I.
Overview of International Activities

HISTORICAL PERSPECTIVE

The National Institutes of Health (NIH) has been linked with the international scientific community since its founding in 1887 as the Laboratory of Hygiene. A principal reason for Congress' establishment of this precursor for the NIH was to combat diseases that were international in scope and threatened the health of U.S. citizens. Shortly before his appointment as the first Director of the Laboratory of Hygiene, Dr. Joseph Kinyoun traveled to Europe to learn new techniques for isolation and identification of bacteria in the laboratories of Robert Koch and Louis Pasteur. Returning to the United States, he proceeded to isolate the cholera microbe from sick crew members of a ship in the port of New York City. These efforts stemmed the importation of the sixth cholera pandemic into the United States, in the first use of the new science of microbiology to address a public health problem.

Ever since the early microbial investigations of Dr. Kinyoun, the NIH has continued a tradition of international research. The components of the NIH with an international program have expanded as the NIH's legislative mandate has broadened. NIH international activities were codified in the International Health Research Act of 1960, which authorized the Public Health Service to provide grants and fellowships to foreign institutions and to facilitate the international exchange of scientists.

Subsequently, the NIH investment in international activities has grown in direct proportion to the overall budget, representing a level of about 1.5%–2% of NIH expenditures over the past two decades. In absolute terms, this represents the largest investment by any U.S. Government science agency in international biomedical research cooperation and reflects an implicit and historical working principle of the NIH—that neither disease nor intellectual pursuit can be confined within national boundaries.

NEW CHALLENGES

With the growing application of biological progress and new technologies to the solution of practical clinical problems, promising advances are possible in the diagnosis, treatment, and prevention of disease. Increasingly, the capacity to capitalize on scientific opportunities and capture the potential of discoveries will depend on scientific interaction on a global scale among biomedical, epidemiologic, and behavioral researchers in the field and in laboratories, together with clinical and technical personnel in all areas of science. The growing interdependence of the world's scientific community is attributable to recent promising developments that present new challenges and opportunities.

EMERGING TECHNOLOGIES

International cooperation enables the U.S. scientific community to share unique or highly sophisticated research methods, technologies, and facilities located abroad. This access grows increasingly important as the biomedical and behavioral sciences become more specialized and at a time when only a cluster of laboratories may be undertaking a specific line of scientific inquiry in molecular genetics, developmental and structural biology, neurobiology, or other highly specialized fields.

The convergence of parallel lines of research through international interaction provides for cross-disciplinary approaches that often catalyze new discoveries. The development of a therapeutic agent, for example, may result from exchange of concepts and methods enabling investigators in one laboratory to determine the amino acid sequence of an important enzyme, researchers in a second to crystallize and define its three-dimensional structure, and scientists in a third to exploit these basic research findings to design a novel drug-delivery system.

POPULATION-BASED STUDIES

The availability of unique populations and environments in other regions of the world presents important opportunities to expand the biomedical knowledge base and conduct studies that could not be undertaken in any one nation. Advances in technologies for analysis of DNA have accelerated the rate of drug and vaccine development and hold promise for new and improved approaches to prevention and treatment. Many of these emerging medical technologies will require studies in regions of the world where there is a high concentration of particular diseases.

A notable example is the development of an effective vaccine for acquired immunodeficiency syndrome (AIDS). This achievement will depend on testing in various countries, because of genetic variability of the virus and increasing incidence of human immunodeficiency virus (HIV) in important cohorts. Other prominent examples of benefit from international field trials include the development of new and improved treatments and preventive measures for diarrheal, respiratory, sexually transmitted, and parasitic diseases; hepatoma and other virus-associated cancers; and cardiovascular diseases.

