHHS) at least one year in advance of any plans to discontinue production of the product;
- Required sponsors of nonapproved designated drugs to notify DHHS of any decision to discontinue active pursuit of approval for the product;
- Permitted grants to be used to help defray the costs of developing medical foods and medical devices for rare diseases or conditions;
- Defined a medical food;
- Directed DHHS to conduct a study to determine if incentives such as tax credits are needed to encourage the development of medical foods and medical devices for rare diseases or conditions; and
- Extended grant-making authority through fiscal year 1990 and increased the amount of money authorized for orphan drug research to \$10 million, \$12 million, and \$14 million in fiscal years 1988, 1989, and 1990, respectively.

Congress passed several bills during the early 1980s that indirectly affected rare disease research and the development of orphan products. The Stevenson-Wydler Technology Innovation Act of 1980 (P.L. 96-480) and the Federal Technology Transfer Act (P.L. 99-502) provided for cooperative industry-university research and for innovation and the transfer of technological advances.<sup>10,11</sup> The Uniform Federal Patent Policy Act of 1980 (P.L. 96-517) amended existing patent and trademark laws to allow small businesses or universities to hold the rights to inventions developed with Federal funds.<sup>12</sup> The Small Business Innovative Development Act of 1982 (P.L. 97-219) stimulated small and minority businesses to seek Federal sup-

port for research and development and encouraged the commercialization of federally sponsored technological advances.<sup>13</sup>

## **OTHER FEDERAL ACTION**

### **DRUG DEVELOPMENT**

The Federal government began to develop orphan drugs early in this century. The Hygienic Laboratory of the Marine Hospital Service, the forerunner of NIH, developed vaccines for Rocky Mountain spotted fever and typhus in the early 1900s. During World War II, the laboratory, in conjunction with the pharmaceutical industry, developed chloroquine for the treatment of malaria and assisted in the mass production of penicillin.

In 1955, the National Cancer Institute (NCI) initiated a cancer drug development program. Since that time, 12 more disease-specific drug programs have been initiated (Table 1). These collaborative programs frequently involve universities, the pharmaceutical industry, and NIH intramural and extramural research and are important in product development.

### **COMMISSIONS AND TASK FORCES**

Beginning in the 1960s, several task forces and commissions addressed the problem of orphan drugs and rare diseases. A Public Health Service (PHS) task force in 1964 investigated the possible shortage of public service drugs—that is, drugs not intended to make a profit for the manufacturer but provided as a service in PHS hospitals.

In 1974, the FDA's Bureau of Drugs set up an Interagency Committee on Drugs of Limited Commercial Value to review drugs known to be useful but not available to the public. The committee report cited hazy definitions, limited government and industry support for development, and legal and insurance questions as problems associated with these drugs. The report considered administrative actions, including economic incentives to develop orphan drugs, but concluded that the scope of the problem was beyond its mission. It recommended further study by FDA to fully define the problem and develop potential solutions.<sup>14</sup> In 1978, the Bureau of Drugs convened the Interagency Task Force on Significant Drugs of Limited Commercial Value to continue the work of the 1974 committee. The task force consisted of representatives from various agencies in the Department of Health, Education, and Welfare; several members of FDA advisory committees; scientific, economic, and legal consultants; and representatives of the pharmaceutical industry.

The group reviewed previous reports in an effort to formulate a policy that would solve the problems of inadequate resources and insufficient motivation for development and distribution.

**Table 1**  
**Federal Drug Development Programs**

<i>Disease/Condition/Drug</i>	<i>Responsible Agency</i>	<i>Year Initiated</i>
Cancer	National Cancer Institute	1955
Malaria/tropical diseases	Walter Reed Army Institute of Research	1963
Vaccines	National Institute of Allergy and Infectious Diseases	1965
Epilepsy	National Institute of Neurological and Communicative Disorders and Stroke	1968
Antivirals	National Institute of Allergy and Infectious Diseases	1969
Contraceptives	National Institute of Child Health and Human Development	1971
Caries (tooth decay)	National Institute of Dental Research	1971
Sickle cell disease	National Heart, Lung, and Blood Institute	1972
Narcotic abuse	National Institute on Drug Abuse	1972
Cooley's anemia	National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases	1973
Blood substitutes	National Heart, Lung, and Blood Institute	1974
Biological response modifiers	National Cancer Institute	1979
Human Immunodeficiency Virus Program	National Institute of Allergy and Infectious Diseases	1987

The task force concluded that the development of such drugs called for the combined support of government, industry, voluntary organizations, and others concerned with health care. It recommended the creation of an advisory board to the Secretary of Health, Education, and Welfare to act on applications for assistance in developing orphan drugs. It emphasized the importance of making orphan drugs available more quickly, without compromising the drug approval process, and it stated that responsibility for developing these drugs should lie with private industry, not the Federal government. The task force drew up a list of compounds whose development appeared to be languishing and a list of marketed and investigational drugs that had been made available by pharmaceutical firms for use in "uncommon diseases and conditions."<sup>15</sup>

In March 1982, DHHS created the Orphan Products Board to promote the development of drugs for uncommon diseases and coordinate the development of orphan drugs among Federal agencies, manufacturers, and voluntary organizations. The board, which advises the Assistant Secretary for Health, was established before the Orphan Drug Act became law but was mandated by the act to continue coordination of all Federal programs involved in orphan product development and rare disease research.

The Orphan Products Board has representatives from several Federal agencies: the FDA, NIH, ADAMHA, CDC, Department of Defense, Department of Education, Health Care Financing Administration, and Veterans Administration. Its surveys of Federal agencies have identified orphan products at early stages of development.

In May 1982, the FDA established the Office of Orphan Products Development (OPD) to spur research and development of promising products. The activities of OPD were later expanded to meet provisions of the Orphan Drug Act. That act and various amendments required FDA to provide written responses to requests for protocol assistance for preclinical and clinical investigations; allowed sponsors to request that a compound be designated as one for a rare disease or condition, in accordance with OPD guidelines; and entitled the first sponsor of a designated orphan drug who obtains market approval of the compound for a specific use to seven years' exclusive marketing rights.

The OPD seeks commercial sponsors for orphan drugs through contacts with manufacturers, publication of notices in the *Federal Register*, and interaction with private organizations. It fosters communication with FDA reviewers involved in the evaluation of an orphan product and brings together investigators with a promising therapeutic concept and representatives of the pharmaceutical industry. It tells investigators, sponsors, and manufacturers about sources of funding for research and itself awards grants and contracts to stimulate the development of orphan drugs. Despite these positive activities, FDA has not promulgated regulations to implement the Orphan Drug Act after six years of existence.

In addition, a number of disease-specific Federal commissions have been established in recent years: National Advisory Commission on Multiple Sclerosis, Commission for the Control of Epilepsy and Its Consequences, Commission for the Control of Huntington's Disease and Its Consequences, Task Force on Organ Transplantation, and the Presidential Commission on the Human Immunodeficiency Virus Epidemic. These commissions have studied rare diseases in depth and have offered useful information and advice to patients, providers, and Congress. The commissions' reports have been used to frame recommendations for legislation, establish programs, build visibility for diseases, and legitimize the special needs of patients.

## ACTIVITIES IN THE PRIVATE SECTOR

### THE PHARMACEUTICAL INDUSTRY

As previous task force studies and congressional surveys have shown, individual pharmaceutical companies have been involved in rare disease research and product development for a number of years, but no organized effort was begun until July 1981, when the Pharmaceutical Manufacturers Association created a Commission on Drugs for Rare Diseases. This voluntary effort was supported by a large segment of the industry and was intended to address the need for more rapid progress in orphan product development. The PMA commission invites and reviews research proposals from scientists, voluntary and government health agencies, and research institutions. When a proposal is rated favorably by the commission and its consultants, the commission gets in touch with potential sponsors. In addition, the PMA Foundation has begun a research award program to stimulate additional research on rare diseases and orphan products in universities.

Early in 1982, the Generic Pharmaceutical Industry Association (GPIA) formed an Institute for Orphan Drugs to fund investigator-sponsored research and make drugs more readily available. In several instances, the GPIA brought together corporate sponsors to share the funding of research projects. These projects have enabled investigators to continue providing lifesaving drugs to persons with orphan diseases.

In 1987, several smaller pharmaceutical companies organized themselves into the Orphan Developers Coalition. This group of small companies is unique in that it focuses exclusively on the development of drugs for rare diseases. It has been very active in this area, reacting quickly to research leads of investigators who need a sponsor to develop their product.

### VOLUNTARY ORGANIZATIONS

Persons with rare diseases and the organizations that represent them are significant forces in many of the research, development, and legislative activities surrounding

rare diseases. Voluntary organizations have established networks of local, state, and national associations that perform important, sometimes lifesaving, services for their members. They are a vital source of information for patients, families, and health professionals. They provide counseling, personal support, referrals, newsletters, and educational materials. Many fund research and pursue advocacy and lobbying efforts.

A key force has been the National Organization for Rare Disorders, founded in 1983. An umbrella organization with a membership of about 100 groups, it has created a data base on rare diseases that is available to subscribers of *Compuserve* and has begun to award grants to investigators.

## **PART II**

### **MEETING PATIENTS' NEEDS**

*“Our dreams for our daughter’s future turned to nightmares as we went from one specialist to another. No one could tell us what was wrong, or why, or how, or what to expect for the future. We lived with this uncertainty for 10 years until her neurologist attended a meeting where she learned of Rett Syndrome.”*

*—Parents of a Girl with Rett Syndrome*

## Chapter 3

### THE NEED FOR INFORMATION

*"I work with many individuals who have rare diseases. The greatest problem these individuals face is the fear of the unknown due to isolation and lack of information."*

*—Representative of a Voluntary Organization*

The most immediate need of anyone with a rare disease is an accurate diagnosis, followed closely by the need for treatment and support services and the need for some means of paying for care. This chapter describes the Commission's findings regarding the availability to patients of information on rare diseases, therapies, and services. Chapter 4 deals with the financing of care.

Patients of all ages, incomes, and geographical areas of the United States have experienced difficulty in obtaining information to meet their needs. The Commission found overwhelming evidence of:

- Difficulty in obtaining a timely and accurate diagnosis,
- Scanty information on rare diseases,
- and much of that incomplete or highly technical, and
- Inaccessible information.

#### TIMELY AND ACCURATE DIAGNOSIS

Diagnosing a rare disease is not easy. Physicians may find themselves attempting to identify a disease they have never seen before, often one with confusing symptoms.

From testimony and surveys the Commission learned that it took nearly one to six years or longer to obtain a diagnosis of their illness. Although physicians cannot be knowledgeable about all diseases, medical educators should train their students to utilize the medical literature and refer to experts and organizations with information on rare diseases when vague and confusing symptoms persist in a patient. About half of the patients in the Commission's survey reported receiving a diagnosis within a year of their first visit to a doctor. For nearly one-third of them, up to five years passed before their disease could be identified; 15 percent went without a diagnosis for six years or more. Patients feel isolated and misunderstood when physicians are unable to diagnose their illness correctly or promptly. Physicians, in turn, are often perplexed by the multitude of—and at times the vague and contradictory nature of—symptoms. Uncertainty about the characterization of some diseases contributes to the already lengthy process of arriving at a diagnosis.

#### INFORMATION ON DISEASES AND EMERGING THERAPIES

Once diagnosed, patients and their families are anxious to find out all there is to know about their disease and often become experts on it. They want information about the cause, prognosis, genetic basis (if any), and future manifestations of the disease; the availability of a cure or, if no cure exists, how to manage the disease; and information on research.

Patients also want information about voluntary support groups and treatment centers. If none exists in their own community, they seek farther—even abroad—for physical and emotional support. Information about such resources may not exist, however. Patients describe the experience of going from one person or organization to another in search of information, while trying to grasp the implications of their illness—usually in the emotional months following diagnosis and often in pain and in failing health.

A majority of respondents to the patient survey found it difficult to locate information related to their illness, specifically information on:

- Research projects for patient participation (76 percent),
- New treatments (74 percent),
- Research advances (73 percent),
- Voluntary support groups (68 percent),
- Written, easy to understand information (61 percent), and
- Location of treatment centers (57 percent).

#### SOURCES OF INFORMATION

##### PHYSICIANS

Most persons with rare diseases seek information from their physicians. They want to know how to cope with the physical manifestations of the illness; what services are available to offer medical, emotional, and financial support and comfort; and what approved therapies and experimental treatments may be available.

**Table 2**  
**Percentage of Physicians (N = 247) Who Were Unable to Find Information for Their Rare Disease Patients**

Type of Information Sought	<i>Result's of Respondents' Searches</i>			
	Did Not Find Information	Found Information	Did Not Know	Did Not Respond
Availability of treatment	21	75	2	1
Location of treatment	24	72	3	2
Name or address of support groups	35	58	5	2
Printed information for patients	42	51	5	2
Name or address of specialists treating the disease	27	70	2	1
Name or address of investigators studying the disease	30	65	4	2
Information summarizing ongoing research	33	62	3	2

\* Percentages read across and may not total 100.0 due to rounding.

Often, that information does not exist. Physicians are themselves frustrated at having nothing readily available to give their patients. As indicated in Table 2 there is a lack of various kinds of information.

Some patients seek information from other sources, including medical books and biomedical journals, which may be outdated, inappropriate, or difficult to understand.

### **VOLUNTARY ORGANIZATIONS**

One ally in the search for information on rare diseases is the voluntary organization. For many patients and their families, these private, non-profit organizations are the sole source of support and information about their disease. Most voluntary organizations are capable of and dedicated to educating patients, their families, physicians, and the general public. They may be small, grass-roots support groups formed by patients and their families, local organizations, or local chapters of large national organizations. Often, they are stretched to or beyond the limits of their financial and personal resources. Most rely on modest fund-raising efforts and donations to support their activities.

Many of the patients who testified at the Commission's public hearings were members or staff of relatively new voluntary organizations; some were associated with large, well-established voluntary organizations. The Commission views voluntary organizations as a national resource. They provide most, if not all, of their services at no charge to the individual or to the country. Patients describe their groups as considerate, kind, caring, compassionate, and understanding. Every effort should be made to maintain

their current status and provide them the opportunity to expand their activities.

Only a relatively small number of patients can participate in voluntary support groups, in part because there are so many rare diseases affecting only a few, widely scattered persons. Patients who find and participate in a support group are generally younger people; they give the group positive ratings for keeping them up to date on information and developments related to their illness. Many patients who have no group have overcome their isolation through letters, videotapes, audiotapes, and telephone conversations. Others have founded support organizations in their own community. By communicating with other patients and concerned families, they have found ways to locate what information there is. They have also found support and companionship, even at a vast distance.

In the Commission's public hearings, patients and their families expressed concern that there are not enough local or national support groups for rare diseases. The Commission found that patients who had a more difficult time to obtain a diagnosis were more likely to participate in a support group. While only 26 percent of patients who were diagnosed in less than a year belong to a rare disease support group, 36 percent of those who were diagnosed within one to five years belong, and 40 percent of those for whom it took more than five years belong. Furthermore, almost all of those who belong to a support group are satisfied with their group's performance on keeping them informed about their disease (40 percent reported their group's performance as excellent, 33 percent as good).

New groups for previously "unorganized" rare diseases are being formed, but they need nurturing and consideration from everyone in the private and public sectors.

One organization that has been very helpful to patients and voluntary support groups alike is the National Organization for Rare Disorders (NORD). NORD is a liaison and information link among more than a hundred voluntary health organizations and the public. It was created by a group of voluntary health agencies, medical investigators, and individuals concerned with rare diseases and provides a multitude of services to patients. It serves as a clearinghouse for information about rare diseases and helps patients and their families get in touch with other patients with the same disorder and their families. In addition to directly funding research through private and philanthropic contributions, the organization collects information about orphan diseases, drugs, and devices and makes its data base available to the public. NORD educates the public and medical professionals about the existence, diagnosis, and treatment of rare diseases. It provides technical support to fledgling support groups and helps established groups to achieve their goals and objectives.

Coalitions of voluntary groups are being formed to strengthen and broaden the effort to educate the public about rare diseases. After all, the public can be expected to become a partner in the fight against rare diseases only if it is made aware of them.

## GOVERNMENT AGENCIES

Patients do not usually look upon the Federal and state health agencies that support biomedical research on rare diseases as allies. Only 20 percent of the patients surveyed indicated they had requested information about their illness or treatment from the government. Congress and NIH were the most frequently mentioned sources of information. Fifty-seven percent of patients surveyed found the information provided useful.

Patients also indicated that they believe the government is not spending enough money on their disease because it is rare. Patients usually expect the budgets of these agencies to include funds for dissemination of information; however, dissemination of information is not usually a program priority. This is not to imply that agencies do not recognize the need for information. Indeed, they occasionally try to get information to health care professionals and expect it to trickle down to the patient. Such information may be disseminated through medical journals, conferences, or pamphlets that are available on request. In every case, getting information to patients through physicians is tangential to larger research programs, which usually focus not on rare diseases directly, but on disease groups that may include rare diseases. In agencies that have a budget for dissemination of information, rare diseases must compete for funds with common diseases and with preventive education programs for healthy people.

The Federal government, directly or indirectly, generates by far the greatest volume of information about rare diseases. This is done in-house or with extramural support at NIH, ADAMHA, FDA, CDC, and HRSA. Materials designed for distribution to the public include fact sheets (one- or two-page statements about specific diseases and their treatment, care, or prevention); booklets that describe in a more comprehensive way what a specific disease is and what can be done to help patients; and research reports, which, even when adapted for the public, may be somewhat difficult to understand. In the latter case, especially if a report is on an early phase of research, a patient may be unable to see the immediate application of new knowledge to his or her disease.

Patients are more likely to seek information from the government if it took them a long time to obtain a diagnosis. Also, people with higher incomes are more likely than people with lower incomes to contact the Federal government, whether their senator, their representative, or an executive agency such as NIH or ADAMHA. These findings from the patient survey have led the Commission to speculate that persons with less education, which is highly correlated with lower income, may be unprepared to consider approaching the government for information.

There is no central, Federal system to coordinate the dissemination of existing information. Federal agencies support at least nine information centers that carry information on some rare diseases. One of them, NICODARD, focuses entirely on rare diseases; however, its funding has been fluctuating over the years from \$25 thousand to \$150 thousand per year, with \$115,000 allocated by FDA in FY 1988. The other information centers are mainly for common diseases or disease groups but encompass various amounts of information on rare diseases.

Over the past two years it has become increasingly evident to the Commission that the pressing need for information is heightened by the absence of a coordinated national information dissemination system with a widely publicized focal point. If patients are not directed to existing information, information centers and clearinghouses will be underutilized.

To support patients in their search for information and to lighten the burden on physicians of providing it, a national information clearinghouse on rare diseases should be maintained. It could be an expansion of NICODARD, or it could be a new entity within the government or outside the public sector. Whatever the case, it will require stable, long-term funding. Besides providing information directly, a national clearinghouse on rare diseases should refer inquirers to regional clearinghouses, appropriate public and private information offices, and to clinical centers and individual investigators focusing on rare diseases. The



clearinghouse would rely on information collected from existing Federal and private clearinghouses. It would also actively search for updated and new information. The Commission is convinced that, once people know where to find information, they will seek it out.

### ***Fact Sheets and Other Nontechnical Information***

Fact sheets are simple, short descriptions of a disease, treatment, or regimen. They originate in Federal information offices, program offices, state health agencies, and voluntary health organizations and are intended for patients and health care providers. Unfortunately, publication budgets in the government are severely limited. As a result, many fact sheets are outdated and updates or new ones cannot be developed and printed.

Federal agencies follow the practice of providing printed information only when it is requested. This approach to distribution conserves limited resources and keeps printing costs to a minimum. Another technique for conserving resources is to delay revising and updating publications—thus the government can end up distributing outdated or inaccurate information about a disease.

One of the strongest concerns expressed at the Commission's public hearings was the apparent restriction on the development and publication of informational materials for persons with rare diseases. Voluntary organizations reported that they have encountered moratoriums on the printing and reprinting of Federal fact sheets, booklets, and other information. The Commission found that this is not precisely the case in Federal agencies, however.

When a program administrator determines that the resources are available to edit, update, or develop new printed materials for external distribution, the proposed project is subject to review by its agency. This review takes into consideration the availability of funds, need, expected utilization, and the relative standing of the publication in the agency's program priorities. If the proposal clears the agency, it is forwarded to the department. The department usually accepts agency recommendations once the need for the publication has been established within the constraints of the department's overall printing budget.

These reviews, as desirable as they may be from a managerial standpoint, create a de facto moratorium on the funding of publications on rare diseases. They force such publications to compete for funds on the basis of conventional cost-benefit ratios (small target population versus relatively high development costs). While the need for them may be great from the perspective of the patient or voluntary organization, the amount of expected use may be small because of the size of the target population.

Agencies are aware of this problem, and they respond that individual needs can be met by direct inquiries to an agency's public information office or to the central information office at NIH. Such offices draw upon a host of

resources and provide the "best" possible response, depending on the availability and nature of the information. There is no question, however, that publications specifically developed for persons with a particular disease are far more valuable than an institute's ad hoc response, no matter how well-intentioned.

The Commission therefore suggests that institutes and agencies review their funding practices for new or revised fact sheets and similar materials on rare diseases. A thorough internal review will most likely point to the adverse influence that utilization (as measured by the number of inquiries) has on the development of fact sheets on rare diseases. Further, fact sheets could be developed jointly with voluntary organizations, which might be able to provide information for a targeted mailing and to share printing and dissemination costs.

### **Recommendation:**

1. Congress should remove constraints on Federal agencies regarding the printing and distribution of rare diseaserelated information.

### ***Research Reports***

The amount of information about rare disease research and its potential clinical applications is overwhelming. It is often difficult, however, for voluntary agencies and lay persons to retrieve it. Even if they can, they may not be able to understand it. Most of it derives from federally supported research and must, by law, be available to the public once it is reported by the investigator to the funding agency, yet most of it is technical information and needs to be translated into an easily understandable form.

Such an undertaking is complex and requires a coordinating office. This office would have to develop close ties to the research community and program administrators in relevant Federal agencies in order to stay abreast of progress in rare disease research and product development. The office would coordinate materials and requests for information with investigators and program administrators; thus making this source of information accessible.

## **ACCESS TO INFORMATION ON PRODUCTS AND TREATMENTS**

Persons with rare diseases need information on where to obtain treatment, whether approved or investigational, and on what services are available to them and their families.

### ***PRODUCTS APPROVED FOR MARKETING***

Because of the high costs of developing a product and meeting FDA requirements for premarketing approval, many firms do not seek approval for additional uses of an approved product (see Chapter 7). As a result, physi-

cians lack complete prescribing information on some products for uses other than those approved by the FDA and which would result in better treatment of some rare diseases. This practice results in a system in which only a few patients benefit from the experience or expertise of a physician who remembers reading or hearing about a new treatment for a particular disease. As a result, many patients could go for years without receiving the benefits of an available therapy. Further, participants at the Commission's hearings indicated that many third-party payers are reluctant to reimburse for uses of products outside the approved indications (see Chapter 4).

### **EXPERIMENTAL DRUGS AND TREATMENTS**

The Commission found that, while patients are generally willing to participate in clinical trials, they often do not know that trials are being offered, or where. In the Commission's survey of rare disease patients, 68 percent indicated a willingness to consider using an experimental treatment. Investigators, on the other hand, often have great difficulty locating patients to participate in trials.

Patients and their families testified and indicated in the survey that the inherent risk of experimental drugs is the greatest barrier to taking them. In the absence of any other treatment, however, patients are often willing to take that risk. Nearly 48 percent of physicians surveyed reported that they would be very hesitant and another 40 percent indicated they were somewhat hesitant to prescribe an investigational drug or device if information about the product were limited. Misunderstandings about trial design can also prevent appropriate communication between investigators and patients. For example, investigators should explain to patients the importance of double-blind studies, in which one group is given an experimental product and another may be given a placebo—and neither group knows which is which.

It is therefore essential to get information about ongoing research to all groups as early as possible. When the

recruitment of patients for a clinical trial becomes difficult, investigators need to work closely with voluntary organizations to inform patients about study design and to promote participation.

### **BARRIERS TO SERVICES**

In addition to medical concerns, patients and their families reported their struggles to obtain appropriate special education services, transportation, counseling, vocational rehabilitation job support, respite care, community-based placements, and other related services. Eligibility for Federal and state services for persons with disabilities and their families is often tied to specific diagnoses or categories of disease. Such lists of diagnoses or categories exclude persons with some rare diseases. For example, The Social Security Administration determines eligibility for disability benefits and insurance on the basis of its *Listing of Impairments*. Patients with rare diseases are often denied these benefits because their specific illnesses are not listed. This forces them to pursue a lengthy and expensive appeals process. With over 5,000 rare diseases known to exist, and the number growing, it is impossible to maintain a current and complete list of disorders.

#### **Recommendations:**

2. Federal and state educational agencies should amend regulations to ensure that persons with rare diseases are not denied appropriate special education services, as mandated by P.L. 94-142.
3. The Social Security Administration should revise the *Listing of Impairments* to determine eligibility for benefits by descriptions of generic problems in addition to specific diagnoses. Similarly, other public and private agencies, such as Crippled Children's Services and Developmental Disabilities Services, should determine eligibility for benefits on the basis of generic problems rather than on lists of disorders alone.

## Chapter 4

### FINANCING PATIENT CARE

*Medical insurance is an overwhelming problem. My employer considers me and my family a liability because our medical policy cost is going up and my son's hemophilia is contributing to the increased cost. Management is constantly looking at and commenting on our medical insurance expense. I shrink and hide and feel guilty.*

—Parent of a Boy with Hemophilia

Americans obtain individual and family health insurance in one of three ways:

- They are provided group insurance by their employers,
- They pay directly for an insurance policy themselves, or
- If they are elderly, disabled, or very poor, they are assisted by public programs such as Medicaid or Medicare.

Most health insurance is obtained as group insurance through employers: approximately 165 million Americans under the age of 65 are covered by some type of group health insurance. More than 1,200 private insurance companies provide group or individual health insurance for over 100 million people; of this number, 78.7 million are covered by Blue Cross, Blue Shield, or joint plans. Health maintenance organizations (HMOs) and self-insured or self-administered plans cover 55 million persons, and 10 million are covered solely by individual health insurance.

In 1986, Blue Cross/Blue Shield paid an estimated \$77.39 billion in benefits; the other private insurance companies paid a total of \$64.3 billion. In 1987, national spending on health care reached \$438.9 billion. The average American spent \$1,721 on health care, and insurers paid an average of \$2,140 per policyholder in claims.<sup>16</sup>

At least 37 million Americans have no health insurance.<sup>17</sup> Their employers do not provide it, they cannot afford it, or they are deemed uninsurable because of a preexisting medical condition. Twenty-eight million more are underinsured. Persons with rare diseases are often uninsurable; those who have insurance often find it inadequate, expensive, or difficult to obtain.

#### INSURABILITY OF PERSONS WITH RARE DISEASES

Millions of Americans experience financial difficulties because of their rare disease. The quality of life for these

patients and their families does not reach the norm for most other Americans. In the Commission's survey of patients, 25 percent reported that health insurance covered only part of their medical expenses, 7 percent had policies that excluded coverage of their illness, and 9 percent had no health insurance at all. These numbers are likely to increase as more restrictive underwriting standards are adopted.

#### DISCRIMINATION

Medical insurance plans often exclude or limit benefits for a preexisting injury or illness, whether rare or common. Sometimes, limitations are lifted after a specified period of time, for example, on the earliest of the following dates: (1) the end of three consecutive months during which no charges were incurred for the preexisting condition or related conditions; (2) the end of six consecutive months during which the employee was continuously insured and actively at work; or (3) the end of 12 consecutive months during which the employee was continuously insured. In such cases, the preexisting condition may be covered on the same basis as any other condition. In other cases, however, an employee covered by a group policy has no guarantee that a chronically ill child or spouse will ever be covered by the policy. This practice creates a group of people who are in great need of insurance but who are unable to obtain adequate coverage.

During its proceedings, the Commission learned of many patients who were unable to obtain adequate—indeed, any—health insurance because of third-party payers' lack of information or misinformation about their rare disease or because payers would not insure their preexisting condition. This discrimination may persist despite determined efforts by individuals and voluntary organizations to give insurers information about the cause, occurrence, clinical history, treatment, and expected outcome of a disease or condition. Insurers are not required to justify their decisions about whom they will cover or to what extent.

The Commission recognizes that some persons with rare diseases do in fact represent a high-risk to insurance companies because their diseases or conditions are costly to treat. These persons are generally unable to obtain or retain insurance coverage.

The Commission is very concerned that all persons with rare diseases or conditions have some type of health insurance coverage. It offers the following suggestions for meeting the insurance needs of these persons:

- Medicaid buy-in,
- Medicare eligibility,
- Risk pools,
- Catastrophic insurance buy-in, and
- Uniformity of Medicaid program benefits.

No one of these options will suffice: some combination of them will be necessary to meet the various needs of the millions of persons with rare disease who have inadequate or no health insurance. The Commission believes that everyone in the United States should have access to health care.

## **GROUP HEALTH INSURANCE**

Group health insurance underwriting is based on the premise that in any large group of individuals there will be only a few persons with medical conditions severe and frequent enough to make them uninsurable risks by individual underwriting standards. Insurers evaluate the risk factors of the group, not the individuals it comprises, and evidence of insurability is seldom required for individual members of large groups. Most premiums for large group policies are based wholly or partly on the group's health experiences rather than on the health experience of all subscribers. If, for example, a few employees of a large company have premature infants or organ transplants, premiums for all employees are raised accordingly. Small employers are often charged higher rates than larger employers, and very small employers cannot get policies that provide coverage for high-risk employees. One way to ensure relatively low rates for everyone and, at the same time, coverage for high-risk individuals, such as those with severe rare diseases, would be to construct the largest possible group. Various "national health insurance" schemes seek to do this by making the entire population of the nation that group.

Because risks cannot be spread broadly enough in small groups to absorb the effects of adverse selection, underwriting standards are stricter for these groups. Most insurance companies feel that, for groups under a certain size (usually 20 employees), even the most restrictive of contractual provisions or coverage of preexisting conditions will not protect them against situations where a program is purchased to provide protection for a specific employee.

For such small groups, the insurer may require a statement of health from the employee and from each dependent.

The insurance industry reports that about 6 percent of all applications for individual and group policies are declined or issued with limitations. Denial of coverage usually occurs only for serious medical reasons or when an applicant is in a category clearly outside the group's parameters of acceptable risk, for occupational or financial reasons. Rare diseases frequently fall into the former category.

Laws have been enacted to prevent interruption of coverage for persons covered by group health insurance who cease to be eligible for that coverage because their employment has been terminated. The availability of continued insurance protection was bolstered by the 99th Congress in the Consolidated Omnibus Budget Reconciliation Act (COBRA) of 1985.<sup>18</sup> Federal law now requires, with some minor exceptions, that all employers of 20 or more persons provide continuation of coverage under the group plan for terminated or laid-off workers and their dependents for 18 to 36 months. The plan also applies to workers whose hours are reduced. Former employees must pay up to 102 percent of premium costs.

Open enrollment, in which group insurance coverage is offered to individuals without regard to health status, was once a common practice. Now, only 11 states and the District of Columbia offer open enrollment periods.

## **INDIVIDUAL HEALTH INSURANCE**

Individual health insurance policies account for only 9 percent of the health insurance in the United States. When an individual buys health insurance, it may be because he or she expects to need it. The insuring organization seeks to protect itself from that possibility by examining a variety of factors before underwriting a policy: the applicant's age, because of the increased incidence of medical problems with age; the applicant's medical history and current physical condition, which indicate the likelihood of an unusual medical treatment or disability in the near future; the applicant's financial status and other insurance; and the risk of injury in the applicant's occupation.

The insurer evaluates this information and decides whether to insure the applicant or not. Most insurers approve 95 percent of individual applications. In some cases, coverage is modified to include smaller benefits or to exclude coverage of a specific preexisting condition. A higher premium may be charged because of the increased likelihood of a claim. For example, a patient with epilepsy who has been seizure-free for 10 years may be denied a policy, offered a policy at increased cost and decreased benefits, or offered a policy that excludes epilepsy from the list of reimbursable conditions.

Perhaps the most difficult aspect of health insurance underwriting is deciding when and how to modify coverage. As stated at one of the Commission's meetings, an insurance company usually feels a responsibility to treat all of its policyholders fairly by establishing premiums at a level consistent with the risk represented by each individual policyholder. Decisions are based on actuarial statistics, such as the risk of increased costs, the number of hospitalizations, and the length of hospitalizations due to chronic conditions. For most rare diseases, however, no actuarial statistics exist. As a result, policies may be denied because the insurer has no basis on which to calculate potential medical costs.

## THE UNINSURED AND UNDERINSURED

An estimated 65 million Americans under the age of 65 have inadequate or no health insurance. Among the 37 million uninsured, approximately 17 million are employed but their employers do not provide insurance. The number of persons without health insurance continues to rise, despite COBRA. Many of the unemployed workers covered by the plan are unable to afford the coverage previously paid for in part by their employers.

As health care costs increase, premiums increase; and higher premiums discourage employers from offering group health insurance to employees. In addition, as diagnostic procedures become more refined, patients are likely to be diagnosed at an earlier stage of life, and insurers will be able to withhold coverage from them and employers may not hire them. There are few laws to prevent health insurance companies from denying benefits to people with preexisting conditions, even though there are no actuarial statistics to prove that the medical expenses for those conditions are unusually high.

Testimony presented in the Commission's public hearings substantiates the general perception that uninsured persons are less likely than insured persons to use medical services. When they become ill, they often stay at home, do not see a physician, and hope that their condition will disappear or become less severe. Because they have no preventive care, they are also more likely than insured persons to be in poor health. Their illnesses cause them to spend one-third more days per year in bed than insured patients.<sup>19</sup>

In recent years, Federal and state legislators and policymakers have targeted specific segments of the uninsured population in an effort to make coverage available. Such efforts include extensions of Medicaid in some states, particularly to mothers and children.

Another means of insuring the otherwise uninsurable has been to pool high-risk patients and make coverage

available through a state-sponsored body. As of September 1987, 15 states had enacted legislation to establish such pools (Table 3). In addition, legislatures in 12 states considered, but did not enact, legislation authorizing a risk pool during 1987. Usually, the state creates an association to operate the program and requires all insurers doing business in the state to join. The association offers the insurance and establishes the premiums. To qualify for a risk pool, applicants must usually prove that they have been rejected for health insurance by one or more insurers. Some states permit enrollment if an applicant has been offered a policy that excluded coverage of a specific medical condition, such as cancer or juvenile diabetes. Some risk pools also include persons who have been offered insurance at a higher rate than that of the risk pool. If the premiums paid do not cover the expenses incurred, the deficits are shared among association members, who may then raise the price of premiums. Insurance premiums for high-risk pools generally cost 150 to 200 percent of average premiums in the state. In addition, they have very high deductibles and usually exclude coverage for preexisting conditions for 6 to 12 months.

The intent of these programs is to protect participants from extraordinary medical costs by limiting yearly out-of-pocket expenses. Such expenses generally range from \$1,000 to \$5,000. The Commission heard of cases where out-of-pocket expenses vastly exceeded \$5,000.

Risk pool insurance policies generally contain customary cost-sharing and benefit-limitation provisions. These include (1) deductibles (for example, the first \$1,000 spent on medical care); (2) a percentage of or cap on covered expenses after the deductible has been met (for instance, 80 percent of the costs of medical care); (3) a waiting period before preexisting conditions are covered; and

**Table 3**  
**States with Health Insurance Risk Pool Programs**

<i>State</i>	<i>Effective Date</i>
Connecticut	April 1976
Minnesota	July 1976
Wisconsin	January 1981
North Dakota	July 1981
Indiana	September 1981
Florida	July 1982
Montana	July 1985
Tennessee	July 1986
Nebraska	September 1986
Iowa	January 1987
Illinois *	April 1987
New Mexico	April 1987
Washington	May 1987
Maine	September 1987
Oregon	September 1987

\* This program has not been funded.

(4) a lifetime cap on medical expenses paid. Some states waive or reduce the waiting period if the individual had another insurance policy in effect before enrolling in the risk pool or if the individual pays a surcharge. Each of these restrictions adversely affects patients with rare diseases. Because people who enroll in high-risk pools usually have very serious and expensive medical conditions, their premiums are very high; many seriously ill people cannot afford them.

## **ELIGIBILITY FOR MEDICAID AND MEDICARE**

*On a personal basis, my family demonstrated to the government that to institutionalize our son would cost the Federal government \$250,000 a year, but to give us assistance would come to less than \$25,000 a year. In the last six years, we have saved the government at least \$1,200,000.*

*—Parent of a Boy with Leukodystrophy*

### **MEDICAID**

Medicaid programs were enacted as part of the Social Security Amendments of 1965 (P.L. 89-97), to provide the poor with access to health care.<sup>20</sup> Funds are provided jointly by state and Federal sources on the basis of an established formula, with a higher Federal share going to states with lower per capita income. A major problem brought to the attention of the Commission was the tremendous differences across states in eligibility requirements, benefits, and provider reimbursement policies. Nationally, Medicaid spent an average of \$1,721 per person in FY 1985. Payments ranged from \$3,384 per person in New York to \$821 in West Virginia. Medicaid paid \$37.5 billion in benefits to 21.8 million recipients in 1985 and \$41.0 billion in benefits to 22.5 million persons in 1986.<sup>21</sup>

At a minimum, states are required to cover everyone receiving benefits under the Aid to Families with Dependent Children program and most people receiving Supplemental Security Income. States may extend Medicaid provisions to other needy groups of individuals, including the medically needy. For the medically needy, eligibility is determined by an annual income below a state's poverty level or medical expenses that reduce income below that level. When a person becomes impoverished by high medical expenses, the financial collapse is referred to as "spend-down." The hardships between the time a person starts to pay high medical bills and the time he or she spends down to poverty level can be devastating, especially when an entire family must lose all of its savings and other financial resources.

Medicaid regulations require participating states to cover the following basic services for all categorically needy recipients:

- Inpatient, outpatient, laboratory, and X-ray hospital services,
- Services in a skilled nursing facility,
- Physician, home health care, nurse-midwife, and family planning services, and
- Early and periodic screening services for children.

States can also cover other services, such as psychiatric services; prescribed drugs, eyeglasses, and dentures; physical therapy; dental services; and private-duty nursing services.

Sociodemographic characteristics, economic conditions, and political attitudes have played and will continue to play an influential role in shaping Medicaid programs as long as Medicaid is administered by the states under broad Federal guidelines. Since the poverty level, which is the eligibility criterion in all states, is higher in some states than in others, poor people do not obtain medical care on an equitable basis. One of the Commission's witnesses explained that in her state she was ineligible for Medicaid, but if she moved to a neighboring state, her medical care would be covered by Medicaid.

### **MEDICARE**

The Medicare program, authorized by Title XVIII of the Social Security Act and put into effect on July 1, 1966,<sup>22</sup> assisted in paying hospital and medical care costs for over 31.7 million persons in 1986. This includes persons age 65 and older, approximately 89,000 persons with end-stage renal disease, and about 2.9 million persons who are receiving Social Security Disability Income benefits.

Medicare consists of two parts. Part A, which is financed by payments made by employers and employees, is a compulsory hospitalization insurance covering 31.2 million enrollees. Part A benefits totaled \$48.9 billion in 1986. Part B, which is financed by monthly premiums from individuals and by the Federal government, is a voluntary supplementary medical insurance that helps pay for physician services, some medical services, and medical supplies not covered under Part A for 30.6 million enrollees. Its benefits amounted to \$25.9 billion in 1986.<sup>23</sup>

Medicare benefits have gone from \$4.5 billion in 1967 to \$74.8 billion in 1986. Part of this is due to the nation's growing number of elderly persons. A small part, beginning in 1973, is due to coverage of persons with certain disabilities; in 1985, nearly 12 percent of benefits paid went to individuals who were either blind or disabled. And part is due to the costs associated with new biomedical technology.

## INSURANCE INDUSTRY CRITERIA FOR REIMBURSEMENT

In deciding whether a procedure, device, or drug is reimbursable, insurance companies first ask if it is experimental, since experimental treatments are not reimbursable. One group may indicate that a treatment is experimental, another that it is safe and effective. Second, if the treatment is not considered experimental, how much will the company pay for it?

In some cases, an insurer excludes coverage because it questions the medical appropriateness of the treatment. "Medical appropriateness" is usually defined in health insurance contracts as "services or supplies that are reasonably necessary" in the treatment of an accidental bodily injury or diagnosed disease. A "reasonably necessary" service or supply must be ordered by a physician and be commonly and customarily recognized by physicians as appropriate in the treatment of the patient's diagnosed illness. Some companies use the term "medically necessary," which means any confinement, treatment, or service that is (1) prescribed by a physician, (2) considered by a majority of the medical profession to be necessary, appropriate, and nonexperimental, and (3) not in conflict with accepted medical standards.

The process by which insurance companies determine what is medically appropriate, reasonably necessary, and generally accepted medical practice includes:

- Reviews of current medical literature and major medical conferences at which new technologies are discussed, and
- Consultations with leading medical technology assessment organizations, including the program for clinical procedure review of the Council of Medical Specialty Societies, the AMA'S Diagnostic and Therapeutic Technology Assessment Project, the assessment report series of the Office of Health Technology Assessment, and the Clinical Efficacy Assessment Program of the American College of Physicians (differences of opinion often arise among these groups, however).

Most insurance organizations have a standard policy and procedure for review of new technologies. It consists of medical society approval, internal medical review, and policyholder interest and preference. For new technologies and treatments there may be differences in coverage among insurers and even among contracts issued by the same company.

## GAPS IN COVERAGE

Many uninsured or underinsured persons with a rare disease experience severe financial hardships resulting from the demands of their disease. Even insured patients face high

out-of-pocket expenses for premiums, deductibles, and co-insurance; in addition, they must pay for services and supplies not covered by their insurance policy. Noncovered expenses frequently include outpatient prescription drugs; eyeglasses; hearing aids; dental care; visiting nurse services; psychological services; physical, speech, and occupational therapy; skilled nursing or long-term care; and over-the-counter drugs and supplies. For children and adults with rare diseases, such services are frequently as important as acute care services and need to be covered by insurance policies.

There is no uniformity of reimbursement for medical foods, over-the-counter drugs, medical supplies, investigational drugs for treatment purposes, or uses of approved products for nonapproved indications. Many patients are confused about what is covered until a claim is submitted for reimbursement. The decision by a carrier as to what is covered and what is not may stall the delivery of services for months, even years.

Such quandaries are brought about by rapid changes in drug and device technology, which can affect length of inpatient hospital stay; rapid shifts from inpatient to outpatient status because of DRG (diagnosis-related group) requirements; and utilization of alternative services such as hospices. Because of innovations and changes in therapy and their lack of information about rare diseases, insurers are frequently indecisive on reimbursement issues. As things now stand, the patient or family must usually provide proof of the need for services and wait several months to be reimbursed.

Despite the gaps in coverage, and the inability of some patients with rare diseases to obtain coverage for health care services or to pay for those services out of their own pockets, many patients continue to receive care. Physicians, laboratories, researchers, hospitals, pharmaceutical companies, state and regional service networks, and others have historically provided services and drugs to those who could not afford to pay. The Commission commends the voluntary contributions of these organizations and individuals and encourages them to continue their compassionate care of individuals suffering from rare diseases, despite the growing pressures on their budgets.

The needs of rare disease patients are sometimes unique because of the nature of rare diseases, but they are needs which are shared by a large number of other Americans who are uninsured or underinsured. The needs of those large numbers of people who lack adequate coverage of health care, long term care, disability income, and life insurance are the subject of ongoing public debates and legislative proposals. As those issues are addressed, the needs of those with rare diseases must not be forgotten. As Congress and others turn their attention to the uninsured in this country, they must be kept aware of those uninsured who have rare diseases to ensure that solutions to address coverage address the unique needs of the rare disease patient and family.



## **AREAS OF PARTICULAR CONCERN**

Of particular concern to the Commission is the adequacy of coverage for the following services and treatments:

- Investigational drugs and devices,
- Ancillary inpatient services related to clinical trials,
- Approved drugs for nonapproved uses,
- Foods used for medical treatment, and
- Over-the-counter products, such as bandages.

Medicare and Medicaid do not now reimburse for these services and treatments, and private insurers frequently follow Medicare and Medicaid's lead.

### **Investigational Drugs and Devices**

Orphan products in investigational research status can be made available to patients with rare diseases through several mechanisms. All require different degrees of effort for the practicing physician or research clinician to obtain approval for the Investigational New Drug Application (IND).

The traditional investigator or manufacturer sponsored IND is generally used for the purpose of conducting clinical investigation of that product prior to receiving approval for marketing to the general public. Most INDs are of this type and the investigator/sponsor assumes responsibility for meeting the requirements of the IND application process.

Another type of an IND is required as part of the emergency use of an investigational drug. In this case an emergency situation exists that does not allow time for submission of the accompanying paperwork required of IND applications. The IND submission is required to be sent to the FDA by the investigator as soon as practicable after receiving the authorization to use the investigational product.

A third category is the treatment IND. In this situation an investigational drug can be obtained for treatment purposes for serious or immediately life-threatening diseases if there is no other comparable or satisfactory alternative therapy to treat a particular disease. Either all clinical trials must have been completed or the drug can be under investigation in a controlled clinical trial under an existing IND. The sponsor must be actively pursuing marketing approval of the investigational drug with due diligence. Standards for approval differ somewhat for serious, as opposed to immediately life-threatening diseases.

The last method of obtaining an investigational product that has received an orphan drug designation is through an open protocol. This is one of the provisions of the Orphan Drug Act. Here, the sponsors are encouraged to develop protocols to include all patients who need the drug

and who cannot be satisfactorily treated by available alternative drugs. In practice, however, open protocols are handled under treatment IND procedures.

Seven products now have treatment IND status for serious or life-threatening illnesses. This number is likely to increase as the program matures and the public continues to press for new treatments. Because the program permits sponsors to charge patients for investigational products, third-party payers, including the Federal government, will have to decide whether to provide reimbursement for products with treatment IND status. Medicare, Medicaid, and most private insurance carriers usually do not provide coverage for such experimental treatments or the required laboratory tests.

Another aspect of the use of investigational drugs is the gray area between biomedical research and health services. In testimony to the Commission, investigators cited the difficulty of convincing insurers of the legitimacy of a claim for ancillary clinical services and the difficulty of convincing funding organizations of the legitimacy of certain research expenditures. These investigators concluded that the determination of whether a particular procedure constitutes a service expense or a research expense depends upon the perspective of the responding entity. Insurance carriers and research funding organizations have different, often conflicting perspectives.

### **Nonapproved Use of Approved Products**

A similar situation exists with regard to approved products used for nonapproved indications (a situation that is not likely to improve without incentives for sponsors to conduct the necessary research, as discussed in Chapter 7). The FDA has stated that using an approved drug for a nonapproved indication is an acceptable part of medical practice, provided the physician has a sufficient scientific basis for the nonapproved use.

Many third-party payers do not provide reimbursement for nonapproved uses of products, however, and this can cost the patient a considerable sum of money. Third-party payers should be made aware of the potential usefulness of these products in reducing or eliminating hospitalizations.

### **Medical Foods**

Medical foods include vitamins, minerals, naturally occurring chemicals, and some infant and adult formulas that are essential to many patients with rare diseases. The Commission recommends that the FDA smooth the way to approval status for these foods and that patients be reimbursed for them, especially when the lack of such foods will lead to mental retardation, coma, or death. Additionally, products should be recognized as medically necessary so that HCFA and other insurers consider them reimbursable.



### *Over-the-Counter Products*

Lack of reimbursement is equally serious in the case of over-the-counter drugs and supplies. Patients with epidermolysis bullosa, for example, may spend \$5,000 to \$10,000 per year for bandages and antibiotic ointments, which must be changed several times a day to prevent infection of blisters. Most patients are not now reimbursed for such products.

### **Recommendations:**

4. Health professionals, institutions, and pharmaceutical companies should continue with their practice of providing free and reduced price services and drugs to those rare disease patients who cannot afford to pay for them.
5. Public and private insurers must ensure access to affordable health insurance for patients with rare diseases.
6. Public and private insurers must ensure access to affordable life insurance for patients with rare diseases.
7. The Central Office of Orphan and Rare Diseases (COORD) should convene a meeting of relevant public and private insurers and patients and their families to resolve the problems in health, disability, and life insurance coverage. Recognizing that such resolution will be difficult to achieve, the Commission recommends the following immediate measures:
  - State insurance commissioners should ensure that insurance plans do not discriminate against persons with rare diseases, including persons with preexisting conditions.
  - Employee benefit managers should ensure that employer-provided group insurance responds to the needs of persons with rare diseases, including persons with preexisting conditions.
  - Public and private insurers should utilize information from COORD to make responsible decisions about coverage of persons with rare diseases, including coverage of appropriate services and treatments such as physical, speech, and respiratory therapies; dental care; medical foods; over-the-counter products; and genetic counseling.
  - States should allow a Medicaid buy-in for persons with rare diseases who cannot otherwise obtain health insurance.
  - Insurers should pool the small groups they cover in order to distribute risk more widely and

extend the availability of insurance to persons with rare diseases.

- The COORD should begin to develop a data base on acceptable medical treatments for rare diseases. In the absence of a technology assessment on a particular therapy, insurers should cover medical expenses of an investigational treatment when it is part of an approved protocol or an approved treatment IND.

### **CLASSIFICATION OF RARE DISEASES**

Improper classification and lack of official recognition of rare diseases pose problems both in the diagnosis and treatment of those diseases and in the reimbursement of patients' expenses. Nearly 6,000 hospitals participate in Medicare's prospective payment system. Under that system, the basis for payment of inpatient services provided for Medicare beneficiaries is the DRG. Diagnoses identified in the World Health Organization's International Classification of Diseases (ICD) are grouped into 23 major categories based on organ systems; these categories are subdivided into the 470 groups in the DRG system. In some instances, there is little emphasis on individual diseases in these groups. As a result, little or no data are gathered on the costs of health care for persons with rare diseases, and insurers have a tendency to ignore or give little emphasis to the rare diseases in a group. Further, the validity of DRGs for rare diseases remains unknown.

In addition, the Commission was told of instances in which rare diseases are not included in conventional classification schemes, such as the ICD. In other instances, rare diseases are not appropriately or adequately classified: the ICD classification number assigned to Marfan syndrome, for instance, is shared by more than 20 other conditions. In still other instances, rare diseases are not included in official lists used by agencies, such as the Social Security Administration, Developmental Disabilities Administration, and Crippled Children's Services, even though those diseases may be found in the ICD.

### **Recommendation:**

8. The U.S. representative to the World Health Assembly should ensure that classification schemes of diseases, particularly the International Classification of Diseases, accurately reflect the state of knowledge about rare diseases.

**PART III**

**RESEARCH**

*“The greatest hope for patients comes ultimately from research.”*

*—Representative of Voluntary Organization*

## Chapter 5

### THE NATURE AND FUNDING OF BIOMEDICAL RESEARCH

The greatest barrier to prevention or diagnosis and treatment of any disease is lack of knowledge about it. Of the more than 5,000 known rare diseases and conditions, some are fairly well understood, but many remain mysteries. Still others have not yet been characterized or named.

The value of research is undeniable; it is not only successful in alleviating the suffering of patients, it is also cost-effective for society. For example, Urocit K, a drug used to treat kidney stones, cost \$1.6 million to develop but has saved from \$58.4 to \$82.2 million per year by reducing the number and duration of hospitalizations and the number of days of work missed. Cysteamine, a new drug for cystinosis, can treat all 100 children who have the disease at a cost of \$50,000 per year. Without the drug, these children would require kidney dialysis or transplantation—at a cost exceeding \$5 million per year.

In many instances, an advance in research on a common disease can have a direct bearing on research into a rare disease. Research discoveries in arthritis, for example, would be expected to assist investigators working on certain rare autoimmune disorders. Conversely, advances in rare disease research can be expected to have applications to common diseases. Penicillamine, for example, was developed for treatment of a rare condition, Wilson's disease. Later, it was discovered to be useful in alleviating the symptoms of rheumatoid arthritis.

In this chapter the Commission discusses the status of health-related research in general and analyzes the peer review process. Chapter 6 focuses exclusively on the funding of rare disease research.

#### BASIC RESEARCH

An atmosphere of boundless scientific opportunity, the chance of doing meaningful work, and adequate funding are essential to attract and retain investigators. Unfortunately, many promising students avoid a career in research because they have misconceptions about it, they lack any incentive to do research, or they had little exposure to research in undergraduate and graduate training or medical school. Many students may simply not know about the existence of most rare diseases.

More experienced investigators may avoid research on rare diseases because they believe that it is less likely to be funded or that the funding is less stable than funding

for other research. In addition, they may be frustrated by the lack of adequate biological sample banks and appropriate animal models. The availability of such resources often determines whether work on a particular disease moves forward at a steady rate or remains static for long periods, during which collection of samples or development of models must be started anew.

The interest of young people could be piqued by establishing and publicizing research training grants that focus on rare diseases. The government and voluntary health organizations could provide financial and moral support. Expressions of interest in specific rare diseases by the NIH research institutes would signal young investigators that opportunities exist in rare disease research. Persons with national fellowships should receive increased or subsidized stipends, with tax relief for trainees supported by small stipends. In addition, NIH should increase stipends to its own fellows, who are still among the lowest-paid investigators in the country.

In short, the research climate should be such that an investigator can work independently on a rare disease, lead a productive career, and be supported by an infrastructure that encourages such careers.

#### CLINICAL RESEARCH

The Commission found that the pathophysiology of many rare diseases is poorly understood. In addition, numerous investigators reported that they were unable to obtain funds for the clinical phases of a study. Funds for such studies are limited because the research is not clearly within the purview of traditional funding sources. Thus, money for clinical studies of rare diseases is scarce, but without the data from such studies, other clinical studies are unlikely to be funded, leading many scientists to conclude that it is not worthwhile to apply for funds to conduct such research on a rare disease.