Future advances to identify genetic markers for inherited diseases and predisposing factors for acquired diseases will require genetic-linkage studies that transcend national borders. Past international cooperation has made possible the identification of genetic markers for thalassemic syndromes, Huntington's chorea, cystic fibrosis, and a hereditary form of colon cancer. This progress was possible through the study of inheritance patterns among populations of countries with a high prevalence of the inherited disease, which enabled scientists to localize and ultimately isolate the disease-related gene.

Population-based research involving cross-cultural comparisons provides new knowledge of the natural history, epidemiology,

TABLE I-1.

International Agreements Involving the NIH, Fiscal Year 1999

Country/Area	Science and Technology	Health	NIH	No. of Agreements
Argentina	1972			1
Armenia	1997		1995 NIH-MOH-AOS	2
Australia			1974 NLM	1
Austria			1993 NIH–FWF	1
Brazil	1994			1
Canada	1997		1982 NLM–CIST	2
Chile	Pending		1997 NIH–CONICYT	1 (1 pending)
China	1991	1998	1987 NEI–ZOC 1996 NLM-CUHK	4
Croatia	1994			1
Czech Republic	1991			1
Egypt	1995	1989		2
Estonia	1994			1
Finland	1992	1982		2
France			1974 NIH–INSERM	1
Germany	1994	1998	1981 NCI–MORT 1983 NLM-DIMDI	4
Hungary	1989		1981 NCI–NIO	2
India			1987 NLM–NIC	1
Israel	1972	1985	1983 NIH–HU 1993 NLM–HU	4
Italy	1993	1981	1978 NLM–ISS 1985 NEI–MOH	4
Japan	1993	1965	1974 NCI–JSPS 1974 NLM–JIST 1976 NEI–JSPS	5
Korea	Pending		1989 NCI–KAMS 1991 NLM-SNU	2 (1 pending)
Kuwait			1981 NLM–MPH	1
Latvia	1994			1
Lithuania	1994			1
Macedonia	1995			1
Mexico	1994	1996	1976 NLM–MOH 1994 NIH-CONACYT	4
New Zealand	1991		1991 NLM–DOH	2
Poland	1997			1
Russia	1993	1994	1987 NEI–IED 1994 NIH–RAS 1997 NLM-SCSML	5
Slovakia	1996			1
Slovenia	Pending			1 (pending)
South Africa	1995		1976 NLM–MRC	2
Spain	1994			1
Sweden			1974 NLM–SMRC	1
Switzerland			1980 NLM–SAMS	1
Turkey	1994			1
Ukraine	1994			1
United Kingdom	1995		1974 NLM–BL	2
Venezuela	1996	1996		2
Taiwan			1987 NLM–EPA 1989 NIH-NSCT	2
Total: 40	**29 (3 pending)**	**10**	**34**	**72 (3 pending)**

and risk factors associated with diseases of public health priority. These studies use geographic differences to discover and differentiate genetic and environmental determinants of disease. Correlations between sodium intake and stroke, for example, were identified and confirmed through international studies. Cross-national investigations also provide for a greater degree of international acceptability of results.

EMERGING DISEASES

The spread of infectious diseases across national borders and the emergence of new pathogens dramatize the need for international cooperation in health research. The rapidity with which the AIDS virus was transmitted among continents highlights the necessity for an effective global sentinel network of basic and clinical researchers to identify new patterns of disease and modes of transmission. Although the AIDS epidemic has exhibited the difficulties of coping with a new infectious disease, AIDS is but one of a dozen new or newly recognized viral diseases that have emerged in recent decades in association with rapid social and ecological change.

RESOURCE SHARING

International cooperation enables the United States and other countries to share the cost and labor of scientific discovery. Leading examples are the initiative to map and measure the sequence of 3 billion nucleotide base pairs in the human genome; efforts to analyze plant, animal, and microbial model organisms; and multicenter, standardized studies requiring the recruitment of an extensive study population.