Rare disease research also suffers from a more widespread malady, that is, the difficulty universities and medical schools are having in recruiting and retaining clinical investigators trained in both medicine and research. These persons are supported by research grants and contracts, tuition, state funding, and, more recently, the medical care they render through some sort of medical service plan. Income from such plans now accounts for over 30 percent of medical schools' revenues—more even than

schools receive from Federal grants and contracts. This has resulted in a shift away from research. In many institutions, vacancies on the faculty are being filled by physicians whose major interest is clinical service rather than basic or clinical research. There has been a noticeable increase in the number of basic scientists with Ph.D.s employed by clinical departments to support research and teaching efforts.<sup>24</sup>

## REGISTRIES

A major barrier to research advances is the scarcity of registries and the lack of public understanding about them. Different kinds of registries have different purposes, but they are all collections of information about certain individuals. At the Commission's public hearings, patients, physicians, investigators, and representatives of voluntary organizations discussed the possibility of a single national registry for all information concerning rare diseases. The Commission is not certain that such a broad registry would be useful.

Registries of physicians and principal investigators are needed to provide information on possible treatment and referral for patients. Access to a registry of specialty physicians would help patients avoid ad hoc decisions on treatment based on what physicians are available locally. The Commission considers support groups to be the most appropriate repository for such information—in fact, many voluntary groups collect such information already—but for most rare diseases there are no such support groups. Alliances of groups or umbrella organizations, such as NORD might provide information to patients without support groups of their own and to small groups that do not have access to computers.

Another kind of registry is a data base of ongoing clinical trials. NIH has one for the clinical trials it sponsors; however, only research institutions have easy access—the public and practicing physicians do not.

A third kind of registry contains information about patients who might be willing to participate in clinical trials. Some voluntary organizations maintain such registries, but the registries include self-reported diagnoses, which are not always accurate or complete. Investigators therefore prefer "scientific" registries. These include data that verify diagnoses, as well as values for certain parameters of a disease, as measured by specific tests. Such registries enable the investigator to select patients at various stages of a disease and to follow the course of their disease. These registries are often coupled with tissue banks and can be used to inform patients about available trials.

Registries of scientific and technical data have been shown to stimulate research on rare diseases, but they are quite expensive to maintain and must usually be funded by Federal institutes or agencies. Costs can be reduced by

clustering them around groups of diseases that require similarly trained investigators and technicians for the collection of information, test data, and biological samples. Those that cut across several rare diseases need to be thoroughly pondered by investigators, in collaboration with voluntary organizations, before being proposed to an appropriate agency.

Highly refined national data and tissue banks are also needed. They should be sophisticated enough to reflect the heterogeneity of rare diseases and the range of manifestations and severity of particular disorders. Federal funding is needed to support such research resources and to keep investigators informed about them.

A central repository for information about registries and data banks is greatly needed so that patients and their physicians can make choices concerning treatment and management of their illness.

## FUNDING

### EXISTING FUNDING

Most funding for health-related research and development comes from one of four sources: the Federal government, private industry, voluntary agencies, and private foundations. Since 1980, the proportion funded by the Federal government has decreased from 59 percent to 47 percent, and the proportion funded by industry has increased from 31 to 42 percent.<sup>25</sup> The Federal government remains the dominant source of funding, however, both through its extramural programs at universities and other nonprofit organizations and its intramural programs. Of the 20-odd Federal departments and agencies that fund health-related research and development, NIH is by far the largest supporter.

Over \$18 billion was projected to be spent on health-related research and development in the United States in 1988 (Table 4). The largest share, \$8.4 billion, was provided by the Federal government.<sup>26</sup>

Most health-related research and development is performed by academic investigators with funds from government sources. About 75 percent of Federal and 90 percent of state and local research and development funds are used to support work in colleges and universities.<sup>27</sup> Voluntary organizations and foundations also support academic investigators. Industry supports investigators in its own laboratories and academic centers.

### THE NEED FOR INCREASED FUNDING

At first glance, the amount of money spent on research and development appears to be sufficient to guarantee continued advancement in medical care. In comparing current and constant dollars, however, it becomes clear

**Table 4**  
**Support for Health-Related Research and Development**  
**in the United States, by Source**

Source	Amount Spent (billions of dollars)		
	FY 1986 (actual)	FY 1987 (estimated)	FY 1988 (projected)
Government	7.916	8.983	9.643
Federal	6.895	7.839	8.447
[NIH]	[5.005]	[5.851]	[6.319]
State and local	1.021	1.143	1.197
Industry	5.915	6.928	7.740
Private, nonprofit	.714	.739	.747
Foundations	.083	.126	.108
Voluntary health agencies	.232	.256	.282
Howard Hughes Medical Institute	.247	.183	.179
Other	.152	.174	.179
Total	14.545	16.649	18.130

that additional funds are needed to sustain a high level of accomplishment in biomedical research. The buying power of the research dollar has shrunk considerably during the past 10 years. The U.S. Department of Commerce's Biomedical Research and Development Price Index, which is useful in translating current dollars into constant dollars, estimates that costs have increased 84 percent since 1978. A dollar awarded in 1978 for research is equivalent to 54 cents today.<sup>28</sup> Although in current dollars, the total amount awarded for investigator-initiated grants at NIH nearly tripled between 1978 and 1987, from \$901 million to \$2.5 billion, in constant dollars, the amount has increased to only \$1.37 billion, a growth rate of 4.5 percent per year. (Table 5)

The Commission is concerned with the recent dramatic deterioration in the ability of the NIH to fund promising research which threatens to slow progress in gaining knowledge of both common and rare diseases. The award rate (percent of approved grants funded) has declined from 38% in 1987, approximately the average for the last 10 years, to just 29% in 1989, with some Institutes now funding just over 20% (Table 6). The annual number of new grants awarded has decreased from 6,447 in 1987 to an estimated 5,324 in 1989. At the same time, the amount by which individual grant funds have been cut (negotiated reduction) has increased from the historical 2.5-5.8% level to over 10%. In addition to its immediate effect of reducing the amount of research being conducted, such cuts have a chilling effect on the future of research by discouraging young professionals from choosing to pursue research careers. The Commission urges that this dangerous trend be reversed and that support be increased by the Congress for all aspects of biomedical research and training as the surest way to make advances that will improve the future for persons with rare disorders.

The Commission considers increased funding of all aspects of biomedical research and training to be essen-

tial if advances are to be made in preventing or treating rare diseases.

#### Recommendations:

9. Congress and the private sector should increase funding for all basic and clinical research and for research training; such increases would raise funding of rare disease research and training as well.
10. Congress should appropriate additional funds to NIH to expand biological sample and human tissue banks and animal models for research on rare diseases and to publicize the availability of such banks and models.
11. Congress should increase extramural funding at ADAMHA, NIH, and FDA for postdoctoral clinical research fellowships in rare diseases by at least 30 fellowships per year for the next three years, and should increase funding for medical student fellowships by 80 fellowships per year for the next three years.
12. Voluntary organizations should be encouraged in their development of patient, physician, and investigator registries to improve patients' access to treatment and to increase research opportunities.
13. The Federal government should provide appropriate funding for registries of scientific and technical data for rare diseases.

#### INVESTIGATORS' PERCEPTIONS ABOUT FUNDING

There was a widespread perception among persons who were surveyed or who gave testimony at the Commission's public hearings that biomedical research projects on common (prevalent) diseases are more readily and adequately funded than those on rare diseases. This view was expressed both by investigators on rare diseases and investigators on prevalent diseases (see Tables 7 and 8). In addition, investigators believe that basic research is more likely to be funded than clinical or applied research. In the Commission's survey of investigators, 75 percent said they would seek funds for basic research first from the Federal government; only 52 percent would turn to the government first for funds for clinical research.

The majority of biomedical investigators surveyed agreed that neither the Federal government nor industry places sufficient emphasis on rare disease research. This perception leads investigators to avoid research projects on rare diseases and is a major barrier to progress. With limited funds available, the critical points in determining which applications will be funded occur during the peer review process.

#### PEER REVIEW

Because of investigators' concerns about peer review, and because of the unparalleled importance of the process

**Table 5**  
**Average Dollars for NIH Traditional Research Project Grants (ROI): FY 1978-1987**

Fiscal Year	Total Dollars				Constant Dollar* Average** by Type (in thousands)		
	Amount (in millions)		Average (in thousands)		New	Competing Continuation	Noncompeting Continuation
	Current	Constant*	Current	Constant*			
1978	901.1	901.1	73.4	73.4	65.7	83.2	73.6
1979	1,118.6	1,033.6	78.1	72.1	65.9	83.6	72.0
1980	1,267.9	1,067.3	84.2	70.9	66.9	86.6	69.3
1981	1,402.6	1,069.2	92.6	70.6	67.4	84.2	68.7
1982	1,456.4	1,022.2	100.4	70.5	67.0	80.4	69.1
1983	1,665.3	1,100.4	109.7	72.5	64.7	81.0	72.7
1984	1,907.5	1,189.9	123.5	77.0	70.3	89.0	76.2
1985	2,174.6	1,284.2	134.5	79.4	73.8	92.3	78.1
1986	2,213.4	1,252.3	136.8	77.4	70.8	83.9	77.5
1987	2,517.9	1,372.1	151.8	82.7	80.4	89.8	81.6

Note: Figures exclude the National Library of Medicine and the Division of Research Resources.

Source: NIH, Division of Research Grants, Information Systems Branch.

\* Based on biomedical research and development price index FY 1978 = 100.

\*\* Supplements to prior year awards are excluded in the computation of average dollars.

**Table 6**  
**Comparison of Funding and Negotiation Rates Among NIH Institutes (In Percent)**

BID	FY 1987 Actual			FY 1988 Actual			FY 1989 Estimate		
	Funding Rate	Negotiation Rate N/C	Comp.	Funding Rate	Negotiation Rate N/C	Comp.	Funding Rate	Negotiation Rate N/C	Comp.
NCI	38.6	0.4	4.5	36.7	3.7	11.7	26.4	2.0	8.9
NHLBI	35.7	1.1	10.9	34.0	9.6	14.9	24.7	11.9	10.1
NICHD	35.6	9.5	9.5	27.0	8.3	12.0	25.3	12.0	10.0
NIDR	33.3	2.6	8.5	28.4	8.1	8.8	21.6	11.5	11.0
NIDDK	40.3	6.9	6.8	33.9	8.3	11.4	32.3	10.0	10.0
NINCDS	43.4	—	—	42.0	4.6	10.9	40.4	10.0	10.0
NIAID	36.8	—	1.4	33.3	6.5	7.4	26.6	9.4	10.0
NIGMS	39.5	2.7	6.0	39.9	7.0	10.3	32.9	9.8	10.0
NEI	53.4	0.6	4.64	48.3	5.7	6.9	43.0	8.5	9.0
NIEHS	32.3	3.9	0.8	31.1	8.1	10.2	25.5	4.4	10.0
NIA	34.3	7.8	9.6	30.0	8.2	20.2	26.7	12.5	10.0
NIAMS	30.8	5.9	7.8	28.0	10.3	15.3	26.8	12.3	11.7
NCNR	61.5	2.5	4.5	45.5	2.0	—	40.9	10.0	10.0
TOTAL NIH	38.3	2.5	5.8	35.3	6.9	11.8	29.3	9.0	9.9
TOTAL NEW GRANTS		6447		6212			5324		

in funding research, the Commission examined the effects of peer review on the funding of rare disease research. The Commission reviewed past studies and was given an extensive briefing on peer review and extramural research funding by the directors of the Office of Extramural Research and the Division of Research Grants at NIH. This section outlines the NIH and ADAMHA peer review system, discusses its strengths and weaknesses, and presents the Commission's findings and recommendations concerning funding of rare disease research through peer review.

**Table 7**  
**Investigators' Perceptions Regarding Funding for Various Types of Research**

Type of Research	Type of Investigator		
	Rare Diseases (N = 303) (percent)	Common Diseases (N = 301) (percent)	Total (N = 604) (percent)
<i>Which type of research is easiest to get funding for?</i>			
Basic research			
on Rare Diseases	5	6	5
on Common Diseases	42	32	37
Clinical research			
on Rare Diseases	5	8	6
on Common Diseases	36	41	39
Don't know	12	13	13
<i>Which type of research is most difficult to get funding for?</i>			
Basic research			
on Rare Diseases	38	36	37
on Common Diseases	4	9	6
Clinical Research			
on Rare Diseases	41	32	36
on Common Diseases	5	8	6
Don't know	12	15	14

### STRUCTURE OF THE SYSTEM

Reviewing grant applications is no easy task. In FY 1988, NIH received over 19,000 competing research project grant applications and 13,987 applications for noncompeting renewals of multiyear grants. Of the competing applications, 13,689 were new applications, 5,286 were competitive renewals, and 230 were competitive supplements. Approximately 25 percent of the new applications were funded. Of the total applications funded, most were unsolicited investigator-initiated research grant proposals; these 6,212 awards averaged \$177,000 for both direct and indirect costs.<sup>29</sup>

Research grant applications submitted to the Public Health Service are received in the Division of Research Grants (DRG). The DRG assigns the application to the appropriate agency or, in the case of NIH, to the appropriate institute. The DRG also assigns NIH applications to

one of nearly 100 initial review groups, called study sections, for the purpose of assessing scientific merit. Eighty to 85 percent of NIH applications are reviewed in DRG study sections, the remainder in review committees of the respective institutes. The application is then reviewed for program and funding consideration by the institute's national advisory council. NIH employs nearly 2,700 external peer reviewers. About 2,300 of them are members of study sections; the other 400 serve on advisory groups. Selection of persons to serve on these committees is critical to the interests of the rare disease community.

### THE GRANT REVIEW PROCESS

Study sections meet three times a year and review grant applications for scientific and technical merit. Advisory councils then assess the applications' relevance to program goals and society's needs.

**Table 8**  
**Investigators' Perceptions Regarding Differences In Support for Rare and Common Disease Research \***

Area Receiving Support	Type of Investigator	
	Rare Diseases (N = 303) (percent)	Common Diseases (N = 301) (percent)
<i>How do you think support for rare disease research compares to support for common disease research?</i>		
Funding		
More	4	9
Less	67	66
About the same	11	11
Don't know	19	14
Facilities		
More	4	5
Less	61	65
About the same	19	13
Don't know	17	16
Student fellowships and training grants		
More	4	4
Less	57	63
About the same	19	11
Don't know	20	22
Research on postdoctoral graduate personnel		
More	4	7
Less	62	62
About the same	18	15
Don't know	16	17
Administrative and secretarial aid		
More	2	5
Less	53	49
About the same	23	19
Don't know	22	26

\* Totals do not add to 100 due to rounding.

## Study Sections

Members of study sections are appointed by the director of NIH. To be considered, an individual must have demonstrated competence and achievement as an independent investigator in a scientific or clinical discipline or research specialty. Most members of study sections are active investigators. Over half hold the rank of full professor.

The following criteria were established to provide balance in the study sections:

- Only one member from the same institution (university or research center) may serve on a study section.
- Membership should be at least 17 percent ethnic minority and 23 percent female.
- No more than 15 percent of the membership may be from New York, California, Massachusetts, or Texas.
- No more than 50 percent of the membership may be from one of four geographical areas: South, Central, East, and West.
- No more than one Federal employee may serve, except in unusual circumstances.
- A year must pass before a committee member can be reappointed to serve on the same or a different committee.
- A member cannot serve on more than one committee concurrently.
- There must be no excessive service; that is, an individual may not serve for more than 8 of the past 12 years.
- After a member completes his or her term of four years on the study section, a year must elapse before another member from the same institution is appointed.

Grant applications may be reviewed by one of the permanent study sections, by one of their standing subcommittees, or by an ad hoc committee convened to consider a specific application or group of applications. Members of the study section discuss each application in light of evaluation criteria established by NIH and decide whether the application warrants funding. The study section does not set program priorities and does not make funding decisions.

The following criteria are used in evaluating applications for research grants and contracts:

- Significance and originality from a scientific and technical standpoint,
- Adequacy of the methodology to carry out the research,
- Experience and qualifications of the principal investigator and staff in the area of the proposed research,
- Reasonable availability of resources (drugs, equipment, and so on) to carry out the research,

- Reasonableness of the proposed budget and duration of the proposed project, and
- Other factors, such as adequate protection of human subjects, animals, and the environment.

The study section decides to approve, disapprove, or defer action on the application to a later date. Each of these actions delivers a message to the investigator. A vote to approve confirms that the application merits financial support (approximately 90 percent of all applications receive such approval). A vote to disapprove signals that, based on review criteria, the application does not merit support. A vote to defer action is a signal that more information is needed.

When approval is recommended, a priority rating is assigned to the project. Each reviewer assigns the application a rating from 1.0 (excellent) to 5.0 (marginally acceptable), from which a combined priority score is then computed. This score becomes part of the application's summary statement, or "pink sheet," which is sent to the advisory council and to the applicant. Applicants may appeal decisions on approval or priority scores they believe are incorrect. The appeal process at NIH can be intimidating, however, and some scientists fear that an appeal might jeopardize future grant applications.

## Advisory Councils

Advisory council members, a third of whom are lay persons, are appointed by the Secretary of DHHS. Nominations are received from NIH, Congress, special-interest groups, and the general public. Members are usually chosen because of their leadership in a specific discipline, widespread interest in a general biomedical area, or understanding of society's health needs. Members of the National Cancer Advisory Board are appointed by the President.

Lay members of advisory councils are private citizens with a special concern in a particular health problem and are often active in related voluntary organizations or private foundations. Scientists are chosen for their leadership in a scientific discipline or specialty related to the mission of the institute. Investigators from colleges and universities, private industry, and the government may serve on the councils.

The advisory council evaluates program priorities and relevance and advises on institute policy. The Council does not usually act on individual grant applications; rather, recommendations for funding to institute staff are made on blocks or groups of applications. According to NIH officials, less than 10 percent of applications are singled out by the advisory council for a special review.<sup>30</sup> Individual consideration may be given because of high



program relevance, special health-related needs, a rebuttal from an applicant concerning the study section review, or concern for an ethical issue.

### ***INSTITUTE ACTION***

After receiving the advisory council's recommendations, the institute ranks the approved applications. Scientific merit, as determined by the summary statements and by percentile ranks or priority scores, program relevance, and availability of funds all play a role in determining which applications are funded, although the priority score or the percentile rank is the decisive element for research grants. At this time the principal investigator is informed of the final funding action.

### ***STRENGTHS OF THE PEER REVIEW PROCESS***

The peer review process has numerous strengths. It encourages individual investigators to submit their ideas for competition with others, thereby promoting creativity and scientific and technical excellence in the research applications. The use of active, successful investigators from across the country as peer reviewers ensures even-handed review and high quality of the proposals funded.

The system is dynamic and provides some degree of flexibility. It permits timely changes in program emphasis. Specific disease-related requests for proposals or applications for set-aside funds can be published and acted on quickly. It allows the Division of Research Grants or the institutes to convene ad hoc committees to review applications that are outside the expertise of an existing study section.

A number of studies of past awards, surveys of scientists, and commission reports have found no significant bias in the grant award process. Further, it is widely supported by the competing scientists themselves, with 86 percent of the 4,100 scientists agreeing in a 1986 survey that the government should use peer review to ensure a high quality of science in its research program.<sup>31</sup>

### ***WEAKNESSES OF THE PEER REVIEW PROCESS***

The peer review process has certain potential weaknesses, however. Peer review has been described as an inexact, subjective process in which scientists judge which investigators and which proposals are most likely to yield the most fruitful results.<sup>32</sup> Prior studies of the peer review process indicated the following perceptions of problems:

- Academic institutions centered on the East Coast, the Upper Midwest, and on the West Coast receive the major share of research funds from the Federal government.
- The peer review system is viewed by some as an “old boy” network in which trusted friends in the academic community serve as reviewers and awards are made based on personal connections rather than scientific merit.
- The process is too conservative; innovative research proposals are not judged appropriately.
- The paperwork and time required of the principal investigator to prepare the proposal are burdensome, particularly when grant awards are made for short periods, usually three to five years.
- Applications for basic research are more likely to be funded than those for applied or clinical research.

### **THE COMMISSION'S REVIEW OF POSSIBLE BIAS IN RARE DISEASE RESEARCH APPLICATIONS**

A subcommittee of the Commission examined for bias 357 approved clinical research grant applications chosen at random from the Fall 1987 submissions to the NIH Division of Research Grants. The subcommittee members independently agreed that 30 represented rare diseases or conditions and 327 represented common indications. The mean priority score for those with an orphan indication was 227.7, with a standard deviation of 82.7, while those designated not rare had a mean priority score of 232.7, with a standard deviation of 87.4. Therefore, in the judgment of the subcommittee, no bias in priority scores was discernible in applications for clinical research on rare diseases or conditions.

The Commission heard from investigators, however, that study sections may fail to recognize the importance of nosological (classification) studies of rare diseases or to recognize that the number of patients in a proposed study constitutes one of the largest cohorts assembled for a particular disease. The Commission is concerned that such attitudes—and the perceptions of investigators that such attitudes exist—could exert a chilling effect on studies of rare diseases.

### ***CONCLUSIONS REGARDING PEER REVIEW***

The Commission agrees with the main conclusion of previous studies of the peer review process—it is not a perfect system, but it is generally equitable in reviewing grant applications and making awards, and it tends to promote scientific excellence.

Some of the problems mentioned by investigators may already have solutions that the investigators do not know

about. This suggests a problem in communication. For example, several principal investigators brought up the problem of review by an inappropriate study section. Investigators may request that their applications be assigned to a specific study section for review and consideration, although the final decision on assignments is with the DRG. Investigators are also encouraged to contact executive secretaries of study sections with their concerns. Executive secretaries are empowered to bring in special reviewers and get outside opinions as needed.

Another concern cited by investigators is study section members' lack of expertise in rare diseases. Since NIH and ADAMHA call in ad hoc reviewers when insufficient expertise exists in a study section, it would be in the best interests of all concerned for rare disease-specific organizations to recommend reviewers and for NIH to request nominations from them. Increased use of ad hoc reviewers familiar with the peer review process, scoring techniques, funding decisions, and the disease being reviewed would be helpful, particularly if they are invited to attend and vote at study section meetings.

The peer review process poses special problems for clinical research in rare diseases. The small number of patients

available for a study, the considerable distance between patients' homes and the research center, and the need for multicenter studies require special consideration from reviewers. Study section members should be encouraged to view these problems not as negative features, but as an opportunity to expand clinical knowledge and provide missing clues about a rare disease or condition.

**Recommendations:**

14. Federal agencies should heighten their awareness of rare diseases. They should declare activities regarding rare diseases to be a high priority of their programs.
15. Funding agencies should ensure that study sections include experts on the rare disease under consideration. When these experts are ad hoc reviewers, they should be allowed to vote on that application.
16. Funding agencies should ensure that advisory councils have representatives from patient and family groups who understand the problems associated with rare diseases.

## Chapter 6

### RESEARCH ON RARE DISEASES

*Research in rare diseases is very important to our understanding of normal human function and eventually leads to treatments for common diseases.*

—Physician Investigator Studying Rare Metabolic Diseases

Responses to the Commission's surveys indicate that in 1987 the Federal government spent \$1.3 billion on rare disease research, foundations spent \$1.6 million, and the pharmaceutical industry spent \$51.6 million for research and development relating to orphan products.

Known spending on rare disease research, therefore, represents only 8.5 percent of the \$16 billion spent on all health-related research and development in the United States that year. Yet rare diseases often require a disproportionately high share of health care resources. For example, genetic disorders, almost all of which are rare, significantly affect 2-5 percent of all patients admitted to children's hospitals and account for 25 percent of all pediatric inpatient hospital days.<sup>33,34</sup> Funding of research that leads to the prevention of such rare diseases or to more effective treatment of patients is likely to be extremely cost-effective for society, as well as beneficial to patients and their families. For these reasons, the Commission concludes that overall funding for rare disease research is inadequate.

#### FEDERAL FUNDING OF RARE DISEASE RESEARCH

The Federal government, through its various agencies and institutes, plays a major role in promoting and supporting research on rare diseases. Its programs include:

- Grants and contracts for research,
- Intramural research,
- Awards to individuals and institutions for research training and career development,
- Development of clinical centers, and
- Dissemination of research findings to encourage applications in clinical practice.

The type of research conducted or funded by a Federal agency is generally dependent on its mandate, the constituency served, and the personnel available to conduct the research.

Of the \$1.3 billion spent on orphan disease research by the Federal government in FY 1987, \$1.15 billion (88.5 percent) was spent by NIH and the remainder by other agencies (Tables 9 and 10 and Figures 1 and 2). *However, of the \$1.3 billion total, over half was spent on approximately 200 rare forms of cancer, leaving about \$640 million for the remaining 4,800 known rare diseases.* The majority of the \$640 million supported basic research. Approximately 63 percent of NIH research funds are devoted to basic studies. Thus, in FY 1987, the Federal government spent only a fraction of \$640 million on direct treatment-related clinical research on the remaining 4,800 known rare diseases.

Few agencies target rare diseases as a research priority, but many support research projects in rare diseases and fund other projects with important implications for rare disease diagnosis and treatment. For that reason, it is difficult to gather exact information about rare disease research at Federal institutions. A more accurate accounting can be made only when agencies implement a much-needed tracking system for funded research and research results.

#### THE NATIONAL INSTITUTES OF HEALTH

The NIH is the premier biomedical research organization in the world. Each year, it conducts or supports 20,000 research activities covering myriad diseases and conditions, including rare diseases. In fulfilling its mission, NIH conducts research in its own laboratories, supports scientists in universities, medical schools, hospitals, and research institutions throughout the United States and abroad, and fosters and supports training in biomedical research.

In FY 1987, NIH reported its total appropriation as \$6.18 billion, 84 percent of which was spent on extramural programs, including research training. Approximately 16 percent of NIH funds were used for intramural research and management of extramural programs. This ratio of intramural to extramural research has been stable for the last decade.

The NIH has 16 institutes or offices that award grants and contracts in support of biomedical research. Eleven of them support rare disease research. Some of the units are disease-oriented institutes, including cancer, arthritis, and digestive diseases. Others focus on an organ or system, such as the heart or eye, or on a discipline, such as general medical sciences or nursing research. In most instances, each unit was established by an act of Congress in response to broad public support.

## Grants

The grant is the oldest and most widely used mechanism employed by NIH to generate new knowledge about all diseases, including rare diseases. There are several types of grants:

- Investigator-initiated grants, also referred to as R01 grants, are research ideas of individual investigators which are sent to NIH by the university or research institute on behalf of the investigator. The institution commits itself to providing some of the research resources and ensuring ethical treatment of research subjects.
- Institute-initiated grants, or program grants, give NIH more control over the research. Program grants are particularly important for rare diseases because they can be used to begin and direct programs where little or no knowledge exists.
- Some grants are designed specifically to achieve certain goals:
  - ☆ training grants for the young or new investigator,
  - ☆ grants for research centers,
  - ☆ grants for innovative research projects of small businesses,
  - ☆ career development grants, to attract physicians to biomedical research, and
  - ☆ investigator-initiated grants that employ new research trainees.

The requirements of some mechanisms are more specific than others. The least specific means of stimulating the submission of grant applications is the program announcement. It is a formal reminder to the research community that a certain program exists and that NIH would like to receive applications in particular areas of interest. No funds are set aside for applications in response to these announcements.

The request for application (RFA) describes a specific initiative in a well-defined area, such as a particular disease. Funds are set aside, and applications compete with each other in a funding cycle. Responses to RFAs usually have an ad hoc review committee. Recommendations of the committee are made to the institute and to its national advisory committee.

The NIH allocated \$4.4 billion for research and development grants in 1987.

## Contracts

The contract mechanism has a very narrow focus. The funding agency contracts to buy a specific, identifiable piece of research or research support. The research is outlined in considerable detail, such as definition of a protocol or a specific set of conditions or criteria that must be met. Contracts are funded by money set aside for specific purposes. In 1987 NIH funded \$544 million in contracts for specific research and services.

## Cooperative Agreements

The cooperative agreement is an assistance mechanism similar to the grant, but in the former NIH (represented by a designated staff member) is a partner in the endeavor. Cooperative agreements are being used more frequently, which indicates increased interest in joint ventures.

## Publicizing Available Funding

Opportunities for grants, contracts, and cooperative agreements are announced in the *NIH Guide for Contracts and Grants*. The FDA and ADAMHA publish announcements there also. The guide is published approximately every 10 days and is distributed without cost to organizations that request it. Current circulation is approximately 25,000. Opportunities for contracts are also announced in the *Commerce Business Daily*, to ensure that the private sector is aware of requests for proposals.

## ATTRACTING AND KEEPING INVESTIGATORS

*A problem more subtle and insidious than funding is the paucity of researchers interested in orphan diseases.*

—*Investigator Studying Huntington's Disease*

Federal funding for and emphasis on biomedical research has encouraged many bright students to become biomedical scientists. Further, the Federal government has encouraged universities, through a variety of programs, to expand their research facilities. As a result, there has been an exponential increase in the rate of advances in health-related research.

At the same time, however, there are not enough basic or clinical investigators engaged in research on rare diseases. The Commission heard from some persons who had convinced Congress to set aside funds for research, only to find few or no acceptable applications for those funds.

**Table 9**  
**Research Dollars Obligated by Federal Agencies To Research Activities on Rare Diseases:**  
**FY 1987**

<i>Federal Agency</i>	<i>Total Dollar Amount Obligated (in \$ millions)</i>	<i>Percent of Total Federal Obligation</i>
<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b>		
Health Resources and Services Administration		
G.W.L. Hansen's Disease Center	\$2.30 (est.)	0.18
Office of Maternal and Child Health	*	*
Food and Drug Administration	5.86	0.45
Alcohol, Drug Abuse, and Mental Health Administration		
National Institute on Drug Abuse	(1)	*
National Institute of Mental Health	*	*
National Institutes of Health	(1,153.78)	
National Cancer Institute	662.02	50.9
National Heart, Lung, and Blood Institute	104.00	8.0
National Institute of Neurological and Communicative Disorders and Stroke	103.91	7.9
National Institute of Diabetes and Digestive and Kidney Diseases	73.10	5.6
National Institute of Allergy and Infectious Diseases	69.04 (1)	5.3
National Institute of Child Health and Human Development	55.86	4.3
Division of Research Resources	30.39	2.3
National Eye Institute	28.56	2.2
National Institute of Arthritis and Musculoskeletal and Skin Diseases	20.64	1.6
National Center for Nursing Research	2.57	0.2
National Institute on Aging	1.57	0.12
National Institute of Dental Research	1.13	0.09
National Institute of General Medical Sciences	.88	0.07
Warren Grant Magnuson Clinical Center	.13	0.01
Fogarty International	*	*
Division of Research Services	*	*
Centers for Disease Control	*	*
<b>DEPARTMENT OF DEFENSE</b>	<b>85.80 (2)</b>	<b>6.6</b>
<b>DEPARTMENT OF ENERGY</b>	<b>3.72</b>	<b>0.29</b>
<b>DEPARTMENT OF AGRICULTURE</b>		
Agricultural Research Service	*	*
<b>DEPARTMENT OF EDUCATION</b>		
National Institute of Disability and Rehabilitation	*	*
<b>INDEPENDENT AGENCIES</b>		
United States Agency for International Development	31.33	2.4
Veterans Administration	20.58	1.6
<b>TOTAL, Federal Obligation</b>	<b>\$1,303.37</b>	<b>100.0 **</b>

(1) Excludes AIDS-related research.

(2) Obligations for "infectious diseases" research. Most diseases studied are in the United States, though they may be common overseas.

\* Data unavailable

\*\* Percentages may not add to 100 due to rounding.

**Table 10**  
**Research Dollars Obligated by NIH Institutes to Research Activities On Rare Diseases:**  
**FY 1987**

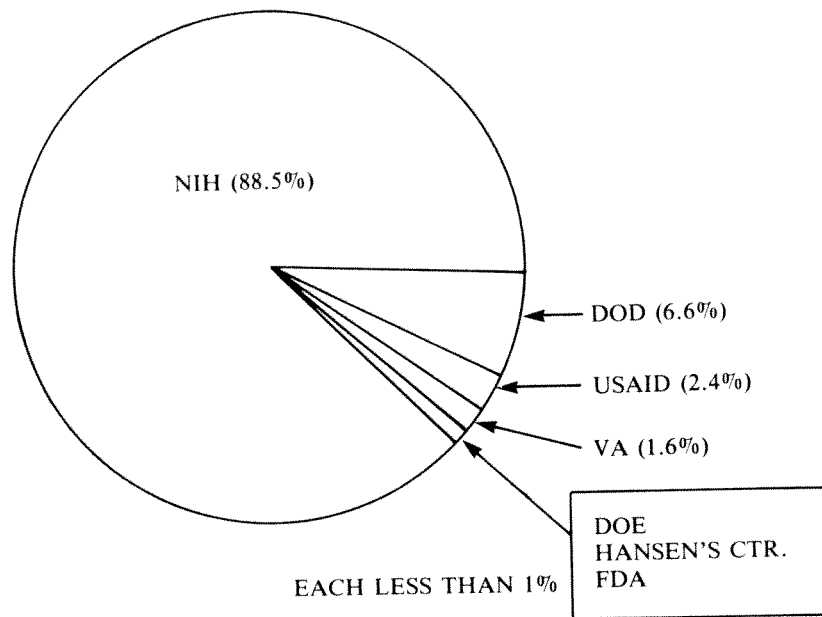
<i>Agency</i>	<i>Total Dollar Amount Obligated (in \$ millions)</i>	<i>Percent of Total NIH Obligation</i>
National Cancer Institute	\$ 662.02	57.6
National Heart, Lung, and Blood Institute	104.00	9.0
National Institute of Neurological and Communicative Disorders and Stroke	103.91	9.0
National Institute of Diabetes and Digestive and Kidney Diseases	73.10	6.4
National Institute of Allergy and Infectious Diseases	69.04 <sup>(1)</sup>	6.0
National Institute of Child Health and Human Development	55.86	4.9
Division of Research Resources	30.39	2.6
National Eye Institute	28.56	2.5
National Institute of Arthritis and Musculoskeletal and Skin Diseases	20.64	1.8
National Center for Nursing Research	2.57	0.2
National Institute on Aging	1.57	0.14
National Institute of Dental Research	1.13	0.10
National Institute of General Medical Sciences	.88	0.08
Warren Grant Magnuson Clinical Center	.13	0.01
Center Fogarty International	*	*
Division of Research Services	*	*
<b>TOTAL</b>	<b>\$1,153.78</b>	<b>100.0**</b>

<sup>(1)</sup>Non-AIDS related research.

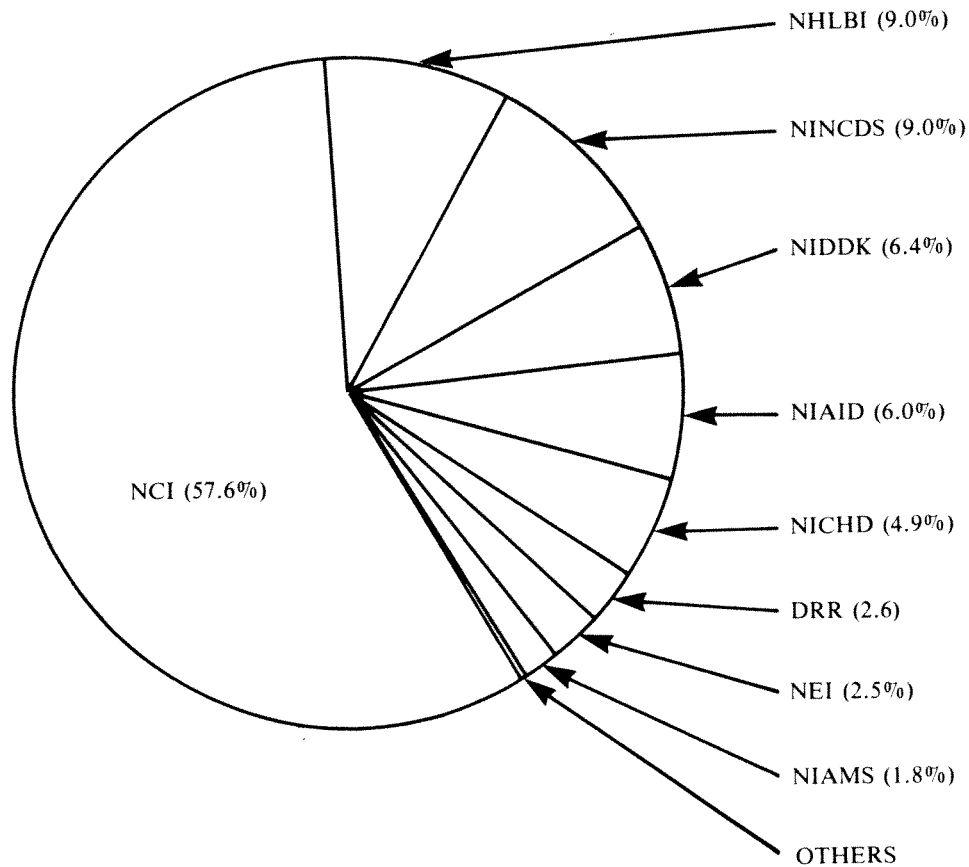
\* Data are unavailable.

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

**Figure 1**  
**Percentage of Research Dollars Obligated by Federals Reporting Research Activities On Rare Diseases: FY 1987**



**Figure 2**  
**Percentage Distribution of NIH Obligations for Rare Disease Research: FY 1987**



OTHERS = NCNR/NIA/NIDR/NIGMS/CLINICAL CTR (<1% EACH)

## RESEARCH TRAINING AND CAREER DEVELOPMENT

Research training is essential to maintain a continuous supply of investigators trained in the disciplines of biomedical research. At NIH, the pool is replenished through research training and career development grants. Nurturing young investigators and attracting or maintaining their interest in rare diseases is of great concern to the Commission.

Selected graduate students are supported by NIH through predoctoral research training grants administered primarily by the National Institute of General Medical Sciences but by some of the categorical institutes as well. Postdoctoral training is also supported through institutional training grants given to universities, medical centers, and similar research centers. Candidates are selected by the director of the institution's training program. In addition, students may apply directly for support of their research programs.

It is important to attract medical students to research. A base of clinical investigators with a strong background in medicine and research methods is critical to ensure competitive clinical grant applications and continued progress in the application of medical science to human disease. Further, studies have shown that it is important to reach medical students early in their training, since they are not likely to change their career direction later on. This area is of great concern to the Commission.

Medical students who are interested in research can become involved through the medical scientist training program or through a combined M.D.-Ph.D. program. The NIH has reported that renewed efforts to attract M.D.s into research have resulted in an increase in the number of physicians being trained under research training grants over the last five years. In 1980, the ratio of Ph.D. to M.D. trainees was about 2 to 1. In 1986, the ratio was about 1 to 1. However, the majority of these trainees conduct basic research rather than clinical research. Furthermore, no special provisions are currently being made to train medical students or physicians in rare disease research or to attract them to this area. The participation of physicians in clinical research, particularly clinical research on rare diseases, must be increased further.

Special awards, such as the First Independent Research Support and Transition (FIRST) Award, have been created to draw the most gifted research trainees into the mainstream of independent biomedical research. This award provides support for five years, thus enabling an investigator to get his or her project under way without having to reapply for funds 18 months after beginning it. Other awards for new investigators offer wider latitude in the criteria applied to their research.

Career development awards are designed to provide an investigator with a bridge between the completion of research training and the development of full independence. Some awards provide a salary and can be supplemented from non-Federal sources. Several are designed to train clinical investigators. Ordinarily, these awards provide limited research support.

A grave problem facing research training and career development has been the hesitancy of Congress to make stipends and salaries for NIH trainees competitive with salaries in the private sector. National Research Service Award (NRSA) stipends were raised from about \$6,500 to \$8,500 for predoctoral students and from between \$16,000 and \$31,000 to between \$17,000 and \$32,000 for postdoctoral fellows, effective in FY 1989. These amounts are still not competitive with salaries in the private sector. An index should be devised so that stipends can be adjusted biennially to control for inflation in the biomedical field. In addition, investigators should be able to expect continued support after their training is completed. Stable, consistent salaries are necessary if Federal programs are to attract the country's best students into biomedical research careers.

## CLINICAL RESEARCH CENTERS

The Commission considers the Clinical Research Centers (CRCs) to be an extremely useful means of conducting rare disease research. At NIH, the Clinical Research Center program supports a network of 78 centers nationwide, most of them discrete units within hospitals of academic medical centers. The centers host investigators whose primary research is funded by other components of NIH, by other Federal, state, and local agencies, and by the private sector.

In FY 1988, 6,567 investigators received nearly \$650 million of research support, derived predominantly from the categorical institutes of NIH, to direct 4,610 research projects on CRCs (Table 11). Funding investigators in CRCs is a cost-effective approach to research for NIH categorical institutes. As a result, the CRC program has become an integral part of their clinical research mission.

The CRCs support both pediatric and adult clinical research. To do so, they provide not only inpatient and outpatient research facilities, but also computerized data management and analysis, specialized laboratories, biostatisticians, and specially trained research nurses and other paramedical staff. In addition, the centers provide an environment in which house staff and medical students can observe the bidirectional nature of research and medical practice.

Some of the most important clinical studies in the United States are conducted in the CRCs. No other research



source addresses the needs of rare disease patients and investigators as directly as they do. They support such traditionally underfunded areas as longitudinal studies, disease delineation, and observational studies, and their flexibility allows basic research findings to be translated rapidly into clinical research.

Despite their excellence and importance, all CRCs are being scaled down—in number of units, number of beds, and number of dollars. These reductions present a serious obstacle to clinical research on rare diseases. For example, since pediatric CRCs in children's hospitals could not compete successfully with pediatric centers in large university hospitals, some of them were eliminated. Yet because of the sheer number of patients they attract, children's hospitals are crucial to the study of rare diseases such as genetic defects and inborn errors of metabolism. Cuts in funding can also affect the investigator's ability to assemble enough patients for a study, which is always a problem in studying rare diseases. Persons with rare diseases are scattered over a wide geographic area and must therefore travel a great distance to a CRC. In addition, their families must stay somewhere. These travel and living expenses, which can be considerable, are most often not covered.

**Recommendations:**

- 17. Congress should increase funding for CRCs by \$40 million over four years to increase the number of CRCs, increase nurses' salaries, and renovate and upgrade facilities.
- 18. Criteria used in evaluating CRCs should emphasize the rare disease research programs conducted or proposed.

**Workshops: A Successful Approach**

One successful approach to the problem of attracting basic and clinical investigators was taken by the Hereditary Disease Foundation of Santa Monica, California. The foundation has created a program of interdisciplinary workshops to stimulate new hypotheses and recruit new investigators to the study of Huntington's disease. Workshops for other rare diseases could be developed along this model and sponsored by private foundations, voluntary agencies, and the Federal government.

**Table 11**  
**Funding of CRCs (N = 78), Investigators, and Research Projects, Fiscal Years 1987 and 1988.**

<i>Fiscal Year</i>	<i>Investigators</i>	<i>Research Projects</i>	<i>NIH Support *</i>
1987	6,395	4,427	\$396.7 million
1988	6,567	4,610	\$511.8 million

\* Primary research support to CRC investigators from other components of NIH. In FY 1987, investigators obtained approximately \$100 million additional research funding from other components of the PHS, other Federal and state agencies, and the private sector, including industry. In FY 1988, that figure was approximately \$150 million.

The workshops designed for Huntington's disease are limited to 15 to 20 scientists in basic and clinical specialties. At least two scientists from each specialty area are present. Most of them have never worked on Huntington's disease, and many had never heard of it before receiving the foundation's invitation. Open, informal discussion is encouraged; slides and speeches are forbidden. Each workshop begins with a presentation by a patient, so investigators are shown from the outset how important their discussions are to individuals' lives.

Each year, several investigators become so intrigued by the ideas presented at the workshops that they develop research proposals. They are encouraged to approach the foundation for "seed money" to test the feasibility of those proposals. Some of the ideas have proved so promising that the investigator subsequently requested NIH funding, usually with success. The foundation considers an active role in stimulating research to be crucial and has reached the conclusion that workshops are an inexpensive and excellent means of attracting investigators.

The Commission also noted that NIH supports interdisciplinary workshops to stimulate investigators' interest in a disease or area that needs attention. Such workshops can greatly benefit rare diseases.

The Commission recognizes the benefits of workshops for recruiting scientists—and their new ideas—from other areas of research. It encourages foundations to consider funding educational workshops in cooperation with voluntary agencies and to provide seed money for testing the ideas generated by the workshops.

**Recommendation:**

- 19. Voluntary organizations, foundations, and Federal agencies should continue to co-sponsor workshops and symposia to attract new and experienced investigators and to stimulate new research hypotheses.

**OTHER RARE DISEASE RESEARCH WITHIN DHHS**

Four agencies within DHHS other than NIH sponsor extramural and intramural rare disease research activities:

- Alcohol, Drug Abuse, and Mental Health Administration
  - ☆ National Institute on Drug Abuse
  - ☆ National Institute of Mental Health
- Centers for Disease Control
- Food and Drug Administration
  - ☆ Office of Orphan Products Development
- Health Resources and Services Administration
  - ☆ Gillis W. Long Hansen's Disease Center
  - ☆ Office of Maternal and Child Health

In the Commission's survey of Federal agencies, it found that most agencies were unable to accurately identify or quantify the financial resources devoted to rare diseases. Those organizations with an active orphan drug component or whose focus was a specific rare disease were able to provide this information. It appears that most federal agencies do not consider rare disease research separately from research on common diseases.

#### **Recommendation:**

20. All government agencies conducting or funding rare disease research should have a mechanism for identifying and monitoring such activities. Resulting data should be provided to Congress annually.

#### ***Alcohol, Drug Abuse, and Mental Health Administration***

The ADAMHA, through the National Institute on Drug Abuse (NIDA) and the National Institute on Mental Health (NIMH), has limited but important roles in rare disease research. Both institutes stimulate research and research training through programs similar to those at NIH. NIDA indicated, however, that there has been a reluctance on the part of pharmaceutical companies to become involved in the development of drugs for the treatment of addictive disorders. In part this reflects economic considerations but as well the stigma associated with drug addicts. Public relations efforts are needed to overcome these obstacles if we are to develop effective treatment for addicts.

The NIMH has responsibility for improving the mental health of the American people by fostering the understanding, treatment, and rehabilitation of the mentally ill and the prevention of mental illness. Basic research and clinical studies in psychiatry, psychology, neurogenetics, neurochemistry, neurophysiology, and cellular and molecular biology are conducted in NIMH intramural facilities. Extramural funds are used to support research at universities, hospitals, mental health centers, and other research facilities across the country.

The NIMH has funded research projects focused on the following rare diseases: pervasive developmental disorders in children, genetic and environmental factors in the transmission of Tourette's syndrome, the relationship between depression in young people and adults, the biomedical and physiological correlates of psychiatric illness, childhood psychopathology, cognitive impairment in obsessive-compulsive disorder, autism, and social phobias. Many of these activities were included in the \$353.8 million obligated for research activities in FY 1986.

The public needs current and accurate information about neuropsychiatric disorders and drug addiction. Due to budget cutbacks in recent years, NIMH and NIDA have

been unable to update educational materials published for the public and professionals.

#### ***Centers for Disease Control***

The CDC is responsible for developing and applying strategies for disease prevention and control and for improving the health of the American people through environmental health and health education activities. It is responsible for controlling the introduction and spread of infectious disease in the United States. It also consults with and assists other nations and international agencies.

The CDC develops collaborative arrangements with other institutions and works with state and local health agencies. In FY 1987, it spent \$6.54 million on extramural and intramural research, including research on rare diseases. No effort has been made at the CDC to differentiate between common diseases and rare diseases. In 1987, it conducted research on poliomyelitis, malaria, plague, Kawasaki syndrome, rabies, and AIDS.

In its prevention and control program, the agency stocks and distributes at no charge anti-infective and antiparasitic drugs for some rare conditions, such as amebiasis, leishmaniasis, and trypanosomiasis; immunobiologics and vaccines for western equine encephalitis; and tularemia skin test antigen. These products either are not licensed or are licensed but not available from commercial sources. Information about the availability of these compounds is widely disseminated through the *Medical Letter*, *Morbidity and Mortality Weekly Report*, *The Journal of the American Medical Association*, and other professional publications.

Results of the Commission's survey of physicians indicate that physicians are particularly familiar with the services of the CDC and use them when necessary.

#### ***Food and Drug Administration***

Although best known for its regulatory activities in the pre- and postmarketing phases of products, including drugs, medical devices, biologics, and medical foods, the FDA also sponsors rare disease research through some of its programs. These include the Office of Orphan Products Development; the National Center for Toxicological Research; the Center for Devices and Radiological Health, which assesses the effects of radiation on human health; the Center for Biological Evaluation and Research, which conducts research on mechanisms of disease pathogenesis and disease prevention; and the Center for Drug Evaluation and Research, which develops animal models for evaluating the short- and long-term effects of drugs and seeks to improve methodologies for evaluating drugs.

#### ***The Office of Orphan Products Development***

The OOPD was formed in 1982 in the Office of the Commissioner of FDA. The Office assists sponsors of orphan

products in obtaining protocol assistance, seeks sponsors for orphan products, and assists the Center for Biologic Evaluation and Research and the Center for Drug Evaluation and Research in understanding rare diseases and orphan products.

The Office determines if a drug or biologic is an orphan product and if so designates it accordingly. This process requires extensive knowledge of both the disease and the product. Since the passage of the Orphan Drug Act in 1983, more than 250 products have been designated as orphan products and 33 designated drugs and biologics have received New Drug Approval or Product Licensing approval.

The Commission commends the staff of the Office of Orphan Products Development for their excellent efforts and creative problem solving. The Commission encourages the Office to continue their efforts to communicate to the FDA the needs of persons with rare diseases and the difficulties in studying products in small patient populations.

The Office of Orphan Products Development also manages a grants program to support both preclinical and clinical studies on the use of drugs, biologics, medical devices, and medical foods for rare diseases. Of the FDA's FY 1987 research budget of \$99.86 million, \$83 million was primarily for in-house product testing, compliance, analytical methods, and standards development. Of the remaining \$16.86 million, \$5.86 million was obligated to support research and review of orphan products. Of the \$5.86 million, \$3.9 million was used for research grants. One grant has led to a marketed product, an angioscopic device used for severe forms of pulmonary emboli.

Through special appropriations, the Office of Orphan Product Development's grants program has grown very slowly but steadily since its inception in 1983. However, the FDA has never received the full amount authorized by Congress for the program. In 1988, Congress increased the authorization for the program to \$10 million for FY 1988, \$12 million for FY 1989 and \$14 million for FY 1990.

The FDA's approach to grant review is somewhat different from that of NIH and ADAMHA. Rather than having standing study sections that conduct the initial review and score the application, the FDA selects ad hoc field reviewers from government, academia, and the pharmaceutical industry. These reviewers provide priority scores for grant applications.

*The National Center for Toxicological Research.* The National Center for Toxicological Research (NCTR) is an integral part of the FDA. Its mission is to conduct research on the pathways associated with carcinogenicity, mutagenicity, and reproductive and

developmental toxicology. The intent in creating the NCTR was to have a coalition directed by both the Environmental Protection Agency and the FDA. The NCTR was to be a common ground upon which industry, academia, and the government could join forces and solve basic problems. With recent changes attributed to the Federal Technology Transfer Act of 1986, many of the investigators at NCTR are now on-site contractors who are not Federal employees. Other Federal agencies reimbursed NCTR \$5 million of its \$25 million budget for FY 1987 to conduct required studies.

The Commission believes that the NCTR is in a position to conduct required toxicological studies of orphan drugs when a commercial sponsor is unable to undertake this task. It has facilities that meet FDA requirements for good laboratory practices, and it is subject to the same FDA inspection as commercial laboratories. Requests for conducting toxicological studies on orphan drugs by the NCTR would have to be approved by the commissioner of FDA. Currently, NCTR is conducting toxicological studies on L-cycloserine with funds from the Office of Orphan Products Development.

#### **Recommendations:**

21. Congress should fully fund the grants program of the FDA's Office of Orphan Products Development at the level authorized by P.L. 100-290 and assure the continuation and expansion of the program.
22. Congress should appropriate additional funds to the FDA for toxicological studies by the National Center for Toxicological Research on selected orphan drugs. Congress should also authorize the National Center for Toxicological Research to use their existing funds to conduct studies on selected orphan drugs.

#### **Health Resources and Services Administration**

In the Commission's survey of Federal agencies, the HRSA reported two offices with rare disease research activities.

*Gillis W. Long Hansen's Disease Center.* The first office, the Gillis W. Long Hansen's Disease Center, is totally devoted to the study of leprosy, for which the center obligated \$2.3 million in FY 1987. Its efforts to educate the public include publication of *The Star*, prepared by patients at the center's Carville, Louisiana, location; publication of the *International Journal of Leprosy*; and publication of a textbook entitled *Leprosy*. The center also conducts seminars and a biennial national research conference.

The center maintains the National Hansen's Disease Register for referral of patients to physicians or regional centers. The register is also a vital source of patients for clinical investigators.

Recent research supported by the center has resulted in the development of macrolides active against *Mycobacterium leprae* and of experimental methods to culture *M. leprae*, and the recognition that leprosy occurs in 15 percent of wild armadillos, which may lead to the development of an antileprosy vaccine.

*Office of Maternal and Child Health.* The second office in HRSA with an interest in rare diseases is the Office of Maternal and Child Health, which has a long history of dealing with rare diseases. It works jointly with state health departments to provide screening programs for newborns. This office is primarily a service program and not a research program. 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, treatment, and management of a variety of genetic conditions such as sickle cell disease, hemophilia, Tay-Sachs disease, and spina bifida.

Since 1935, the Federal government and the states have worked together to provide crippled children's services, child welfare services, and maternal and child health services. For the most part, the states provided the services, which were paid for by Federal dollars and matching state dollars.