Opportunities to share important resources are also presented through international cooperation. Collaborating investigators in other countries have provided more than one-half of all compounds that have been screened for antineoplastic or antiviral activity at the NIH. GenBank, a computerized source of information on genetic sequence, was developed in concert with the European Molecular Biology Laboratory. Sharing of genetically modified rabbit models developed in Japan provided observations that led to the discovery of the role of critical receptors in the atherosclerotic process.

Other examples of the benefits of international cooperation include the following:

- highly specialized treatments for rare or uncommon hereditary disorders and acquired disorders, when no one country can recruit an adequate number of patients for meaningful study;
- the shared use of sophisticated and costly instruments that are beyond the effective resources of any one institution, such as particle accelerators to study macromolecular structures;
- foreign registries for cancer and other diseases that have supplemented population studies in the United States; and
- international repositories for standardized chemicals, cloned genes, viruses, and antisera, as well as international donor registries for bone marrow.

INTERNATIONAL RELATIONS

The international role of the NIH is expanding as a result of what has been characterized as a changing world order. Global

political and economic realignments have immediate relevance to a Federal science agency with an international mission and to universities that have forged international relationships. These global changes include the collapse of communism and the emergence of new democracies, European economic integration, the economic ascendancy of Japan and neighboring Pacific Rim nations, and widening disparities in health and economic status between industrial and developing nations.

HIGHLIGHTS OF RECENT INTERNATIONAL SCIENTIFIC ACTIVITIES

This report discusses the international activities of NIH components: work undertaken intramurally, by staff or visiting foreign scientists, and extramurally, by NIH grantees collaborating with foreign colleagues or by scientists in other countries.

Appendix B gives an overview of the major funding mechanisms through which the NIH supports these diverse activities. All foreign requests for NIH awards undergo the same stringent peer review process as do domestic applications for NIH support. Research proposals must justify the need for NIH international projects to be carried out overseas by foreign scientists.

Many international activities are conducted under bilateral agreements between the United States and other governments. These agreements, usually established through the U.S. Department of State, may have a broad science and technology scope or a specific health focus. Table I-1 provides a list of international agreements involving the NIH. International activities also include NIH participation in meetings, conferences, and workshops, many of which are sponsored by multinational organizations such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO).

Table I-2 shows total expenditures for NIH international programs by activity and component for fiscal year 1999 (FY 99). During FY 99, the NIH expended $272.4 million of its appropriated funds on international activities. That sum represented about 1.7% of the NIH's $15.6 billion budget for FY 99.

For FY 99, the funding breakdown included $148.6 million for research awards (including $120.0 million for grants and $28.6 million for contracts); $108.7 million for scientist awards ($94.4 million for foreign scientists in the United States, $6.3 million for U.S. scientists abroad, and $8.0 million for bilateral exchanges including conferences); $4.2 million for travel; and $10.9 million for program support. This funding distribution is summarized in Figure I-1. The annual NIH budgets for international expenditures from FY 85 through FY 99 are summarized in Figure I-2.

FIGURE I-1.

NIH International Activities Funding by Mechanism, Fiscal Year 1999 (in millions of dollars)

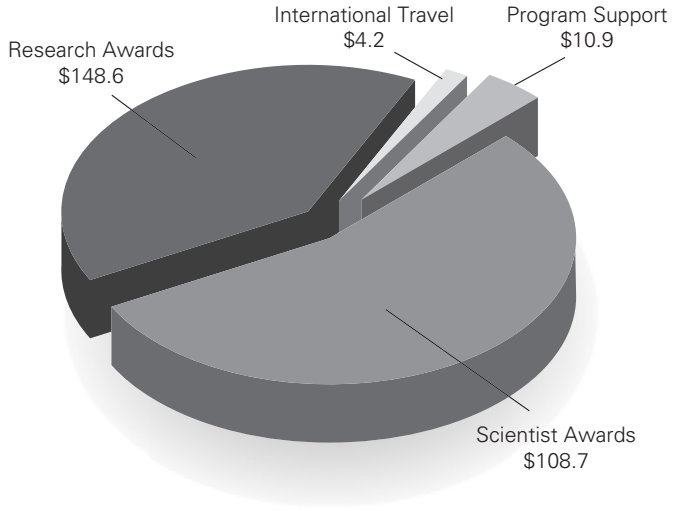


Table I-3 lists NIH expenditures during FY 99 for research and training awards by country or area and by type of award. In addition to awards by scientists at foreign institutions, the NIH awarded approximately $6.1 million in grants, contracts, and cooperative agreements to multilateral organizations in FY 99.

Table I-4 provides a historical summary of NIH support for international research and training awards (excluding travel and program support) since FY 50. In recent years, there has been a precipitous rise in the numbers of domestic grants with foreign components. This increase demonstrates the increase in collaboration between U.S. and foreign investigators.

John E. Fogarty International Center for Advanced Study in the Health Sciences

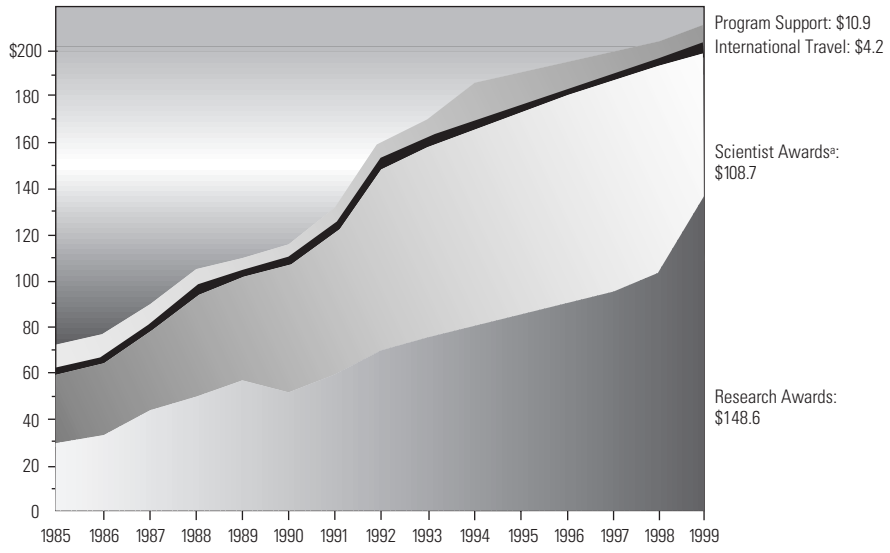
In FY 99, the John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) supported collaboration among scientists at Johns Hopkins University, Baltimore, Maryland, and the Universidad Peruana Cayetano Heredia and Asociación Benefica Proyectos en Informatica, Salud, Medicina, y Agricultura, Lima, Peru, to develop a porcine model in cysticercosis for the detection of immunologic protection that allows assessment of vaccine efficacy. This research team also developed a rapid and reliable method for detecting tuberculosis, to be used by health officers in developing countries. The test, called the microscopic observation broth drug-susceptibility assay, can detect tiny amounts of the tuberculosis bacteria in sputum samples from patients within 9 days, instead of the 3- to 4-week period required by traditional culture methods. Characteristic strings and tangles of tuberculosis bacterial growth can be observed in inexpensive liquid media through a simple light microscope. This method can also be used to determine whether a particular strain of tuberculosis is resistant to any drug, without the use of radioactive isotopes or fluorescent indicators.