In 1981, the maternal and child health block grant changed that. Now, 85 percent of the Federal appropriation (almost \$500 million in FY 1987) is allocated to the states for their programs; the other 15 percent, the set-aside, is used by the Federal government to support Special Projects of Regional or National Significance (SPRANS). These projects include training; hemophilia diagnosis and treatment; genetic disease screening, counseling, and referral; and grants for maternal and child health improvement projects.

Finding ways to help children with chronic or disabling conditions develop to their fullest potential is a particular concern of the rare disease community. SPRANS could utilize these funds to conduct research and develop model service programs that would produce long-term beneficial effects for children with rare diseases.

**Recommendation:**

23. Congress should recognize that the Maternal and Child Health Block Grant, particularly through the SPRANS program, is a signifi-

cant prevention, education, and service delivery program for children with rare diseases. Congress should therefore increase the funding for this program.

**EPIDEMIOLOGICAL STUDIES**

Accurate information about the incidence and prevalence of a disease, as well as the geographical distribution of patients, can be extremely important for the investigator or planner who proposes a project, the reviewers who evaluate the proposal, and for members of the health delivery system who implement resulting treatments. Epidemiological studies of small populations are expensive, however, and have not been given priority in funding decisions.

Program and policy decisions in health research are often made on the basis of epidemiological information. What is the size of the problem? Does it affect certain subpopulations disproportionately? What is the estimated incidence? How many people are actually diagnosed? How many receive treatment? What are the morbidity and mortality rates? How much does the disease cost the nation? Even when an investigator has located a large kindred for a genetic disease, for example, vital information may be lost because he or she cannot obtain funding for an epidemiological study.

The National Center for Health Statistics (NCHS), which worked with Commission staff in designing the Commission's surveys, acknowledged the absence of reliable statistical information about rare diseases, the need for such information, and the difficulty of collecting it. Unless funds are appropriated specifically for obtaining such information or interagency agreements effect a transfer of funds, the NCHS is unable to make the collection of rare disease statistics a program priority. The FDA requires submission of prevalence data by sponsors applying for an orphan drug designation, but since there have been very few epidemiological studies on rare diseases, such data often do not exist.

**Recommendation:**

24. The National Center for Health Statistics should determine the prevalence of rare diseases in the United States.

**RARE DISEASE RESEARCH IN OTHER FEDERAL AGENCIES**

Five departments or agencies outside DHHS reported rare disease research activities: the Department of Defense, the Department of Education, the Department of Energy, the United States Agency for International Development, and the Veterans Administration.

### *Department of Defense*

The Department of Defense (DoD) supports research on infectious diseases, such as malaria, that are rare in the United States but can be a threat to personnel deployed overseas. Both intramural and extramural research are sponsored, and proposals are reviewed separately by the Army, Navy, and Air Force. The proposals are evaluated for scientific merit either by in-house committees or by joint in-house and extramural committees.

A ratio of rare disease research to total DoD medical research expenditures cannot be estimated, because the number of infectious diseases that are of interest to the DoD and rare in the United States cannot be established. The Army spent \$293 million in fiscal 1987 on medical research; 29 percent of this was spent on infectious disease research, most of which relates to tropical diseases that are rare in the United States.

### *Department of Education*

The National Institute on Disability and Rehabilitation Research (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, methods, and devices that help improve the quality of life for disabled people.

The NIDRR grant and fellowship applications undergo staff and peer review. Peer reviewers are Federal employees with expertise in particular areas or non-Federal scientists. The NIDRR obligated \$56.2 million for research in FY 1987 but has no means of identifying how much of that was for rare disease research.

The NIDRR supports the National Rehabilitation Information Center. This center responds to requests for information on rehabilitation issues from educators, manufacturers, investigators, families, and other interested parties.

### *Department of Energy*

The Department of Energy (DOE) supports the development of beneficial applications of energy-related technologies, such as radioactive nuclides, radiopharmaceuticals, imaging instrumentation, and particle beams for the diagnosis, treatment, and study of diseases. These technologies are very often important to rare disease diagnosis, research, and therapy.

Investigator-initiated grant proposals are reviewed by ad hoc external peer reviewers and then by in-house scientific panels. The total research obligation for DOE's Office of Health and Environmental Research in FY 1987 was \$196.57 million. Of this, \$26.82 million was spent on

nuclear medicine and about \$3.7 million on research technologies that relate to rare diseases. Approximately 2 percent of the total research budget supported rare disease-related research. Examples of successful efforts include 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, which will be tested for use in angiography; and the use of proton beams to treat arteriovenous malformations.

At this time, DOE does not support clinical research and does not have the equivalent of clinical trials. When its studies proceed to the clinical stage, therefore, the recruitment of patients as research subjects could become a problem. If DOE intends to support this type of research, efforts to locate the required patients should begin as soon as possible. (Voluntary organizations could help in finding patients.) If this technology is to be transferred to other government agencies, a formal coordination mechanism should be put in place.

### *United States Agency for International Development*

The United States Agency for International Development (USAID) helps developing countries achieve self-sustaining economic growth by improving the health and well-being of their populations. In the health sector, the USAID's primary goal is to improve the health status and life expectancy of the population, especially by reducing infant and child mortality. The agency seeks to promote research on diseases of public health importance in the developing world, particularly diseases for which there are inadequate research incentives in industrialized countries and inadequate research resources in developing countries.

All research funded by the USAID is extramural. The agency encourages proposals from institutions located in developing countries. Proposals are reviewed by technical committees composed of both USAID and outside experts. In FY 1987, the USAID obligated \$31.3 million for research projects, nearly all of which were related to diseases that are rare in the United States.

Major clinical research activities focus on treating diarrhea and testing vaccines. Recent accomplishments include improved methods for diagnosing typhoid fever, diarrheal diseases, malaria, and tuberculosis; completion of field trials of a new vaccine for measles; demonstration of the higher efficacy of a new vaccine against typhoid fever; documentation of longer protective immunity provided by a new oral vaccine for cholera; and development and testing of new oral rehydration solutions that reduce the volume, duration, and rate of diarrheal fluid losses.

Since USAID research is undertaken primarily in or for less developed countries, it poses special problems for basic and clinical research. The target populations, often infants

and children, are frequently in a poor state of health. They may be malnourished or live in unsanitary conditions, and they exhibit high levels of polyparasitism. This environment, combined with the ethical issue of using children as research subjects, presents great problems for clinical investigators. The USAID views the lack of native laboratories, adequate laboratory equipment, and support from the private sector, particularly pharmaceutical firms, as additional problems.

The USAID supports its own clearinghouse, which focuses on funded projects and programs and provides documents of interest to investigators and the public.

### *Veterans Administration*

The Veterans Administration (VA) hospital system is a valued training ground for physician-investigators, and its projected budget decreases are of concern to the Commission. The mission of the VA is to provide health care to eligible veterans. The VA conducts biomedical, prosthetic, and health service research, including research that focuses on rare diseases. All of it is intramural and is conducted by VA clinicians and nonclinicianscientists in VA hospitals. Research proposals are first reviewed locally for scientific merit. Proposals requesting funds from the central research and development program are also reviewed by a merit review board, which is analogous to NIH study sections.

About 90 percent of the research proposals considered for central office funding are generated by VA clinician-scientists, most of them physicians, who are pursuing their interest in immediate or long-range health care for veterans. The majority of research projects funded are clinical studies. In FY 1987, the VA spent \$194.7 million to support research and research training activities. Of this amount, \$20.6 million (10.6 percent) was spent on rare disease research.

## **PRIVATE SECTOR FUNDING OF RARE DISEASE RESEARCH**

The Commission surveyed three non-Federal sources of funds for research on rare diseases—voluntary organizations, foundations with an interest in health, and the pharmaceutical industry.

### ***VOLUNTARY ORGANIZATIONS***

*The role of rare disease voluntary groups has been more significant than it should have been. They have filled a gap that public policy and corporate motivations have left wide open. The significance of the role is a sad commentary on the lack of recognition of a need.*

—Representative of Voluntary Organization

Voluntary organizations play an important role in the development of knowledge about orphan diseases, a role limited only by the size of their budgets. Although they are not a major source of research funds, they provide some independent grant support, provide a much larger amount of seed money, and, most important, recruit investigators and provide them with continued encouragement.

Information about the ability of voluntary organizations to fund research was gathered for the Commission by the National Organization for Rare Disorders (see Chapter 1). The information shows that:

- Biomedical research, clinical trials, and scientific meetings are rated as important activities by the oldest, most generously supported organizations.
- For organizations 5 to 10 years old, biomedical research ranks among the three most important activities, measured in dollars.
- For organizations 11 or more years old, biomedical research is one of the two most important activities, measured in dollars.
- Research grants are provided by 50 of the 113 organizations surveyed. The grants range from \$10,000 to \$53,000.
- Fourteen organizations award 1 grant per year, 12 award 2 or 3 grants per year, 2 award 150 to 200 grants per year, and 1 awards 700 grants per year.
- Of the grant-awarding organizations, 36 indicate that investigators who received seed money from them subsequently received grants from the Federal government.
- Thirty-five organizations provide funds to stimulate the entry of scientists and physicians into biomedical research, such as fellowships.

Voluntary organizations cannot carry the burden of initiating and supporting research alone, nor can they be a major contributor to the effort. Their activities focus on providing seed money and generating interest in areas where there was none previously. The Commission wishes to encourage and support these activities of voluntary organizations.

### **Recommendations:**

25. Voluntary organizations with common research and education interests should be encouraged to form and participate in alliances and coalitions in order to enhance the use of their scarce dollars.
26. No additional regulatory changes should be made in IRS 501(c) rules restricting voluntary organizations' fund-raising activities or their advocacy role. Voluntary organizations should not be restricted in educating congressional and Federal personnel about the needs of their constituents.
27. The Federal government should not inhibit the fund-raising activities of nonprofit

voluntary organizations through the Unrelated Business Income Tax law and regulations.

28. The Federal government should not increase the bulk-mail rates for voluntary organizations, because this would limit the ability of these organizations to reach the people they serve.
29. Congress should enact the Volunteer Protection Act without delay to protect volunteers from legal suits. Many rare disease voluntary organizations cannot afford, and sometimes cannot obtain, liability insurance for volunteers. The absence of such insurance often discourages volunteers from donating critically needed time and talent.

## FOUNDATIONS

To determine what role private foundations play in funding research on rare diseases, the Rockefeller University conducted for the Commission a pilot survey of 106 foundations interested in health issues (see Chapter 1). The results show that:

- Forty-three foundations fund biomedical research; they devote, on average, 17.5 percent of their budgets to such grants.
- Twelve fund rare disease-related grants; 8 of the 12 reported that such grants account for 1 percent or less of their annual budgets.
- The 12 foundations funding rare disease-related activities spend about \$1.6 million for these activities.
- Forty-five report that policy restrictions against disease-specific research prevent them from funding grants on specific rare diseases.

The Commission also participated in a round-table discussion on June 9, 1988, with representatives of the Howard Hughes Medical Institute and The Robert Wood Johnson Foundation. The Howard Hughes Medical Institute, with an endowment of about \$5.2 billion, and The Robert Wood Johnson Foundation, with \$2 billion in assets, are the two largest private philanthropies in the United States with a sole interest in health issues.

The discussion revealed that:

- Neither of the philanthropies funds research on specific diseases. The Howard Hughes Medical Institute supports productive biomedical investigators rather than specific diseases, and The Robert Wood Johnson Foundation concentrates on health problems rather than specific diseases.
- The Howard Hughes Medical Institute indirectly supports rare disease-related research by funding investigators whose interests include rare diseases. Approximately 44 (24 percent) of the investigators

supported by the institute are working on some 61 rare diseases. Support for these investigators is approximately \$15 million.

- The Howard Hughes Medical Institute funds basic and clinical biomedical investigators; The Robert Wood Johnson Foundation funds programs related to health service delivery.
- Neither of the philanthropies funds clinical trials of therapeutic agents, and neither is likely to do so. Private philanthropies consider this to be in the purview of industry.
- Most private philanthropies are unaware of the significance of rare diseases in the health care system and consider that special-purpose foundations and voluntary organizations are the best vehicles for generating knowledge on specific diseases.

The Commission has concluded that, as presently structured, foundations have only a limited ability to respond to outside communications and requests about understudied problems such as rare diseases. The Commission has also concluded that their potential for funding research on rare diseases is largely unexplored. This is due primarily to mutual lack of understanding on the part of foundations and voluntary organizations. Often foundations misperceive the wealth of the voluntary sector: one foundation noted that voluntary agencies can raise more money with poster children than foundations are able to give them. It is essential that each fully understand what the other does and that foundations begin to respond to the need for research on rare diseases.

Foundations need to understand that only a tiny fraction of the 5,000 or so known rare diseases are represented by well-funded voluntary organizations or special-purpose foundations. Voluntary organizations need to learn to work within the constraints created by the idiosyncracies of the philanthropic system. For example, if a foundation cannot fund disease-specific research or clinical trials, voluntary organizations representing similar diseases can form coalitions to determine what basic biomedical knowledge would be beneficial to them. If a foundation supports investigators rather than research, such coalitions could develop recruiting programs to assist investigators in applying for grants from the foundation.

## THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry is second only to the Federal government in its funding of research and development. That support totaled \$6 billion in 1986. Results of the pilot survey done for the Commission underreport the industry's involvement in rare disease research and development of products for rare diseases, for two reasons. Many firms combine research and development costs



in their budgets, and rare disease and nonrare disease research activities may not be differentiated until very late in the developmental stages, if at all.

The 37 firms responding to the survey indicated that they spent \$54.6 million in FY 1987 on rare disease research and the development of products for rare diseases (see Table 12). These firms reported that \$190.3 million in research funds had been allocated to the 118 approved or investigational products for rare diseases mentioned in the survey. An additional \$95.4 million is expected to be spent on the 81 products under development.

The FDA has granted 257 orphan product designations since the Orphan Drug Act was passed in 1983. This includes 59 in 1987 and 74 in 1988. Figure 3 presents the industry's orphan product development activities since the act was passed.

Since 1983, 33 orphan products have been approved for marketing by the FDA. The Commission commends those firms that have devoted personnel and financial resources to the development of orphan products and expects many of the designated orphan products to obtain either treatment IND status or product approval from the FDA. The Commission suggests that all firms with potential products for rare diseases take advantage of the services and available programs to stimulate rare disease research and orphan product development.

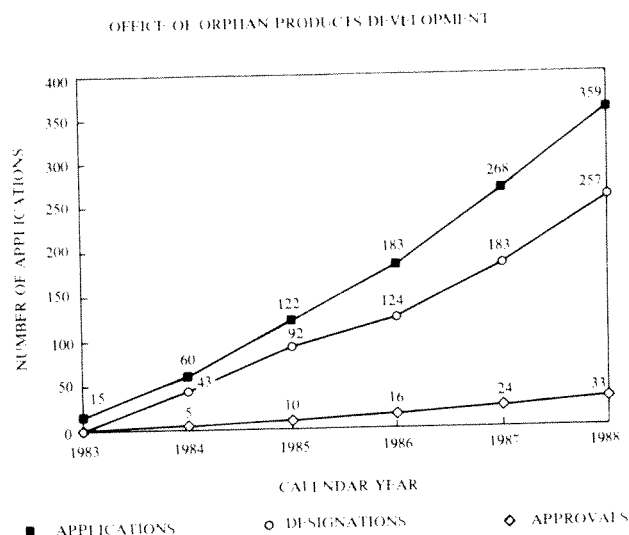
The pharmaceutical industry is a key element in the development of orphan products for rare diseases. Without its commitment, it is unlikely that products will become available. The Commission encourages pharmaceutical firms to bring orphan products to the marketplace.

**Table 12**  
**Results of the Survey of the Pharmaceutical Industry: FY 1987**  
(Millions of Dollars)

	<i>PMA</i> ( <i>N</i> = 17)	<i>ODC</i> ( <i>N</i> = 6)	<i>GPIA</i> ( <i>N</i> = 3)	<i>ABC</i> ( <i>N</i> = 11)
Marketed Products	29	7	0	1
Investigational Products	43	11	5	22
Amount Spent on Orphan Product Research and Development	\$ 51.6		\$ 3 (1 firm)	
Previously Funded Orphan Product Development Costs	\$164.1 (10 firms)	\$24.7	\$ 1.5 (2 firms)	
Anticipated Future Expenditures	\$ 62.5 (7 firms)	\$15.9	\$17 (2 firms)	

Note: PMA is the Pharmaceutical Manufacturers Association; ODC is the Orphan Developers Coalition. GPIA is the Generic Pharmaceutical Industry Association; ABC is the Association of Biotechnology Companies.

**Figure 3**  
**Cumulative Designations and Actions**





## PART IV

### PRODUCT DEVELOPMENT AND COORDINATION WITH RESEARCH

*“There are medications that have been tested in clinical investigations and found effective for a limited number of patients, but have never gone beyond that stage. Means must be found to encourage pharmaceutical manufacturers to test and market products that will help us.”*

*—Patient with Sjogren’s Syndrome*

## Chapter 7

# PRODUCT DISCOVERY, DEVELOPMENT, AND AVAILABILITY

The Commission found desperate need for more products to treat persons with rare diseases. Patients, caregivers, physicians, biomedical researchers, and representatives of voluntary organizations and the pharmaceutical industry all called for a comprehensive, systematic program to discover and develop not only orphan drugs, but medical foods and medical devices as well.

In this chapter the Commission describes barriers to orphan product discovery and development, the availability of orphan products after approval, and means of enhancing technology transfer. In chapter 8 it addresses the need for coordination of research and development activities among and within the public and private sectors.

### DISCOVERY AND DEVELOPMENT OF ORPHAN PRODUCTS

The development of products to treat persons with rare diseases, like the development of products to treat persons with common diseases, is a lengthy, complex, and costly process. According to the Pharmaceutical Manufacturers Association, it takes an average of 10 years and \$97 million to develop a drug from initial synthesis to approval and subsequent marketing. For a new molecular entity (NME), roughly two to three years of this time is spent in gaining approval from the FDA. Because firms usually apply for a patent early in the development process, they have exclusive market rights for only about seven years after approval. This is a relatively brief period for recouping research and development costs, especially when the market for a product is small, as it is for orphan products.

The Orphan Drug Act and its amendments provide a number of economic incentives for the development of orphan products (see Chapter 2), and these incentives have largely proved effective. They have also proved controversial. On the one hand, they have provoked charges that exorbitant profits are being made from the sale of some approved orphan products. On the other hand, they have been criticized as being too weak to be of more than limited value.

The Commission recognizes the plight of patients and their families who are unable to afford a product for a rare

condition, yet it is convinced that economic incentives are essential to stimulate discovery and development of orphan products. Most orphan products are not, in fact, profitable for their manufacturers; for this reason the Commission believes, as discussed below, that incentives should be strengthened.

At the same time, the Commission is very concerned that the potential for abuse of the incentives in the Orphan Drug Act will threaten its future. The Commission therefore urges that if abuses are clearly documented, Congress consider limited corrective legislation.

Several pharmaceutical firms have developed programs to guarantee that all patients are able to obtain needed orphan medication at a reasonable cost or no cost. The Commission commends these firms and encourages other manufacturers to adopt this practice when a particularly costly product enters the marketplace.

Another stimulus to orphan product discovery and development has been the establishment of coalitions spanning the public and private sectors. These coalitions typically involve an academic investigator, a voluntary organization, the pharmaceutical industry, ADAMHA, CDC, FDA, and NIH. Coalitions assisted in the development of such drugs as Urocit K (Potassium Citrate), Pentam (Pentamidine Isethionate), and Calcibind (Cellulose Sodium Phosphate).

### BARRIERS TO PROGRESS

The Commission found barriers to orphan product development in the following areas: weak economic incentives; lack of access to new molecular entities; problems related to professional and product liability; problems in preclinical and clinical research; and the lengthy drug approval process.

#### Weak Economic Incentives

In the ten years before passage of the Orphan Drug Act in 1983, 10 products considered orphan drugs by today's standards gained FDA approval; since then, 33 designated orphan products have received FDA approval. This clearly indicates the value of existing incentives in speeding the rate

of orphan drug development but does not indicate the nature of the products approved. Some of the products were compounds that had existed before 1983 and had been neglected or whose development for orphan indications had been stalled for lack of a corporate sponsor. The number of products in this category will decrease as the initial flurry of development and marketing activity subsides.

Other orphan products approved since 1983 were new molecular entities (NME)—compounds not previously approved by FDA. The discovery that an NME has therapeutic value can come about through serendipity, deliberate synthesis, testing, and screening, a clinical trial, or some combination of these. Thus the central question in assessing the effectiveness of current incentives is: "Have they stimulated pharmaceutical companies to apply to rare diseases the same goal-oriented methods of product discovery and development that they apply to common diseases?" Simply counting the number of NMEs that become orphan products does not provide an accurate answer because of the long lag time to development and availability.

While there is at present no conclusive answer, the Commission believes that the incentives offered by the Orphan Drug Act are not compelling enough to warrant the diversion of corporate resources towards discovery and development of products for the rare diseases. Although some of the innovative orphan products were found serendipitously, the development of orphan products must not be left to chance.

It appears that the Commission is not alone in its belief that existing incentives are not powerful enough to spur the development of NMEs for rare diseases. For years the federal government has been involved in research and product development for certain rare diseases, notably epilepsy and various cancers, because the efforts of pharmaceutical companies in these areas were inadequate. (Establishing Federal drug development programs for any significant fraction of the remaining 4800 known rare diseases would be impractical, however.)

Persons testifying before the Commission indicated that the development of additional orphan products depends upon maintaining and expanding existing incentives. One representative of a small, new pharmaceutical company and one academic investigator indicated that if they had known what was in store for them, they would probably not have undertaken the sponsorship of their respective orphan drugs. The company representative also stated that his company could not afford to develop any additional orphan drugs.

Respondents to the survey of pharmaceutical manufacturers indicated that the most important incentive of the Orphan Drug Act has been the 7 years' exclusive marketing provision. They also cited several other incentives that

they believed would stimulate rare disease research and orphan product development:

- More flexible regulatory requirements for new product approvals;
- Reduction of long-term toxicity studies and elimination of carcinogenicity studies for products seeking to meet premarketing approval for use in patients with rare diseases;
- Extension of the tax credit provision of the Orphan Drug Act to all phases of rare disease research; and
- A fast-track review system for products to prevent, diagnose, or treat rare diseases.

Data from the Department of the Treasury show that the tax credit provision of the Orphan Drug Act has not been the major inducement it was intended to be. For taxable year 1985, approximately \$217,000 of credit was claimed on corporate tax returns. Fears of a tremendous loss of tax dollars to fund rare disease research appear unfounded.

The Commission also believes that patent protection for naturally occurring and biotechnology products should be strengthened. One factor in the high cost of some naturally occurring and biotechnology products is inadequate patent protection—competing products can be expected to enter the marketplace shortly after the original product is approved.

#### **Recommendations:**

30. The Commission recommends that incentives to stimulate the development of new orphan products be increased. Potential incentives include:
  - Increasing the period of exclusive approval from the current seven years,
  - Extending tax credits to all developmental activities, and
  - Extending the patent on one currently marketed patented product for every orphan product approved by the FDA. The Commission recommends, however, that this incentive be available only to companies that have established a systematic drug discovery and development program for non-cancer, non-AIDS rare diseases and that receive an approved NDA or premarketing licensing approval for a designated orphan product.
31. Congress should enact intellectual property protections for those biotechnology products not currently protected by the Patent and the Food, Drug and Cosmetic acts.

The Commission believes that providing patent extensions will produce the most significant increase in the number of new molecular entities for the treatment of noncancer and non-AIDS rare diseases.

## Lack of Access to New Chemical Compounds

Once an adequate test procedure is available, the tedious process of screening appropriate new drugs begins. This process could be accelerated by systematically giving investigators access to new chemical compounds developed by private industry and Federal agencies. All too often, products are studied for only one or two conditions; more widespread screening could greatly expand their potential usefulness.

### Recommendation:

32. The FDA's Office of Orphan Products Development should establish a program to act as a resource and assist investigators with promising orphan products to gain access to reference Drug Master Files and to obtain a sponsor.

## CONCERNS ABOUT LIABILITY

*"I was informed by one pharmaceutical firm that because of business considerations, including product liability, they could not embark upon the production of human surfactant from amniotic fluid. Another corporation was extremely interested, however. They also concluded that product liability issues were so great that it was not possible to compete in this marketplace."*

—Investigator of Rare Diseases

The Commission has heard frequent references to "liability issues," most often in regard to health care generally, but increasingly in connection with rare diseases. Concerns have been expressed that the potential liability of pharmaceutical or device companies and of practicing physicians with regard to research into and treatment of rare diseases may act as a deterrent to these activities. The Commission is not aware of any situations in which liability has been an actual barrier to the achievement of research or treatment goals regarding rare diseases. In a number of instances, however, concerns about liability have led to significant delays in product development and increased liability insurance costs. The Commission is sensitive to liability as it affects research and treatment generally and is concerned that patients with rare diseases not be adversely affected.

The Commission believes that the problem of liability is largely one of perception rather than fact. Nevertheless, to the extent that perceptions influence behavior, they constitute a real obstacle to rare disease research and treatment. The Commission is convinced that behavior has been influenced by perceptions about liability.<sup>35</sup> The

high cost of product liability insurance for orphan product development is based in large part on fear that the manufacturer may be found liable for adverse effects of the drug. Similarly, physicians who might otherwise treat patients with rare diseases may be deterred from doing so in the absence of adequate insurance coverage for the use of orphan drugs. Apart from the perception of a liability problem, the cost of both product and professional liability insurance has risen to the point where it constitutes a burden on research and treatment budgets.

## Product Liability

Concerns surrounding product liability stem primarily from a number of judicial decisions related to childhood vaccines and other pharmaceutical products, such as contraceptives. In those cases, liability was imposed on the manufacturers even in the absence of any showing of a defect in the manufacture of the products or of "traditional" negligence on the part of the manufacturers.<sup>36</sup> Essentially, the courts seem to have been developing a form of distributive justice, under which the manufacturers are deemed to be in a better position to provide compensation for adverse reactions than those who suffer them.<sup>37</sup> Because of this, prices of vaccines and other drugs have risen dramatically, reflecting both manufacturers' increased insurance premiums and their establishment of reserves to meet potential awards.

This situation also gave rise to the National Vaccine Injury Compensation Act.<sup>38</sup> Earlier, manufacturers' concerns about liability had led the Federal government to assume liability for the swine flu vaccine before the manufacturers would agree to release it.<sup>39</sup> Similar concerns about liability have been expressed in anticipation of an approved vaccine for AIDS.

The cases described above, while not dealing directly with the investigational stages of drug or device development, have had an impact on that process. The Commission is not aware of any cases of liability being assessed against a manufacturer for injuries incurred during the clinical testing of new drugs and devices. The informed consent and Institutional Review Board processes appear to protect manufacturers against liability at this stage, assuming the absence of negligence or deviations from the approved protocol. Nevertheless, perceptions about liability at the investigational stages have acted as barriers to development of orphan drugs and devices. In several instances, academic researchers told the Commission that they had been instructed not to give orphan drugs to patients because of their parent institutions' concerns about liability.

Similarly, the Commission is unaware of cases in which researchers or physicians treating patients during the

investigational stages of development were found liable on the basis of prescribing an unapproved treatment. There do appear to have been some cases based exclusively on medical malpractice.<sup>40</sup> Nonetheless, a number of respondents in the Commission's survey of physicians indicated their unwillingness to prescribe investigational drugs based on concerns about "legal" issues of "liability".

The Commission has found that both manufacturers and health care providers perceive liability to be a problem at the research and development stage. Further, this perception constitutes a serious problem, because it leads to especially cautious behavior. The cost of adequate insurance protection may be an obstacle to research, particularly for small companies or academic institutions sponsoring orphan products.

Once approval for a new drug or device has been obtained from the FDA and marketing begins, the potential for liability increases. The manufacturer's responsibilities (some of which apply at earlier stages as well) include compliance with good manufacturing practices, complete description of known side effects, prompt updating of warning statements to reflect new information, and avoidance of overpromotion through advertising which might be viewed as diluting the effect of otherwise adequate warning statements.

### **Professional Liability**

Health care providers must, of course, treat persons with rare diseases in a manner consistent with their professional responsibilities. The potential for liability lies primarily in medical malpractice, as opposed to product liability. Accordingly, the application of standards respecting malpractice should be the same for rare diseases as for medical practice generally.

### **Effects on Treatment**

The Commission knows of several instances in which concerns about liability have hampered the process of developing treatments for rare diseases or delayed the availability of approved treatments. For example, the liability insurer for one approved orphan drug cancelled coverage of it; manufacturers of a number of products have indicated their reluctance to release those products without insurance coverage or explicit agreements by others to indemnify them in the event of liability. These instances have involved smaller companies and individual academic researchers. They are of particular concern to the rare disease community, however, because to date smaller companies and individual investigators have been a significant source of new drugs for rare disorders.

A dramatic example of how liability concerns have affected the availability of a preventive vaccine for a rare disease involves the Japanese encephalitis virus. A vaccine which has been found to be effective against the virus<sup>41</sup> is available abroad but is not licensed in the United States. The vaccine was available in the United States from 1982

to 1987 under the terms of an IND application administered by CDC, but in 1987 it was withdrawn by the manufacturer because of concerns about liability.<sup>42</sup> The manufacturer has an arrangement with the Department of Defense for vaccination of certain military personnel, however, but only because the Department of Defense agreed to indemnify the manufacturer in the event of any liability attributable to the vaccine.

The Commission is concerned that liability not constitute a barrier to research into or treatment of persons with rare diseases, either in terms of delays or increased costs. Liability has been addressed in more general terms by other deliberative bodies. Proposals to establish compensation requirements for injured research subjects were analyzed by the Health, Education, and Welfare Secretary's Task Force on the Compensation of Injured Research Subjects (January 1977) and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (June 1982). Reform of product liability law has been on the agenda of the U.S. Congress in recent years. States have been experimenting with a number of legislative solutions, ranging from the establishment of insurance pools to such tort reform such as caps on awards for pain and suffering and limitations on punitive damages. Medical liability was addressed at great length in the report of the Task Force on Medical Liability and Malpractice, addressed to the Secretary of Health and Human Services and issued in August 1987. State legislatures have been developing approaches to issues related to medical liability. Specific tort reform has already been enacted to a limited extent with regard to childhood vaccines in the National Vaccine Injury Compensation Act.

### **Recommendations:**

33. Congress and state legislatures should promptly resolve product and professional liability issues.
34. Congress should consider special relief in instances where concerns about liability pose insurmountable obstacles to progress on rare diseases.
35. Forums seeking general solutions to the issue of liability should pay special attention to the implications of those solutions for the development of orphan products and the treatment of persons with rare diseases.

## **PROBLEMS IN PRECLINICAL AND CLINICAL RESEARCH**

### **Toxicology Studies**

Before clinical trials of a new agent can be conducted in human beings, appropriate toxicity tests must be performed in animals to ensure the safety of the product. Animal studies, however, are highly specialized and can be very expensive and time-consuming. Most academic biomedical

investigators do not have the proper facilities or the expertise to conduct them. In addition, toxicology studies are not traditionally funded by NIH. Nonetheless, FDA requires such tests from private industries and Federal agencies responsible for substances in the food and drug supply. Recently, these required studies have been criticized by persons concerned about animal rights.

The Commission recognizes the need for humane use of animals but opposes legislation that would restrict their use in research. Experiments on animals have advanced the scientific understanding of numerous rare and common diseases and have resulted in the saving of millions of human lives. If drug development is going to be productive, the continued use of animals in experiments is essential. This is especially true when an animal model of a human disease exists.

Originally, the Orphan Drug Act did not provide funds for animal toxicity studies, and some investigators found themselves stalled at this point in their research. The 1988 amendments permitted animal toxicity studies to be conducted using funds from the grants program; however, no new funds were appropriated for that purpose. Additionally, the act still does not provide most companies with adequate incentives to fund the required preclinical studies.

#### **Recommendation:**

36. The Federal government should not create barriers to the humane use of animals in biomedical research.

#### **Early Clinical Studies**

Investigators described to the Commission their need for assistance in developing appropriate dosage forms for research and treatment. In early clinical studies it is important to collect as much information as possible about the drug and the disease. Most clinical investigators do not have the expertise to develop a dosage form that provides optimal absorption, distribution, metabolism, and excretion in the human body. In addition, a chemical in its basic form may look, taste, or smell unpleasant. Therefore, palatable, easily ingested dosage forms need to be developed.

The Commission encourages pharmacists and the pharmaceutical industry to take an active role in developing dosage forms that are agreeable to patients at every stage of research. Investigators should seek assistance in the early stages of consideration of a clinical study to allow adequate lead time for developing and producing a satisfactory dosage form.

Funding organizations need to realize that many products for rare diseases are often nothing more than shelf chemicals in need of a refined dosage form, or at least a dosage form suitable for administration to animal and human sub-

jects. These development costs are an essential component of a grant application, and funding for them should be provided.

#### **Recommendation:**

37. The FDA's Office of Orphan Products Development, in conjunction with the pharmaceutical industry, schools of pharmacy, and existing consortia, should develop and implement a system to help investigators develop appropriate dosage forms.

#### **Clinical Trials: Patient Volunteers**

Patients indicated a need for education about the nature and purpose of clinical trials. They urged investigators to find alternatives to doubleblind studies in which placebos are used. To patients seeking relief from a condition that has no cure or alternative treatment, or whose symptoms cannot be alleviated, such doubleblind studies represent not the possibility of treatment, but the potential denial of treatment. Every effort should be made to minimize patient participation in the placebo phase of a clinical trial. This could be accomplished by using a study design that minimizes the time a patient is likely to receive a placebo.

Patients' testimony and responses to the Commission's survey indicate that it is difficult to locate ongoing clinical trials and that persons willing to participate in them often endure economic and social hardships. Patients cited the need for a central source of both lay and professional information regarding clinical trials. In addition, they were dismayed that third-party payers would not reimburse them for the costs of investigational drugs or ancillary clinical services. Many patients indicated that they could not afford to participate in trials located far from their homes because the projects did not or could not cover the costs of transportation.

The National Cancer Institute operates the Physician Data Query (PDQ) data base, which lists the type and location of clinical trials with cancer drugs. A PDQ system should be developed to track clinical trials on all orphan products so that patients who want to participate will be able to locate them.

Clinical researchers, patients, and attending physicians alike mentioned the lack of patients available for clinical trials in a given geographic area. Investigators deplored the lack of funds for patient transportation to clinical trials and described their inability to find enough persons with a particular disorder who could afford the cost of travel. Other investigators described the logistical and scientific problems associated with taking research to the patient—that is, conducting multicenter research projects. They agreed that the time and effort needed to develop an acceptable research protocol and to identify a sufficient number of patients for

a study were significant deterrents to research on rare diseases. It was reported to the Commission that in several instances NIH peer reviewers gave poor scores to proposals because of the small size of their cohorts, citing them as insufficient for a study. Assembling a sufficiently large cohort of patients is a need that should be addressed in any proposed program to discover and develop orphan products.

The Commission encourages and recognizes the need for adequate and well-controlled trials to establish the safety and efficacy of products for rare diseases. However, it is essential that funding and regulatory agencies recognize the limited population available for study. Efforts should be made to assist investigators in meeting the rigorous standards for funding by NIH or approval by the FDA.

### **The Federal Drug Approval Process**

The development of orphan drugs, devices, and foods is exceedingly slow and expensive—and much of that time and money is consumed in meeting FDA regulations. Testimony presented to the Commission pointed out the need for a more flexible and sensitively administered process for review of orphan products. Investigators cited instances in which over half the total supply of a costly product was consumed by mandatory testing for purity, shelf life, and other properties. Upon further investigation, it became known that this action was a misinterpretation of FDA testing requirements.

Investigators also emphasized the need for a special understanding on the part of FDA review personnel of the unique aspects of clinical research on rare diseases, particularly the number of patients required and available for clinical trials. They requested greater flexibility regarding the types of studies required for approval of an orphan product. For instance, longterm toxicity or carcinogenicity studies are unnecessary for patients whose alternative is imminent death.

Participants in the Commission's public hearings and respondents to its surveys agreed that the regulatory review process must be expedited, without unduly compromising safety, when an illness is life-threatening or an experimental therapy is the only therapy available. In discussing the problem of timeliness, some researchers and individuals representing patients expressed their perception that the FDA is staffed by concerned but overworked individuals. They cited examples of service above and beyond the normal standard, as well as delays caused by an apparent lack of communication between and within reviewing divisions at the FDA.

Industry sponsors of orphan products indicated a willingness to draft the summary basis of approval or develop

labeling at an earlier stage of the New Drug Application process. In particular, industry sponsors requested that the FDA adhere to the 180-day requirement for review of New Drug Applications for orphan products. Review is often delayed for months by FDA division personnel.

The Commission heard about difficulty in obtaining information from the FDA. Investigators and representatives of both voluntary agencies and industry cited the need for easier access to information about FDA requirements. Many academic researchers were frustrated by the difficulty of obtaining information about IND applications. They requested that existing information about the IND process and requirements be widely disseminated and that IND application forms accompany it. Pharmaceutical manufacturers are especially concerned that today, six years after the Orphan Drug Act became law, regulations to implement the act have not yet been promulgated by the FDA.

Some investigators spoke of varying degrees of difficulty in meeting the requirements of an IND, as well as of their own institutional review boards, without a commercial sponsor. Others sought an expanded role for the FDA's Office of Orphan Products Development in the review and approval process.

The Commission recognizes that many of these problems are currently being addressed by the FDA or are limited to certain review divisions. Some are caused by gaps in communication about FDA procedures.

The FDA must work to eliminate perceptions of it as an unbending agency, rigid in its requirements for product approval. The Commission heard of several cases in which the agency was extremely helpful to clinical investigators and smaller firms. The Commission encourages the FDA to maintain this level of assistance and cooperation and extend it to all firms involved with the development of products for rare diseases. Many of the small pharmaceutical companies taking an active role in developing orphan products are limited in their resources and experience. Guidance and assistance are critical to these firms; a wrong step might delay the availability of an orphan product for years.

### **Recommendations:**

38. The FDA should develop and conduct an educational program for its product review personnel regarding problems unique to the development of products for rare diseases.
39. The FDA should maintain appropriate flexibility with respect to regulatory requirements for the approval of orphan products, especially with respect to protocol design, and the number and kinds of preclinical and clinical studies.

40. Congress should appropriate sufficient funds and full-time-equivalent positions to support the orphan product review activities of the FDA. In FY 1990 these numbers should increase by \$4 million and 50 full-time-equivalent positions. In addition, the FDA should increase the FTEs of the Office of Orphan Products Development to the full complement of 15. Currently the OPD has been authorized 14 staff, but only 7.3 belong to the Office; 7 are on loan from elsewhere in the agency. In order to function effectively, a minimum of 15 staff members are needed. Additional staff should be assigned as the workload increases.
41. The FDA should expedite orphan product approval by:
  - classifying all orphan products as 1A,
  - making all designated orphan products eligible to obtain a treatment IND or an open protocol,
  - encouraging the sponsor to develop draft labeling and seek inspection of their manufacturing facilities at earlier stages of development.
42. If FDA institutes user fees for the NDA review process, FDA should waive any such fees for orphan products, where appropriate.

#### *A Model for Drug Development: The NCI Program.*

After reviewing a number of product development programs, the Commission found that the National Cancer Institute's (NCI) drug development program most nearly meets the needs of patients with rare diseases. This program has helped save and improve the quality of many cancer patients' lives. It represents a particularly successful marriage of Federal and corporate efforts and serves as a model for the development of drugs for rare diseases (all cancers other than lung, breast, colorectal, and prostate are rare conditions).

By 1950, the pharmaceutical industry and the scientific community were actively involved in developing new cancer drugs by screening chemical and antibiotic compounds. Clinical programs were proliferating, and industry could no longer afford the total cost of bringing new treatments for cancer to market. Pressure from the public and the clinical community grew. At the insistence of the Senate Appropriations Committee, the Cancer Chemotherapy National Service Center was established in 1955, and the NCI's Drug Development Program was begun. The program was cosponsored by several Federal agencies, the Damon Runyon Fund, and the American Cancer Society.

In 1965, an evaluation of the program by the NCI led to its reorganization and an increased emphasis on development of therapy. This included describing the natural history of the disease, developing new ways of studying the use of drugs in combination with other therapies, and educating

physicians in the use of the new treatments. The program screens 10,000 or more compounds per year; 4 to 6 of them appear promising enough to evaluate in human beings. Even fewer drugs complete the FDA's New Drug Application process.

The NCI drug development program illustrates what can be achieved with a combination of public need and interest, government support, and industry participation. Even when a potential product is not within the financial reach of the pharmaceutical industry, it can be brought to the applied stage by Federal impetus. The NCI program is flexible; interactions with the pharmaceutical industry vary, depending on the degree of need for Federal support and guidance.

Despite its marked success, however, the program's resources have dwindled in recent years. In FY 1984, for instance, the budget for the preclinical program was \$32.4 million, with 72 full-time-equivalent positions to administer it. By FY 1988, it had been reduced to \$26.6 million and 46 positions. Because at least half of the full-time-equivalent personnel were spending half of their time on the AIDS program, the effective number of staff in 1988 was 34. This disturbing situation is exacerbated by the shrinking value of the dollar.

#### **THE AVAILABILITY OF ORPHAN PRODUCTS AFTER APPROVAL**

Patients and pharmacists have experienced unannounced interruptions in the supply of drugs known to be useful for one or more orphan conditions. This can happen for several reasons. Often, only one company manufactures a particular orphan drug, and that company may withdraw it from the marketplace at any time. The 1988 amendments to the Orphan Drug Act addressed this problem by requiring that a company inform DHHS of its intent to stop manufacturing an orphan drug, biologic, or antibiotic at least one year beforehand. This requirement should be extended to devices and medical foods. As another example of supply problems, patients with narcolepsy expressed their concern about the continued availability of the medications used to treat that disease: many of these medications are classified as schedule 2 controlled substances and are subject to reduced availability and increased costs because of production quotas established for them by the Drug Enforcement Administration. This problem could be alleviated by agency consideration of the use of controlled substances for legitimate medical purposes.

Patients also described long and torturous journeys to locate a pharmacy that would stock, compound, or special-order their required medications. They have encountered reluctance from retail pharmacies to compound a drug or



to stock one that has a limited consumer potential. Patients are encouraged to alert their pharmacists to the need for special orphan drugs that may not be generally available to avoid interruption of therapy. Since orphan products may be difficult to obtain, pharmacists are encouraged to communicate to the patient the need for timely requests for medication.

This struggle has been alleviated for some patients by the establishment of a regional distribution system that can deliver drugs to local pharmacists within a reasonable time. The Commission lauds such initiatives and knows of at least one pharmacy chain that has set up such a system in a 30-state area.

**Recommendations:**

43. The Drug Enforcement Administration should recognize the legitimate use of controlled substances in the treatment of persons with rare diseases and should not interfere with the ability of physicians to prescribe controlled substances when medically necessary.
44. Pharmacists should recognize the special needs of patients with rare diseases and assist patients to obtain orphan products.

**Use of Unapproved Drugs**

Because the need for orphan drugs is so acute, patients and their physicians sometimes resort to the use of nonapproved drugs—that is, drugs approved in foreign countries but not in the United States.

The Commission heard from patients who were using drugs approved and available only in a foreign country. These patients described their efforts to locate supplies of foreign drugs and their stressful trips abroad to obtain them. They presented examples of both outstanding cooperation and bureaucratic resistance from attending physicians, Federal regulatory agencies, and customs and postal officials. They also described the problems of obtaining a sponsor for U.S. approval and marketing of certain foreign drugs and the generally unacceptable length of time between foreign approval and FDA approval of drugs.

The FDA has recently issued guidelines for the use of drugs in the United States that have been approved in foreign countries. The Commission commends the FDA's efforts to enable patients to obtain a personal supply of a nonapproved product to treat their serious or life-threatening condition; however, the Commission feels that a constant domestic supply of such a product would be much more useful to all patients.

**Recommendation:**

45. Sponsors of drugs approved in other countries should be encouraged to seek FDA approval

for those drugs and to participate in treatment INDs and open protocol programs.

**Nonapproved Uses of Drugs**

The Commission also heard from persons with rare diseases who are using drugs approved by the FDA for other conditions. In such cases, obtaining the drug is relatively simple, because physicians can legally prescribe marketed drugs for any condition. Reimbursement from insurers, however, poses a significant problem. In addition, experience indicates that the sponsor of a marketed drug will not ordinarily support clinical studies for a new use of the drug, especially when its patent life is limited or when the patient population is small.

The use of drugs for nonapproved indications needs to be addressed by the FDA and the pharmaceutical industry. In the case of marketed drugs, industry needs much more powerful incentives to support research for new indications for rare diseases. The research effort could range from developing a suitable dosage form for administering the drug to conducting clinical trials, to filing an abbreviated New Drug Application. The regulatory process should be modified to encourage the development of new indications for rare diseases for previously approved drugs.

**Recommendation:**

46. The FDA should expedite and encourage the addition of new rare disease indications to the labeling of marketed products.

**MEDICAL DEVICES AND MEDICAL FOODS**

The same problems that apply to orphan drugs also apply to orphan medical devices. These problems include development of an appropriate study protocol; insufficient flexibility of the regulatory process, especially regarding the number of patients needed for clinical trials, the length of testing required for approval, and the need for expeditious review; weak economic incentives for development; the need for a commercial sponsor to mass produce and market the product; the need for steady, reliable sources of devices; and reimbursement problems for uses outside the approved labeling indications. The Commission encourages sponsors, whether they be individual investigators or firms, to initiate at the earliest possible stage of product development discussions on the needs and problems of the premarketing approval process.

The Commission received testimony from patients with rare diseases who were unaware that the approval of medical devices was, for the most part, disease-specific. For example, a morphine-infusion pump approved by FDA for treatment of pain in terminal cancer patients was not

approved for treatment of patients suffering from the intractable pain caused by reflex sympathetic dystrophy, a rare condition. Thus the Health Care Financing Administration would not permit reimbursement for the continued use and refilling of the pump, even though the expenses for implanting the pump were reimbursed. This situation is similar to that faced by a patient whose rare disease can be treated by a drug approved only for a common condition. In another example, small contact lenses used by infants with cataracts are manufactured only once or twice a year; when the supply is exhausted, patients cannot get lenses until the next yearly supply is manufactured. Such concerns are similar to those raised with respect to availability of drugs.

Before needs regarding medical devices can be met, a working definition of an orphan medical device must be established. A congressionally mandated study is currently undertaking this task.

Another category of products is needed by some patients with rare diseases. Patients with inborn errors of metabolism such as phenylketonuria (PKU) or propionic acidemia need medical foods in order to avoid brain damage or death. Agents to treat some of these conditions are available from health food stores. Other agents are manufactured by corporations that market infant formulas. Products in this category include naturally occurring chemicals, vitamins, minerals, and special infant and adult formulas. Because these products are classified as foods and usually make no direct therapeutic claims, they are not subject to the regulatory process required for drug approval.

This situation creates problems for physicians, patients, and researchers alike. Physicians find it disquieting to prescribe a substance whose purity and composition are relatively unknown. Patients find it nearly impossible to convince thirdparty payers that this nonprescription food product is really a life-sustaining medication for which they should be reimbursed. Patients also fear that the composition of their product may be altered without notification or that production will be abruptly discontinued due to insufficient demand. Researchers are unable to find industry sponsors for the development of medical foods because of the products' limited patent rights, if any, and their classification as foods instead of drugs. In addition, many of these foods are unpalatable to children, and improvements will not be made unless manufacturers have a clear indication of profitability.

The Commission considers that the definition of medical foods provided in the Orphan Drug Amendments of 1988 is acceptable; however, guidelines for the use of medical foods need to be established. The DHHS is studying the incentives of the Orphan Drug Act to determine whether they are needed to encourage the development of

medical devices and foods.

#### **Recommendations:**

47. Congress should amend the Orphan Drug Act to provide incentives for the development of orphan medical devices and medical foods.
48. Medical foods are life-sustaining and should be reimbursed by private and public insurers.

### **STIMULATING TECHNOLOGY TRANSFER**

Investigators discussed with the Commission the difficulty of attempting to convince commercial sponsors of the need for and value of a new treatment for a rare disease. Although a few investigators have conducted all of the required studies, developed a New Drug Application for the FDA, and obtained a commercial sponsor for their product, such occurrences are rare. Most investigators do not possess all the resources required to convert scientific knowledge into useful products.

The Commission identified two pieces of legislation that should help stimulate technology transfer: 1) the Small Business Innovation Development Act and 2) the Federal Technology Transfer Act.

#### **The Small Business Innovation Development Act**

The Small Business Innovation Development Act of 1982 (Public Law 97-219, as amended by Public Law 99-443) is designed to stimulate technological innovation, use small businesses to meet Federal research and development needs, foster and encourage minority and disadvantaged persons to participate in technological innovation, and increase commercialization by the private sector of innovations derived from Federal research and development activities.<sup>43</sup>

Federal agencies with an annual extramural research and development budget of \$100 million or more are required to reserve specified percentages of that budget for a Small Business Innovation Research (SBIR) program. Of the agencies doing research on rare diseases, four (DHHS, DoD, DOE and the Department of Education) have SBIR programs. The funding agency or department often identifies the kind of research needed from investigators.

The SBIR program consists of three phases. Phase I awards grants to establish the technical merit and feasibility of proposed research or research and development efforts and to determine the quality of performance of the small business before providing further Federal support in phase II. Grants in phase I are usually for \$50,000 or less and cover approximately six months' work.

Phase II awards grants to continue the research or research and development begun in phase I. Funding decisions are based on the results of phase I and on the scientific and technical merit of the phase II application. Grants are usually for \$500,000 or less (including both direct and indirect costs) and for two years or less. Phase II grants are nonrenewable, and only one phase II award may be made for any SBIR project.

Phase III involves no SBIR funding. In it, the small business commercializes the results of the research and development funded in phases I and II. Some Federal agencies may provide add-on funds for research and development not funded under SBIR or enter into production contracts for products or processes intended for use by the U.S. government.

In 1988, NIH expects to make 300 phase I awards and ADAMHA expects to make 20. The CDC and the FDA will make 2 awards each.

#### **Recommendation:**

49. NIH, ADAMHA, and FDA should inform investigators involved in orphan products development and seeking financial support from Federal agencies of the potential usefulness of the SBIR program.

#### **The Federal Technology Transfer Act**

The Federal Technology Transfer Act of 1986 (Public Law 99-502) amends the Stevenson-Wydler Technology Innovation Act of 1980 (Public Law 96-480). It promotes technology transfer by authorizing government-operated laboratories to enter into cooperative research and development agreements (CRADAs) with other Federal agencies; units of local or state governments; industrial organizations, including corporations, partnerships, limited partnerships, and industrial development organizations; private foundations; nonprofit organizations, including universities; or individuals, including licensees of inventions owned by the Federal agency. In developing a CRADA, special consideration is given to small businesses and to businesses located in the United States that are likely to manufacture the invention in the United States.

Under these agreements, the Federal laboratory may grant collaborating parties certain rights to inventions made by Federal employees, and Federal employees are encouraged to commercialize their inventions. The intent is both to encourage Federal employees to take their work beyond the research stage and to seek non-Federal sponsors for development. The act requires the Federal agency to:

- Pay the inventor at least 15 percent of the royalties or other income received as a result of the invention,
- Guarantee a fixed minimum payment each year that royalties are received, and
- Provide appropriate incentives (from royalties) to laboratory employees who contribute substantially to the technical development of a licensed invention (Payments are generally not permitted to exceed \$100,000 per year to any one person, unless the President approves a larger award; any amount over \$100,000 per year is considered a presidential award).

The inventor is not the only one to benefit from the invention. The balance of the royalties or other income derived from the invention is to be transferred to the Federal laboratory where the invention took place. These funds may be used to (1) pay expenses incidental to the administration and licensing of inventions, (2) reward scientific and technical employees, (3) further scientific exchange among the agency's laboratories, (4) further the education and training of employees, consistent with the research and development mission of the agency, and (5) enhance the potential for transfer of the technology developed in Federal laboratories.

#### **Recommendations:**

50. Federal employees should be encouraged to use the incentives of the Federal Technology Transfer Act of 1986 to bring their products to the marketplace, and Federal agencies should make available as rapidly as possible the intellectual property of employees and agencies.
51. The Central Office of Orphan and Rare Diseases should periodically screen and publicize the National Technical Information Service's list of intellectual property available for licensing.

## Chapter 8

# THE NEED TO COORDINATE RESEARCH AND DEVELOPMENT EFFORTS

The Commission was particularly disturbed to discover that many of the barriers to progress in understanding rare diseases and treating patients are caused not only by a lack of funding, but also by lack of coordination of existing resources. Time after time, persons testifying at the Commission's hearings or responding to its surveys cited instances in which a treatment was delayed for this reason. At the same time, the Commission became increasingly aware that there do exist some cooperative efforts and coordinating bodies, but that many persons and agencies are not aware of them.

The Commission suggests the following guidelines for coordinating efforts:

- When a research or educational activity is considered, all involved parties should be informed of the plans and invited to participate.
- Sensitivities of each group must be raised to acknowledge the capabilities, activities, and responsibilities of all participants.

### AREAS IN WHICH COORDINATION IS NEEDED

#### DUPLICATION OF EFFORT

Because rare diseases are so numerous and diverse, because there are so many different sources of funding for research and development, and because researchers work in so many and such widely scattered locations, non-productive duplication of effort is a constant danger.

It is essential that individual researchers and groups concerned with rare diseases communicate their activities and findings to each other. The Commission's surveys reveal that 20 of the 25 private foundations that fund biomedical research cofund research with other organizations, including the pharmaceutical industry, voluntary organizations, academic institutions, the Federal government, and other foundations. Voluntary organizations frequently co-fund efforts in rare disease research. In fact, all of these

groups indicated their willingness to co-fund important rare disease research. Each has unique talents, services, and resources that will be helpful when properly coordinated.

There is also a need for greater coordination among voluntary organizations themselves. These groups serve an important function in U.S. society—they supplement, at a nominal cost, the services provided by the public sector and link patients with researchers and physicians. As the number and size of these voluntary organizations increase, so does their ability to affect research. It is therefore imperative that mechanisms be established to facilitate coordination among these organizations. Their potential for attracting researchers and funding small projects and fellowships should not be wasted on redundant or duplicative efforts.

#### REGULATORY SNAGS

Several persons testifying before the Commission cited the need for improved coordination among the research activities supported by NIH, voluntary organizations, the pharmaceutical industry, and the review and approval activities of the FDA. For example, results of some research supported by NIH could not be used to substantiate claims of safety or efficacy for an orphan product because the research protocol did not conform to FDA requirements. Such lapses cause delay and necessitate costly repetitions of studies. In some cases, the effort to obtain FDA approval may be abandoned altogether. Applicants for NIH clinical research grants related to rare diseases should be encouraged to seek timely protocol assistance from the FDA and to design protocols that will meet FDA testing requirements. Agencies and principal investigators need to understand that this is not a maneuver to exert control over funded research; rather, it is a means of using existing financial resources wisely.

Improved coordination between the research-granting activities of NIH and the FDA is also needed. For example, approved grant applications for clinical research on rare diseases that NIH is unable to fund should be auto-

matically forwarded to the FDA's Office of Orphan Products Development for consideration.

**Recommendations:**

52. Federal agencies and the private sector should inform clinical investigators of rare diseases of the protocol assistance available from the FDA. Investigators should ensure that their clinical study protocols meet FDA requirements for adequate, well-controlled studies.
53. The FDA, ADAMHA, and NIH should ensure that grant applications which cannot be funded by one agency are forwarded to the others for consideration.

**UNDERUSED COORDINATING BODIES**

There are at present several mechanisms designed to coordinate research and development efforts, among them:

- The Office of Orphan Products Development in FDA,
- The Orphan Products Board in the Office of the Assistant Secretary for Health,
- The Commission on Drugs for Rare Diseases of the Pharmaceutical Manufacturers Association,
- The Orphan Developers Coalition,
- The Institute for Orphan Drugs of the Generic Pharmaceutical Industry Association,
- The Association of Biotechnology Companies.

The availability of these coordinating groups must be publicized, and persons concerned with rare diseases need to use them to avoid wasting precious research dollars on duplicative or improperly designed trials.

Investigators whose work may contribute to the development of a therapy for a rare disease are encouraged to ally themselves with an appropriate voluntary organization, the Office of Orphan Products Development, or product manufacturers. Findings with therapeutic potential for rare diseases must not be lost in the sea of scientific knowledge. For example, the results of an NIH-supported study of a chemical substance used by a drug addict who developed Parkinson's disease were lost for many years. Current follow-up studies are shedding light on the causes of Parkinson's disease.

Federal agencies communicate with each other about rare disease research through participation on interagency coordinating committees and the Orphan Products Board. Many of the agencies and voluntary organizations also work with each other and with private foundations, professional associations, academic researchers, and the pharmaceutical industry.

Many organizations cosponsor conferences and workshops and produce publications. Benefits from such meetings include dissemination of new ideas, information about ongoing research, identification of promising areas for new research, and a forum for research results.

At present there is no single mechanism to link the various groups concerned with rare disease research and product development. The usefulness of existing bodies is limited because of their relatively limited scope. The Commission believes that many of the problems surrounding rare disease research and product development will be resolved when there is a coordinating link among these groups.

**PART V**

**CONCLUSION**

## Chapter 9

# THE CENTRAL OFFICE OF ORPHAN AND RARE DISEASES

Progress is being made in almost every area the Commission studied. Research on rare diseases is being funded, Congress has enacted economic incentives for orphan product discovery and development, and voluntary organizations have been formed to give patients and their families moral support and practical information. But this progress has been excruciatingly slow and uncertain, for a number of reasons.

The Commission found overall funding of rare disease research to be inadequate. The Federal government, which sponsors the bulk of biomedical research in the United States, spent \$1.3 billion on rare disease research in 1987, over half for research on rare cancers and the remainder on the 4,800 other known rare diseases. Part of the funding problem lies in the fact that Federal agencies seldom separate rare diseases from prevalent diseases when they determine their research priorities. As a result, rare disease research, with its unconventional problems and procedures, suffers. Inadequate funding can create other problems as well. The Commission found a general perception among the investigators it surveyed that basic and clinical research on rare diseases are less likely to be funded than such research on common diseases. This perception discourages investigators from undertaking research on rare disease.

Equally important is the lack of a clear focus in Federal research on rare diseases. There is no effective central mechanism to coordinate research or to link investigators with patients, practicing physicians, the pharmaceutical industry, and funding sources. Results of the Commission's surveys clearly indicate the need for such a mechanism.

Discovery and development of orphan products have been stimulated by recent legislation, but only to the extent that 33 new products have been approved since 1983. If more are to be brought to market in the next six years, economic incentives for the pharmaceutical industry will have to be strengthened and extended to medical foods and medical devices. In addition, the labyrinthine Federal approval process for new orphan products or new uses of

existing products will have to be untangled. Procedures need to be clarified and, consistent with safety, simplified to speed approval.

Clearly, research and development are essential if rare diseases are to be prevented or patients diagnosed and treated. But there are other, more immediate needs of patients and their families that are not being met. Information—both for physicians making diagnoses and for patients seeking to understand their disease—is often outdated or simply unavailable. Forty-two percent of physicians surveyed by the Commission were unable to provide their patients with any useful written information on their disease. Investigators cite difficulty finding patients for clinical trials, and patients cite difficulty finding out about, or getting to, those trials.

The availability of products to treat persons with rare diseases is also a major problem. Some patients must bring into this country products approved in other countries but not in the United States. Others must pay out-of-pocket for a product approved for other uses or simply available over the counter. Many worry that an available drug will be taken off the market or that an over-the-counter drug's formula will be changed.

Finally, most patients find it extremely difficult to pay for their medical care. Not only can the care itself be expensive, patients frequently encounter discrimination when they seek health insurance. This is the one area in which the Commission found no progress in recent years. The Commission estimates that millions of rare disease patients in the United States have either inadequate or no health insurance coverage at all. This situation exists because health insurance is not offered, the patients and their families cannot afford it, or patients are insured for everything except the rare disease, because the disease predated the insurance policy. To be eligible for assistance under Medicaid, some families must spend down to their state's poverty level. The Commission finds this situation intolerable. Adequate health insurance should be available to all persons with a rare disease—and families should not have to be destitute before Medicaid benefits become available.

The Commission believes that progress in these areas must be made—and made more quickly than in the past. If this is to be done, then patients and the persons most closely associated with them—family, physicians, investigators, and voluntary organizations—need an advocate in the Federal government. The Commission recommends the establishment of the Central Office of Orphan and Rare Diseases (COORD).

## RESPONSIBILITIES OF COORD

### COORDINATION

Health professionals, foundations, voluntary organizations, the pharmaceutical and device industry, the Federal government, insurers and universities and colleges have roles in rare disease prevention or diagnosis and treatment. The importance of coordinating these roles to avoid duplication of research or the funding of studies that do not meet the scientific standards required by Federal funding agencies cannot be overemphasized. The Commission heard testimony that most research projects are discrete entities set up with little understanding of what is needed to move results into clinical areas or to product development and approval for marketing. Rarely do basic and clinical investigators funded by NIH, private organizations, the pharmaceutical industry, or the FDA meet at early stages to discuss research and development plans for promising products. Failure to bring these individuals and organizations together can result in years of needless delay in developing a product.

Both private and public funding agencies need to be aware of the FDA's standards for product approval when they are funding preclinical and clinical research. With the country's financial and research personnel resources becoming scarcer, the nation cannot afford to expend them on studies intended to serve as the basis for safety and efficacy claims when these studies in truth do not meet the FDA's basic requirements. The Commission heard testimony that many investigators are unaware of existing means of requesting assistance in designing a protocol, locating patients, or finding a sponsor for an orphan product after promising research results are obtained. It is essential that procedures be established for a smooth transition of research results from the basic stage to that of a marketable product. At the present time, there is no one office to facilitate this process.

Existing offices and programs do not have the mandate to deal with the needs identified by the Commission. The FDA's Office of Orphan Products Development has made commendable efforts to stimulate development, but its mandate is limited. The mandate of the Orphan Products Board is somewhat broader, but its goals are too narrow and its staff too small to meet the current needs.

The COORD should be placed in the Office of the Assistant Secretary for Health and modeled after offices such

as the Office of Disease Prevention and Health Promotion and the Office of Minority Health. From that organizational location in OASH, the COORD can have access to the key policy makers throughout the Department and can work with the agencies with programs relevant to rare disease progress. COORD should remain at this location as long as the coordinating activities are enhanced by that location, and in the model of the Office of Smoking and Health, it could later be relocated if appropriate to one of the operational agencies of the Public Health Service.

The Commission discussed a suggestion that an institute for rare diseases be established at the National Institutes of Health, but it quickly and strongly concluded that this approach would be inefficient and counterproductive. In addition to increasing administrative costs, it would put more distance between scientists and programs, when the object should be to bring them closer together.

COORD would provide the strong central coordinating function under a broad mandate to deal with complex issues of research funding, investigators' capabilities, insurance practices, the interests and needs of pharmaceutical manufacturers and voluntary organizations, and the delivery of treatment by physicians and clinical investigators.

### EDUCATION

The nation has an overwhelming need not only for detailed information about particular rare diseases, but also for timely dissemination of it to all parties concerned—patients and their families, physicians and other health care delivery personnel, professional organizations, investigators, voluntary organizations and grassroots support groups, private foundations, pharmaceutical manufacturers, and the general public. Congress and Federal agencies supporting research on rare diseases also need timely and accurate information. Much information of this sort already exists, but dissemination of it is hindered by lack of funding, agencies' ignorance of each others' programs, and overlap of responsibilities. In cases where up-to-date information does not exist, agencies may distribute outdated or inaccurate information.

Voluntary organizations have done yeoman work in gathering and disseminating information and in educating the public. It is time the Federal government lent a hand. Besides its own activities in these areas, the COORD should encourage the activities of existing voluntary organizations and the development of new organizations. In addition, it should conduct training and educational sessions for voluntary organizations to acquaint them with Federal mechanisms for funding research, use of Federal services, the product review process, and Medicare and Medicaid funding procedures in order that these organizations may better serve their constituents.

The Commission believes that COORD, with its wide ranging responsibilities as advocate, coordinator, and



educator, is needed to implement the recommendations presented in this report. By establishing such an office, this country will clearly signal its intention to alleviate the suffering of the millions of Americans who have a rare disease.

**Recommendation:**

54. Congress should establish by statute and appropriate such funds as necessary for a Central Office of Orphan and Rare Diseases (COORD) in the Office of the Assistant Secretary for Health to coordinate the rare-disease related research, regulatory, educational and service activities of physicians, investigators, foundations, voluntary organizations, patients and families, pharmaceutical manufacturers, insurers and Federal agencies.

COORD shall:

- foster the implementation of the recommendations of the National Commission on Orphan Diseases,
- respond to new needs and issues as they arise, including proposals for legislation and regulations with implications for rare disease patients

- collect, develop, and disseminate information on rare diseases,
- promote a "Year of Rare Diseases" to educate the public,
- subsume the current responsibilities of the Orphan Products Board, and
- report to Congress on Federal activities related to rare diseases.

To assist COORD in its activities,

- the Assistant Secretary for Health should appoint an advisory board composed of persons knowledgeable about rare diseases, such as representatives of voluntary organizations, clinicians, investigators, pharmaceutical manufacturers, insurers, foundations, and government, including the FDA's Office of Orphan Product Development;
- existing Federal activities related to rare diseases, especially such activities in the FDA, NIH, ADAMHA, and CDC, should be continued and strengthened; and
- the Congress should provide full and stable funding for a central source of comprehensive information about rare diseases.

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## GLOSSARY

ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
AIDS	Acquired Immunodeficiency Syndrome
AMA	American Medical Association
B/I/D	Bureaus, Institutes, and Divisions (NIH)
CDC	Centers for Disease Control
CLINICAL CENTER	Warren Grant Magnuson Clinical Center
CRADA	Cooperative Research and Development Agreement
CRISP	Computerized Retrieval of Information of Scientific Projects (NIH)
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 (NIH)
GPIA	Generic Pharmaceutical Industry Association
HCFA	Health Care Financing Administration
HIAA	Health Insurance Association of America
HRSA	Health Resources and Services Administration
ICD	International Classification of Diseases
IRG	Initial Review Group
MARC	Minority Access to Research Center Program
MERIT	Method to Extend Research in Time
MMWR	Morbidity and Mortality Weekly Report (CDC)
MSTP	Medical Scientist Training Program
NASA	National Aeronautics and Space Administration
NCHS	National Center for Health Statistics (CDC)
NCI	National Cancer Institute
NCNR	National Center for Nursing Research
NCOD	National Commission on Orphan Diseases (OASH)
NCTR	National Center for Toxicological Research (FDA)
NEI	National Eye Institute
NIA	National Institute on Aging
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NICODARD	National Information Center for Orphan Drugs and Rare Diseases (FDA)
NIDA	National Institute on Drug Abuse (ADAMHA)
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDRR	National Institute on Disability and Rehabilitation Research

NIDR	National Institute of Dental Research
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health (ADAMHA)
NINCDS	National Institute of Neurological, Communicative Disorders, and Stroke
NLM	National Library of Medicine
NORD	National Organization for Rare Disorders
NRSA	National Research Service Award
NTIS	National Technical Information Service
OASH	Office of the Assistant Secretary for Health
ODC	Orphan Developers Coalition
OMAR	Office of Medical Applications of Research (NIH)
OMCH	Office of Maternal and Child Health (HRSA)
OPB	Orphan Products Board (OASH)
OPD	Office of Orphan Products and Development (FDA)
OTC	Over the Counter Product
PDQ	Physician 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
SBIR	Small Business Innovation Research Program
SPRANS	Special Projects of Regional or National Significance (OMCH/HRSA)
USAID	United States Agency for International Development
USDA	United States Department of Agriculture
VA	Veterans Administration

**APPENDIX A**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH  
PUBLIC HEALTH SERVICE

NATIONAL COMMISSION ON ORPHAN DISEASES

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Public Law 99-91  
99th Congress

## An Act

To amend the orphan drug provisions of the Federal Food, Drug, and Cosmetic Act and related laws.

Aug. 15, 1985  
[S. 1147]

*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,*

Orphan Drug  
Amendments of  
1985.  
21 USC 301 note.

## SECTION 1. SHORT TITLE.

This Act may be cited as the "Orphan Drug Amendments of 1985".

## SEC. 2. MARKET PROTECTION.

Section 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360cc) is amended—

- (1) by striking out "and for which a United States Letter of Patent may not be issued" in subsection (a);
- (2) by striking out "and if a United States Letter of Patent may not be issued for the drug" in subsection (b); and
- (3) by striking out "UNPATENTED" in the title of the section.

## SEC. 3. ANTIBIOTIC DRUGS.

## (a) DESIGNATION.—

(1) Section 525(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360aa(a)) is amended—

- (A) by striking out "or" at the end of paragraph (1), by redesignating paragraph (2) as paragraph (3), and by inserting after paragraph (1) the following:
 

"(2) if the drug is an antibiotic, it may be certified for such disease or condition under section 507, or";
- (B) by striking out "before" in paragraph (3) (as so redesignated);
- (C) by inserting after "505" in the last sentence a comma and the following: "certification of such drug for such disease or condition under section 507,"; and
- (D) by striking out "licensing under section 351 of the Public Health Service Act for such disease or condition" and inserting in lieu thereof "licensing of such drug for such disease or condition under section 351 of the Public Health Service Act".

(2) Section 526(a)(1) of such Act (21 U.S.C. 360bb(a)(1)) is amended—

- (A) by striking out "or" at the end of subparagraph (A) and by striking out subparagraph (B) and inserting in lieu thereof the following:
 

"(B) if a certification for such drug is issued under section 507,

or

"(C) if a license for such drug is issued under section 351 of the Public Health Service Act,"; and
- (B) by striking out "the approval or license" and inserting in lieu thereof "the approval, certification, or license".

(3) Section 527 of such Act (21 U.S.C. 360cc) is amended—

(A) by striking out “or” at the end of paragraph (1) in subsection (a), by redesignating paragraph (2) as paragraph (3), and by inserting after paragraph (1) the following: “(2) issues a certification under section 507, or”;

(B) by inserting after “505” in the first sentence of subsection (a) a comma and the following: “issue another certification under section 507,”;

(C) by inserting after “holder of such approved application” in subsection (a) a comma and the following: “of such certification,”;

(D) by inserting after “approval of the approved application” in subsection (a) a comma and the following: “the issuance of the certification,”;

(E) by striking out “or a license” in subsection (b) and inserting in lieu thereof a comma and the following: “if a certification is issued under section 507 for such a drug, or if a license”;

(F) by inserting after “application approval” in subsection (b) a comma and the following: “of the issuance of the certification under section 507,”;

(G) by striking out “, if the drug is a biological product,” in subsection (b);

(H) by inserting after “under section 505” in subsection (b) a comma and the following: “issue another certification under section 507,”;

(I) by inserting after “holder of such approved application” in subsection (b) a comma and the following: “of such certification,”;

(J) by inserting after “application” in subsection (b)(1) a comma and the following: “of the certification,”; and

(K) by inserting after “other applications” in subsection (b)(2) a comma and the following: “issuance of other certifications,”.

42 USC 236 note **SEC. 4. NATIONAL COMMISSION ON ORPHAN DISEASES.**

(a) **ESTABLISHMENT.**—There is established the National Commission on Orphan Diseases (hereinafter referred to as the “Commission”).

(b) **DUTY.**—The Commission shall assess the activities of the National Institutes of Health, the Alcohol, Drug Abuse, and Mental Health Administration, the Food and Drug Administration, other public agencies, and private entities in connection with—

Research and  
development

- (1) basic research conducted on rare diseases;
- (2) the use in research on rare diseases of knowledge developed in other research;
- (3) applied and clinical research on the prevention, diagnosis, and treatment of rare diseases; and
- (4) the dissemination to the public, health care professionals, researchers, and drug and medical device manufacturers of knowledge developed in research on rare diseases and other diseases which can be used in the prevention, diagnosis, and treatment of rare diseases.

(c) **REVIEW REQUIREMENTS.**—In assessing the activities of the National Institutes of Health, the Alcohol, Drug Abuse, and Mental Health Administration, and the Food and Drug Administration in connection with research on rare diseases, the Commission shall review—

Grants  
Contracts

- (1) the appropriateness of the priorities currently placed on research on rare diseases;
- (2) the relative effectiveness of grants and contracts when used to fund research on rare diseases;

Research and  
development.

(3) the appropriateness of specific requirements applicable to applications for funds for research on rare diseases taking into consideration the reasonable capacity of applicants to meet such requirements;

(4) the adequacy of the scientific basis for such research, including the adequacy of the research facilities and research resources used in such research and the appropriateness of the scientific training of the personnel engaged in such research;

(5) the effectiveness of activities undertaken to encourage such research;

(6) the organization of the peer review process applicable to applications for funds for such research to determine if the organization of the peer review process could be revised to improve the effectiveness of the review provided to proposals for research on rare diseases;

(7) the effectiveness of the coordination between the national research institutes of the National Institutes of Health, the institutes of the Alcohol, Drug Abuse, and Mental Health Administration, the Food and Drug Administration, and private entities in supporting such research; and

(8) the effectiveness of activities undertaken to assure that knowledge developed in research on nonrare diseases is, when appropriate, used in research on rare diseases.

(d) COMPOSITION.—The Commission shall be composed of twenty members appointed by the Secretary of Health and Human Services as follows:

(1) Ten members shall be appointed from individuals who are not officers or employees of the Government and who by virtue of their training or experience in research on rare diseases or in the treatment of rare diseases are qualified to serve on the Commission.

(2) Five members shall be appointed from individuals who are not officers or employees of the Government and who have a rare disease or are employed to represent or are members of an organization concerned about rare disease.

(3) Four nonvoting members shall be appointed from—

(A) the directors of the national research institutes of the National Institutes of Health; or

(B) the directors of the institutes of the Alcohol, Drug Abuse, and Mental Health Administration, which the Secretary determines are involved with rare diseases.

(4) One nonvoting member shall be appointed from officers or employees of the Food and Drug Administration who the Secretary determines are involved with rare diseases.

A vacancy in the Commission shall be filled in the manner in which the original appointment was made. If any member of the Commission who was appointed to the Commission as a director of a national research institute or an institute of the Alcohol, Drug Abuse, and Mental Health Administration or as an officer or employee of the Food and Drug Administration leaves that office or position, or if any member of the Commission who was appointed from persons who are not officers or employees of the Government becomes an officer or employee of the Government, such member may continue as a member of the Commission for not longer than the ninety-day period beginning on the date such member leaves that office or position or becomes such an officer or employee, as the case may be.

(e) **TERM.**—Members shall be appointed for the life of the Commission.

(f) **COMPENSATION.**—

5 USC 5332.

(1) Except as provided in paragraph (2), members of the Commission shall each be entitled to receive compensation at a rate not to exceed the daily equivalent of the annual rate of basic pay in effect for grade GS-18 of the General Schedule for each day (including traveltime) during which they are engaged in the actual performance of duties as members of the Commission.

(2) Members of the Commission who are full-time officers or employees of the Government shall receive no additional pay by reason of their service on the Commission.

(g) **CHAIRMAN.**—The Chairman of the Commission shall be designated by the members of the Commission.

5 USC 5101 et seq., 5331.

(h) **STAFF.**—Subject to such rules as may be prescribed by the Commission, the Commission may appoint and fix the pay of such personnel as it determines are necessary to enable the Commission to carry out its functions. Personnel shall be appointed subject to the provisions of title 5, United States Code, governing appointments in the competitive service, and shall be paid in accordance with the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates.

(i) **EXPERTS AND CONSULTANTS.**—Subject to such rules as may be prescribed by the Commission, the Commission may procure temporary and intermittent services under section 3109(b) of title 5 of the United States Code, but at rates for individuals not to exceed the daily equivalent of the basic pay payable for grade GS-15 of the General Schedule.

Government organization and employees.

(j) **DETAIL OF PERSONNEL.**—Upon request of the Commission, the head of any Federal agency is authorized to detail, on a reimbursable basis, any of the personnel of such agency to the Commission to assist the Commission in carrying out its functions.

(k) **ADMINISTRATIVE SUPPORT SERVICES.**—The Administrator of General Services shall provide to the Commission on a reimbursable basis such administrative support services as the Commission may request.

(l) **GENERAL AUTHORITY.**—The Commission may, for the purpose of carrying out this section, hold such hearings, sit and act at such times and places, take such testimony, and receive such evidence, as the Commission considers appropriate.

(m) **INFORMATION.**—The Commission may secure directly from any department or agency of the United States information necessary to enable it to carry out this section. Upon request of the Chairman, the head of such department or agency shall furnish such information to the Commission.

(n) **REPORT.**—The Commission shall transmit to the Secretary and to each House of the Congress a report not later than September 30, 1987, on the activities of the Commission. The report shall contain a detailed statement of the findings and conclusions of the Commission, together with its recommendations for—

(1) a long range plan for the use of public and private resources to improve research into rare diseases and to assist in the prevention, diagnosis, and treatment of rare diseases; and

(2) such legislation or administrative actions as it considers appropriate.

(o) **TERMINATION.**—The Commission shall terminate 90 days after the date of the submittal of its report under subsection (n).

(p) **FUNDS.**—The Director of the National Institutes of Health shall make available \$1,000,000 to the Commission from appropriations for fiscal year 1986 for the National Institutes of Health.

#### SEC. 5. FINANCIAL ASSISTANCE.

(a) **QUALIFIED TESTING.**—Section 5 of the Orphan Drug Act (21 U.S.C. 360ee) is amended—

- (1) in subsection (a) by striking out “clinical”; and
- (2) by amending subsection (b)(1) to read as follows:

“(1) The term ‘qualified testing’ means—

“(A) human clinical testing—

“(i) which is carried out under an exemption for a drug for a rare disease or condition under section 505(i) of the Federal Food, Drug, and Cosmetic Act (or regulations issued under such section); and 21 USC 355.

“(ii) which occurs after the date such drug is designated under section 526 of such Act and before the date on which an application with respect to such drug is submitted under section 505(b) or 507 of such Act or under section 351 of the Public Health Service Act; and 21 USC 360bb.

“(iii) which occurs after the date such drug is designated under section 526 of such Act and before the date on which an application with respect to such drug is submitted under section 505(b) or 507 of such Act or under section 351 of the Public Health Service Act; and 42 USC 262.

“(B) preclinical testing involving a drug for a rare disease or condition which occurs after the date such drug is designated under section 526 of such Act and before the date on which an application with respect to such drug is submitted under section 505(b) or 507 of such Act or under section 351 of the Public Health Service Act.”

(b) **AUTHORIZATION.**—Subsection (c) of such section 5 is amended to read as follows: 21 USC 360ee.

“(c) For grants and contracts under subsection (a) there are authorized to be appropriated \$4,000,000 for fiscal year 1986, \$4,000,000 for fiscal year 1987, and \$4,000,000 for fiscal year 1988.”

#### SEC. 6. TECHNICAL CORRECTIONS.

(a) **PUBLIC LAW 98-619.**—The paragraph following the heading “**EDUCATION FOR THE HANDICAPPED**” under title III of the Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriation Act, 1985 (Public Law 98-619) is amended— 98 Stat. 3324.

(1) by inserting after “shall” the first time it appears a comma and the following: “except for part D of such Act,”; and

(2) by adding at the end thereof the following: “The amounts available for such part D shall be available for obligation on October 1, 1984, and shall remain available until September 30, 1985.”

(b) **PUBLIC LAW 98-527.**—Section 122(b)(4)(C) of the Developmental Disabilities Assistance and Bill of Rights Act (42 U.S.C. 6022(b)(4)(C)) is amended to read as follows: 98 Stat. 2670.

“(C) Notwithstanding subparagraph (E)(i), upon application of a State, which under section 133(b)(4)(C) of this Act (as in effect on October 18, 1984) was permitted to make expenditures for services without regard to the requirements of section 133(b)(4)(B) of this Act (as so in effect) the Secretary, pursuant to regulations which the Secretary shall prescribe, may permit a portion of the funds which, pursuant to subparagraph (E)(i), must otherwise be expended under 42 USC 6063.

the State plan of such State for service activities in the priority services, to be expended in fiscal years 1985, 1986, and 1987 for the additional services for which expenditure was permitted under section 133(b)(4)(C) (as so in effect) if the Secretary determines that—

42 USC 6063

98 Stat. 2679.  
42 USC 6041,  
6061, 6081.

“(i) such additional services are not priority services;

“(ii) such additional services are not services for which funds are otherwise available under part C, D, or E; and

“(iii) the expenditures of such State on service activities in the priority services has reasonably met the need for those services in such State in comparison to the extent to which the need for such additional services has been met in such State.”.

**SEC. 7. AREA HEALTH EDUCATION CENTERS.**

42 USC 295g-1. Section 781(a)(2) of the Public Health Service Act (42 U.S.C. 295g-7(a)(2)) is amended by redesignating subparagraphs (A), (B), and (C) as clauses (i), (ii), and (iii), respectively, and by striking out all that precedes clause (i) (as so redesignated) and inserting in lieu thereof the following:

Contracts.  
Schools and  
colleges.

“(2)(A) The Secretary shall enter into contracts with schools of medicine and osteopathy—

42 USC 295g-1  
note.

“(i) which have previously received Federal financial assistance for an area health education center program under section 802 of the Health Professionals Educational Assistance Act of 1976 in fiscal year 1979 or under paragraph (1), or

“(ii) which are receiving assistance under paragraph (1), to carry out projects described in subparagraph (B) through area health education centers for which Federal financial assistance was provided under paragraph (1) and which are no longer eligible to receive such assistance.

“(B) Projects for which assistance may be provided under subparagraph (A) are—”.

21 USC 360aa  
note.

**SEC. 8. EFFECTIVE DATE.**

(a) **GENERAL RULE.**—Except as provided in subsection (b), this Act and the amendments made by this Act shall take effect October 1, 1985.

(b) **EXCEPTION.**—The amendments made by sections 2, 3, and 6(a) shall take effect on the date of the enactment of this Act. The amendment made by section 6(b) shall take effect October 19, 1984. The amendments made by section 7 shall take effect October 1, 1984 and shall cease to be in effect after September 30, 1985.

Approved August 15, 1985.

**LEGISLATIVE HISTORY—S. 1147 (H.R. 2290):**

HOUSE REPORT No. 99-153 accompanying H.R. 2290 (Comm. on Energy and Commerce).

CONGRESSIONAL RECORD, Vol. 131 (1985):

May 23, considered and passed Senate.

June 17, 18, H.R. 2290 considered and passed House; S. 1147, amended, passed in lieu.

July 25, Senate concurred in House amendment with amendments.

July 31, House concurred in Senate amendments.

○

**PUBLIC LAW 100-290—APR. 18, 1988**

**ORPHAN DRUG AMENDMENTS OF 1988**

102 STAT. 90

PUBLIC LAW 100-290—APR. 18, 1988

Public Law 100-290  
100th Congress

An Act

Apr. 18, 1988  
[H. R. 3459]

To amend the Federal Food, Drug, and Cosmetic Act to revise the provisions respecting orphan drugs, and for other purposes.

Orphan Drug  
Amendments of  
1988  
DURHAM.  
21 USC 301 note.

*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,*

SECTION 1. SHORT TITLE.

This Act may be cited as the "Orphan Drug Amendments of 1988".

SEC. 2. DESIGNATION AS AN ORPHAN DRUG.

(a) **REQUEST.**—Section 526(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb(a)(1)) is amended by adding after the first sentence the following: "A request for designation of a drug shall be made before the submission of an application under section 505(b) for the drug, the submission of an application for certification of the drug under section 507, or the submission of an application for licensing of the drug under section 351 of the Public Health Service Act."

(b) **DISCONTINUANCE.**—Section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) is amended by redesignating subsections (b) and (c) as subsections (c) and (d), respectively, and by adding after subsection (a) the following:

"(b) A designation of a drug under subsection (a) shall be subject to the condition that—

"(1) if an application was approved for the drug under section 505(b), a certificate was issued for the drug under section 507, or a license was issued for the drug under section 351 of the Public Health Service Act, the manufacturer of the drug will notify the Secretary of any discontinuance of the production of the drug at least one year before discontinuance, and

"(2) if an application has not been approved for the drug under section 505(b), a certificate has not been issued for the drug under section 507, or a license has not been issued for the drug under section 351 of the Public Health Service Act and if preclinical investigations or investigations under section 505(i) are being conducted with the drug, the manufacturer or sponsor of the drug will notify the Secretary of any decision to discontinue active pursuit of approval of an application under section 505(b), approval of an application for certification under section 507, or approval of a license under section 351 of the Public Health Service Act."

SEC. 3. FINANCIAL ASSISTANCE.

(a) **MEDICAL DEVICES.**—Section 5 of the Orphan Drug Act (21 U.S.C. 360ee) is amended—

(1) in subsection (a), by inserting "(1)" after "assist in" and by inserting before the period a comma and "(2) defraying the costs



of developing medical devices for rare diseases or conditions", and

(2) in subsection (b)(2)—

(A) by inserting "(1) in the case of a drug," after "means" in the first sentence and by adding before the period in that sentence a comma and "(2) in the case of a medical device, any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical device for such disease or condition will be developed without assistance under subsection (a)", and

(B) by striking out "under this subsection" in the last sentence and inserting in lieu thereof "under section 526 of the Federal Food, Drug, and Cosmetic Act".

(b) **MEDICAL FOODS.**—Section 5 of the Orphan Drug Act (21 U.S.C. 360ee) is amended—

(1) in subsection (a) (as amended by subsection (a)), by inserting before the period a comma and "and (3) defraying the costs of developing medical foods for rare diseases or conditions",

(2) in subsection (b)(2) (as amended by subsection (a)), by inserting before the period at the end of the first sentence a comma and "and (3) in the case of a medical food, any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without assistance under subsection (a)", and

(3) by adding at the end of subsection (b) the following: "(3) The term 'medical food' means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

(c) **AUTHORIZATION.**—Section 5(c) of the Orphan Drug Act (21 U.S.C. 360ee(c)) is amended to read as follows:

"(c) For grants and contracts under subsection (a) there are authorized to be appropriated \$10,000,000 for fiscal year 1988, \$12,000,000 for fiscal year, 1989, \$14,000,000 for fiscal year 1990."

(d) **STUDY.**—The Secretary of Health and Human Services shall conduct a study to determine whether the application of subchapter B of chapter V of the Federal Food, Drug, and Cosmetic Act (relating to drugs for rare diseases and conditions) and section 28 of the Internal Revenue Code of 1986 (relating to tax credit) to medical devices or medical foods for rare diseases or conditions or to both is needed to encourage the development of such devices and foods. The Secretary shall report the results of the study to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate not later than one year after the date of the enactment of this Act. For purposes of this section, the term "rare diseases or conditions" has the meaning prescribed by section 5 of the Orphan Drug Act (21 U.S.C. 360ee).

Taxes  
21 USC 360aa  
note.

Reports.

102 STAT. 92

PUBLIC LAW 100-290—APR. 18, 1988

**SEC. 4. NATIONAL COMMISSION ON ORPHAN DISEASES.**

Section 4(n) of the Orphan Drug Amendments of 1985 (42 U.S.C. 236) note) is amended by striking out "September 30, 1987" and inserting in lieu thereof "February 1, 1989".

**Approved April 18, 1988.**

**LEGISLATIVE HISTORY—H.R. 3459:**

HOUSE REPORTS: No. 100-473 (Comm. on Energy and Commerce).  
CONGRESSIONAL RECORD, Vol. 134 (1988):  
Mar. 22, considered and passed House.  
Mar. 31, considered and passed Senate.

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## APPENDIX B



THE SECRETARY OF HEALTH AND HUMAN SERVICES  
WASHINGTON, D.C. 20201

## C H A R T E R

### National Commission on Orphan Diseases

#### Purpose

The National Commission on Orphan Diseases (hereinafter referred to as the "Commission"), created by Public Law 99-91, will evaluate current research activities in the area of orphan diseases. It will also evaluate the use, application, and dissemination of the information on all human diseases (including antibiotics and biologics), medical devices and medical foods gained from the research. Finally, the Commission will examine current processes for offering research support in the area of rare diseases.

The term "orphan diseases" denotes rare diseases or conditions which (a) affect less than 200,000 persons in the U.S., or (b) affect more than 200,000 persons in the U.S. 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 or condition will be recovered from sales in the U.S. The term "orphan diseases" includes diseases rare in the U.S., but common elsewhere.

#### Authority

21 U.S.C. 360cc, as amended. The Commission is governed by provision of Public Law 92-463 (5 U.S.C. Appendix), which sets forth standards for the formation and use of advisory committees.

#### Function

The Commission shall assess the activities of the National Institutes of Health, the Alcohol, Drug Abuse, and Mental Health Administration, the Food and Drug Administration, other public agencies, and private entities in connection with:

- (1) basic research conducted on rare diseases;
- (2) the use in research on rare diseases of knowledge developed in other research;

- (3) applied and clinical research on the prevention, diagnosis, and treatment of rare diseases; and
- (4) the dissemination to the public, health care professionals, researchers, and drug and medical device manufacturers of knowledge developed in research on rare diseases and other diseases which can be used in the prevention, diagnosis, and treatment of rare diseases.

In assessing the activities of the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health Administration; and the Food and Drug Administration in connection with research on rare diseases, the Commission shall review:

- (1) the appropriateness of the priorities currently placed on research on rare diseases;
- (2) the relative effectiveness of grants and contracts when used to fund research on rare diseases;
- (3) the appropriateness of specific requirements applicable to applications for funds for research on rare diseases taking into consideration the reasonable capacity of applicants to meet such requirements;
- (4) the adequacy of the scientific basis for such research, including the adequacy of the research facilities and research resources used in such research and the appropriateness of the scientific training of the personnel engaged in such research;
- (5) the effectiveness of activities undertaken to encourage such research;
- (6) the organization of the peer review process applicable to applications for funds for such research to determine if the organization of the peer review process could be revised to improve the effectiveness of the review provided to proposals for research on rare diseases;
- (7) the effectiveness of the coordination between the national research institutes of the National Institutes of Health; the institutes of the National Institutes of Health; the institutes of the Alcohol, Drug Abuse, and Mental Health Administration; the Food and Drug Administration; and private entities in supporting such research; and

- (8) the effectiveness of activities undertaken to assure that knowledge developed in research on nonrare diseases is, when appropriate, used in research on rare diseases.

#### Structure

The Commission shall be composed of twenty members appointed by the Secretary of Health and Human Services as follows:

- (1) Ten members shall be appointed from individuals who are not officers or employees of the Government and who by virtue of their training or experience in research on rare diseases or in the treatment of rare diseases are qualified to serve on the Commission.
- (2) Five members shall be appointed from individuals who are not officers or employees of the Government and who have a rare disease or are employed to represent or are members of an organization concerned about rare disease.
- (3) Four nonvoting members shall be appointed from:
  - (A) the directors of the national research institutes of the National Institutes of Health; or
  - (B) the directors of the institutes of the Alcohol, Drug Abuse, and Mental Health Administration,

which the Secretary determines are involved with rare diseases.

- (4) One nonvoting member shall be appointed from officers or employees of the Food and Drug Administration who the Secretary determines are involved with rare diseases.

A vacancy in the Commission shall be filled in the manner in which the original appointment was made. If any member of the Commission who was appointed to the Commission as a director of a national research institute or an institute of the Alcohol, Drug Abuse, and Mental Health Administration or as an officer or employee of the Food and Drug Administration leaves that office or position, or if any member of the Commission who was appointed from persons who are not officers or employees of the Government becomes an officer or employee of the Government, such member may continue as a member of the Commission for not longer than the ninety-day period beginning on the date such member leaves that office or position or becomes such an officer or employee, as the case may be.

The chairman of the Commission shall be designated by the members of the Commission.

Members shall be appointed for the life of the Commission.

Management and support services shall be provided by the Office of the Assistant Secretary for Health.

#### Meetings

Meetings shall be held approximately four times a year at the call of the chair with the advance approval of a Government official, who shall also approve the agenda. A Government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings shall be conducted and records of the proceedings kept, as required by applicable laws and departmental regulations.

#### Compensation

- (1) Except as provided in paragraph (2), members of the Commission shall each be entitled to receive compensation at a rate not to exceed the daily equivalent of the annual rate of basic pay in effect for grade GS-18 of the General Schedule for each day (including travel time) during which they are engaged in the actual performance of duties as members of the Commission.
- (2) Members of the Commission who are full-time officers or employees of the Government shall receive no additional pay by reason of their service on the Commission.

#### Annual Cost Estimate

Estimated annual cost for operating the committee, including compensation and travel expenses for members but excluding staff support, is \$295,350. Estimate of annual man-years of staff support required is 4.0, at an estimated annual cost of \$154,046.

Reports

The Commission shall transmit to the Secretary and to each House of the Congress a report no later than September 30, 1987, on the activities of the Commission. The report shall contain a detailed statement of the findings and conclusions of the Commission, together with its recommendations for:

- (1) a long-range plan for the use of public and private resources to improve research into rare diseases and to assist in the prevention, diagnosis, and treatment of rare diseases; and
- (2) such legislation or administrative actions as it considers appropriate.

Termination Date

The Commission will terminate 90 days after the date of the submittal of its final report.

APPROVED:

MAR 27 1986

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Date

*Chas. P. Bowen M.D.*  
Secretary





## APPENDIX C

## Appendix C

### IMPLEMENTATION OF RECOMMENDATIONS

The Commission put forth 54 recommendations. They address the Commission's mandate to recommend legislative and administrative actions to increase, in the public and private sectors, research on rare diseases and development of orphan products. These recommendations involve the Congress, departments and agencies in the Executive Branch of the Federal government, State agencies, voluntary organizations, foundations, the pharmaceutical and insurance industries, and health professionals.

The cost of implementing all recommendations is estimated at \$45.6 million for the first year. This amount does not include recommended increases for funding for research on rare diseases and biomedical research in general. Many of the recommendations will not incur any costs; others will be costly at first glance, but will be cost beneficial in the long run.

The Commission believes that these recommendations will serve as a blueprint for rare disease activities for the next decade, and will stimulate the development of new and better treatments for rare diseases. Recommendations are grouped by target organization and are numbered according to the order in which they appear in the body of the report. Page numbers refer to the location of the recommendations in the body of the report.

#### CONGRESS

☆ Congress should establish by statute and appropriate such funds as necessary for a Central Office of Orphan and Rare Diseases (COORD) in the Office of the Assistant Secretary for Health to coordinate the rare-disease related research, regulatory, educational and service activities of physicians, investigators, foundations, voluntary organizations, patients and families, pharmaceutical manufacturers, insurers and Federal agencies. (See recommendation 54, p. 73)

#### COORD shall

- foster the implementation of the recommendations of the National Commission on Orphan Diseases,
- respond to new needs and issues as they arise, including proposals for legislation and regulations with implications for rare disease patients
- collect, develop, and disseminate information on rare diseases,
- promote a "Year of Rare Diseases" to educate the public,
- subsume the current responsibilities of the Orphan Products Board, and
- report to Congress on Federal activities related to rare diseases.

To assist COORD in its activities,

- the Assistant Secretary for Health should appoint an advisory board composed of persons knowledgeable about rare diseases, such as representatives of voluntary organizations, clinicians, investigators, pharmaceutical manufacturers, insurers, foundations, and government, including the FDA's Office of Orphan Product Development;
- existing Federal activities related to rare diseases, especially such activities in the FDA, NIH, ADAMHA, and CDC, should be continued and strengthened; and
- the Congress should provide full and stable funding for a central source of comprehensive information about rare diseases.

- ☆ Congress should remove constraints on Federal agencies regarding the printing and distribution of rare disease-related information. (See recommendation 1, p. 20)
- ☆ Congress and the private sector should increase funding for all basic and clinical research and for research training; such increases would raise funding of rare disease research and training as well. (See recommendation 9, p. 35)
- ☆ Congress should appropriate additional funds to NIH to expand biological sample and human tissue banks and animal models for research on rare diseases and to publicize the availability of such banks and models. (See recommendation 10, p. 35)
- ☆ Congress should increase extramural funding at ADAMHA, FDA, and NIH for postdoctoral clinical research fellowships in rare diseases by at least 30 fellowships per year for the next three years, and should increase funding for medical student fellowships by 80 fellowships per year for the next three years. (See recommendation 11, p. 35)
- ☆ Congress should increase funding for CRCs by \$40 million over four years to increase the number of CRCs, increase nurses' salaries, and renovate and upgrade facilities. (See recommendation 17, p. 47)
- ☆ Congress should fully fund the grants program of the FDA's Office of Orphan Products Development at the level authorized by P.L. 100-290 and assure the continuation and expansion of the program. (See recommendation 21, p. 49)
- ☆ Congress should appropriate additional funds to the FDA for toxicological studies by the National Center for Toxicology.

colological Research on selected orphan drugs. Congress should also authorize the National Center for Toxicological Research to use their existing funds to conduct studies on selected orphan drugs. (See recommendation 22, p. 49)

☆ Congress should recognize that the Maternal and Child Health Block Grant, particularly through the SPRANS program, is a significant prevention, education, and service delivery program for children with rare diseases. Congress should therefore increase the funding for this program. (See recommendation 23, p. 50)

☆ No additional regulatory changes should be made in IRS 501(c) rules restricting voluntary organizations' fund-raising activities or their advocacy role. Voluntary organizations should not be restricted in educating congressional and Federal personnel about the needs of their constituents. (See recommendation 26, p. 52)

☆ The Federal government should not inhibit the fund-raising activities of nonprofit voluntary organizations through the Unrelated Business Income Tax law and regulations. (See recommendation 27, p. 52)

☆ The Federal government should not increase the bulk-mail rates for voluntary organizations, because this would limit the ability of these organizations to reach the people they serve. (See recommendation 28, p. 53)

☆ Congress should enact the Volunteer Protection Act without delay to protect volunteers from legal suits. Many rare disease voluntary organizations cannot afford, and sometimes cannot obtain, liability insurance for volunteers. The absence of such insurance often discourages volunteers from donating critically needed time and talent. (See recommendation 29, p. 53)

☆ The Commission recommends that incentives to stimulate the development of new orphan products be increased. Potential incentives include:

- Increasing the period of exclusive approval from the current seven years,
- Extending tax credits to all developmental activities, and
- Extending the patent on one currently marketed patented product for every orphan product approved by the FDA. The Commission recommends, however, that this incentive be available only to companies that have established a systematic drug discovery and development program for non-cancer, non-AIDS rare diseases and that receive an approved NDA or premarketing licensing approval for a designated orphan product. (See recommendation 30, p. 58)

☆ Congress should enact intellectual property protections for those biotechnology products not currently protected by the Patent and the Food, Drug and Cosmetic acts. (See recommendation 31, p. 58)

☆ Congress and state legislatures should promptly resolve product and professional liability issues. (See recommendation 33, p. 60)

☆ Congress should consider special relief in instances where concerns about liability pose insurmountable obstacles to progress on rare diseases. (See recommendation 34, p. 60)

☆ Forums seeking general solutions to the issue of liability should pay special attention to the implications of those solu-

tions for the development of orphan products and the treatment of persons with rare diseases. (See recommendation 35, p. 60)

☆ The Federal government should not create barriers to the humane use of animals in biomedical research. (See recommendation 36, p. 61)

☆ Congress should appropriate sufficient funds and full-time-equivalent positions to support the orphan product review activities of the FDA. In FY 1990, these numbers should increase by \$4 million and 50 full-time-equivalent positions. In addition, the FDA should increase the FTEs of the Office of Orphan Products Development to the full complement of 15. Currently the OPD has been authorized 14 staff, but only 7.3 belong to the Office; 7 are on loan from elsewhere in the agency. In order to function effectively, a minimum of 15 staff members are needed. Additional staff should be assigned as the workload increases. (See recommendation 40, p. 63)

☆ Congress should amend the Orphan Drug Act to provide incentives for the development of orphan medical devices and medical foods. (See recommendation 47, p. 65)

## FEDERAL AGENCIES

☆ The Federal government should provide appropriate funding for registries of scientific and technical data for rare diseases. (See recommendation 13, p. 35)

☆ Federal agencies should heighten their awareness of rare diseases. They should declare activities regarding rare diseases to be a high priority of their programs. (See recommendation 14, p. 40)

☆ Funding agencies should ensure that study sections include experts on the rare disease under consideration. When these experts are ad hoc reviewers, they should be allowed to vote on that application. (See recommendation 15, p. 40)

☆ Funding agencies should ensure that advisory councils have representatives from patient and family groups who understand the problems associated with rare diseases. (See recommendation 16, p. 40)

☆ Voluntary organizations, foundations, and Federal agencies should continue to co-sponsor workshops and symposia to attract new and experienced investigators and to stimulate new research hypotheses. (See recommendation 19, p. 47)

☆ All government agencies conducting or funding rare disease research should have a mechanism for identifying and monitoring such activities. Resulting data should be provided to Congress annually. (See recommendation 20, p. 48)

☆ NIH, ADAMHA, and FDA should inform investigators involved in orphan products development and seeking financial support from Federal agencies of the potential usefulness of the SBIR program. (See recommendation 49, p. 66)

☆ Federal employees should be encouraged to use the incentives of the Federal Technology Transfer Act of 1986 to bring their products to the marketplace, and Federal agencies should make available as rapidly as possible the intellectual property of employees and agencies. (See recommendation 50, p. 66)

☆ Federal agencies and the private sector should inform clinical investigators of rare diseases of the protocol assistance

available from the FDA. Investigators should ensure that their clinical study protocols meet FDA requirements for adequate, well-controlled studies. (See recommendation 52, p. 68)

- ☆ The FDA, ADAMHA, and NIH should ensure that grant applications which cannot be funded by one agency are forwarded to the others for consideration. (See recommendation 53, p. 68)

#### **FEDERAL AND STATE EDUCATIONAL AGENCIES**

- ☆ Federal and state educational agencies should amend regulations to ensure that persons with rare diseases are not denied appropriate special education services, as mandated by P.L. 94-142. (See recommendation 2, p. 21)

#### **NATIONAL INSTITUTES OF HEALTH**

- ☆ Criteria used in evaluating CRCs should emphasize the rare disease research programs conducted or proposed. (See recommendation 18, p. 47)

#### **FOOD AND DRUG ADMINISTRATION**

- ☆ The FDA should develop and conduct an educational program for its product review personnel regarding problems unique to the development of products for rare diseases. (See recommendation 38, p. 62)
- ☆ The FDA should maintain appropriate flexibility with respect to regulatory requirements for the approval of orphan products, especially with respect to protocol design and the number and kinds of preclinical and clinical studies. (See recommendation 39, p. 62)
- ☆ The FDA should expedite orphan product approval by
  - classifying all orphan products as 1A,
  - making all designated orphan products eligible to obtain a treatment IND or an open protocol,
  - encouraging the sponsor to develop draft labeling and seek inspection of their manufacturing facilities at earlier stages of development. (See recommendation 41, p. 63)
- ☆ If FDA institutes user fees for the NDA review process, FDA should waive any such fees for orphan products, where appropriate. (See recommendation 42, p. 63)
- ☆ The FDA should expedite and encourage the addition of new rare disease indications to the labeling of marketed products. (See recommendation 46, p. 64)
- ☆ The FDA's Office of Orphan Products Development should establish a program to act as a resource and assist investigators with promising orphan products to gain access to reference Drug Master Files and to obtain a sponsor. (See recommendation 32, p. 59)
- ☆ The FDA's Office of Orphan Products Development, in conjunction with the pharmaceutical industry, schools of pharmacy, and existing consortia, should develop and implement a system to help investigators develop appropriate dosage forms. (See recommendation 37, p. 61)

#### **DRUG ENFORCEMENT ADMINISTRATION**

- ☆ The Drug Enforcement Administration should recognize the legitimate use of controlled substances in the treatment of persons with rare diseases and should not interfere with the ability of physicians to prescribe controlled substances when medically necessary. (See recommendation 43, p. 64)

#### **NATIONAL CENTER FOR HEALTH STATISTICS**

- ☆ The National Center for Health Statistics should determine the prevalence of rare diseases in the United States. (See recommendation 24, p. 50)

#### **SOCIAL SECURITY ADMINISTRATION**

- ☆ The Social Security administration should revise the Listing of Impairments to determine eligibility for benefits by descriptions of generic problems in addition to specific diagnoses. Similarly, other public and private agencies, such as Crippled Children's Services and Developmental Disabilities Services, should determine eligibility for benefits on the basis of generic problems rather than on lists of disorders alone. (see recommendation 3, p. 21)

#### **CENTRAL OFFICE OF ORPHAN AND RARE DISEASES (COORD)**

- ☆ The Central Office of Orphan and Rare Diseases (COORD) should convene a meeting of relevant public and private insurers and patients and their families to resolve the problems in health, disability, and life insurance coverage. Recognizing that such resolution will be difficult to achieve, the Commission recommends the following immediate measures:
  - State insurance commissioners should ensure that insurance plans do not discriminate against persons with rare diseases, including persons with pre-existing conditions.
  - Employee benefit managers should ensure that employer-provided group insurance responds to the needs of persons with rare diseases, including persons with pre-existing conditions.
  - Public and private insurers should utilize information from COORD to make responsible decisions about coverage of persons with rare diseases, including coverage of appropriate services and treatments such as physical, speech, and respiratory therapies; dental care; medical foods; over-the-counter products; and genetic counseling.
  - States should allow a Medicaid buy-in for persons with rare diseases who cannot otherwise obtain health insurance.
  - Insurers should pool the small groups they cover in order to distribute risk more widely and extend the availability of insurance to persons with rare diseases.
  - The COORD should begin to develop a data base on acceptable medical treatments for rare diseases. In the absence of a technology assessment on a particular therapy, insurers should cover medical expenses of an investigational treatment when it is part of an approved protocol or an approved treatment IND. (See recommendation 7, p. 29)
- ☆ The Central Office of Orphan and Rare Diseases should periodically screen and publicize the National Technical Infor-

mation Service's list of intellectual property available for licensing. (See recommendation 51, p. 66)

#### **U.S. REPRESENTATIVE TO THE WORLD HEALTH ASSEMBLY**

☆ The U.S. representative to the World Health Assembly should ensure that classification schemes of diseases, particularly the International Classification of Diseases, accurately reflect the state of knowledge about rare diseases. (See recommendation 8, p. 29)

#### **INSURERS**

☆ Public and private insurers must ensure access to affordable health insurance for patients with rare diseases. (See recommendation 5, p. 29)

☆ Public and private insurers must ensure access to affordable life insurance for patients with rare diseases. (See recommendation 6, p. 29)

☆ Medical foods are life-sustaining and should be reimbursed by private and public insurers. (See recommendation 48, p. 65)

#### **VOLUNTARY ORGANIZATIONS**

☆ Voluntary organizations should be encouraged in their development of patient, physician, and investigator regis-

tries to improve patients' access to treatment and to increase research opportunities. (See recommendation 12, p. 35)

☆ Voluntary organizations with common research and education interests should be encouraged to form and participate in alliances and coalitions in order to enhance the use of their scarce dollars. (See recommendation 25, p. 52)

#### **PHARMACEUTICAL INDUSTRY**

☆ Sponsors of drugs approved in other countries should be encouraged to seek FDA approval for those drugs and to participate in treatment INDs and open protocol programs. (See recommendation 45, p. 64)

#### **PHARMACISTS**

☆ Pharmacists should recognize the special needs of patients with rare diseases and assist patients to obtain orphan products. (See recommendation 44, p. 64)

#### **HEALTH SERVICES INDUSTRY**

☆ Health professionals, institutions, and pharmaceutical companies should continue with their practice of providing free and reduced price services and drugs to those rare disease patients who cannot afford to pay for them. (See recommendation 4, p. 29)