Investigators trained under and supported by FIC's AIDS International Training and Research Program (AITRP) at Johns Hopkins University, Baltimore, Maryland, and Case Western Reserve University, Cleveland, Ohio, were the principal foreign collaborators on a study in Uganda that was funded by the National Institute of Allergy and Infectious Diseases (NIAID) through the HIV Network (HIVNET) Program. In this study,

TABLE I-2.
Total Expenditures for NIH International Programs by Activity and NIH Component, Fiscal Year 1999 (in thousands of dollars)

	NCI	NHLBI	NIDCR	NIDDK	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	NIA	NIAMS
Research Awards												
Grants												
Foreign Research Grants	12,294	2,785	1,024	2,825	2,658	5,372	1,080	2,068	1,542	380	1,356	206
Foreign Components of Domestic Grants	11,581	4,064	1,644	2,416	4,123	21,011	939	6,965	98	2,131	4,157	688
Subtotal	23,875	6,849	2,668	5,241	6,781	26,383	2,019	9,033	1,640	2,511	5,513	894
Contracts												
Foreign Contracts	5,104	701	—	—	172	2,146	—	619	—	227	—	—
Foreign Components of Domestic Contracts	3,267	1,399	—	—	—	10,737	—	810	—	—	—	—
Subtotal	8,371	2,100	—	—	172	12,883	—	1,429	—	227	—	—
Scientist Awards												
Foreign Scientists												
Intramural Research Program	17,034	5,996	2,923	7,605	4,527	7,335	—	6,023	1,445	3,457	2,634	1,936
Research Fellowships	—	—	—	—	—	—	—	—	—	—	—	—
Scholars-in-Residence	—	—	—	—	—	—	—	—	—	—	—	—
International Training and Research Grants	—	—	582	—	—	799	—	440	—	150	160	—
Subtotal	17,034	5,996	3,505	7,605	4,527	8,134	—	6,463	1,445	3,607	2,794	1,936
U.S. Scientists												
Research Fellowships/Work Study	117	32	—	37	124	78	123	95	—	—	—	—
Minority International Res. Training Program	—	—	—	—	—	—	—	—	—	—	—	—
Subtotal	117	32	—	37	124	78	123	95	—	—	—	—
Bilateral Exchanges/Conferences	1,700	300	315	259	45	—	—	226	111	1,156	361	51
International Travel	1,220	124	291	128	229	597	2	241	49	48	133	40
ICD Program Support	1,428	515	485	16	—	160	—	340	28	115	119	3
Total NIH	53,745	15,916	7,264	13,286	11,878	48,235	2,144	17,827	3,273	7,664	8,920	2,924

FIGURE I-2.
NIH International Research Awards, Scientist Awards, Travel, and Program Support, Fiscal Years 1985–1999 (in millions of dollars)



[a]Since fiscal year 1989, expenditures for "Bilateral Exchanges/Conferences" have been reported under "Scientist Awards." In previous NIH annual reports, they were listed under "Program Support." All figures were made comparable for this graph.

administration of single doses of the antiretroviral drug nevirapine to HIV-infected mothers and their newborn infants reduced HIV transmission by one-half compared with transmission after zidovudine (AZT) therapy. Because AZT is 70 times more expensive than nevirapine and because a single dose of nevirapine at birth is much easier to administer than the multidose regimen of AZT, nevirapine offers the best alternative to reduce mother-to-infant HIV transmission in developing countries. AITRP-affiliated scientists are continuing to collaborate on follow-up studies to determine the ability of nevirapine to reduce HIV transmission associated with breast-feeding.

In FY 99, FIC established the International Maternal and Child Health Research and Training Program to enable U.S. institutions to support training-related research on maternal and child health issues that are predominantly endemic in or that affect people living in developing nations. The Program is designed to increase expertise of scientists in developing countries in biomedical, behav-

NIDCD	NIMH	NIDA	NIAAA	NINR	NCRR	NHGRI	NCCAM	FIC	NLM	OD	CC	CIT	CSR	TOTALS	FUNDS EXPENDED US	FUNDS EXPENDED ABROAD
78	2,612	3,145	365	581	157	—	—	—	—	—	—	—	—	40,528	—	X
430	6,555	1,587	946	456	609	1,638	62	7,283	100	—	—	—	—	79,483	—	X
508	9,167	4,732	1,311	1,037	766	1,638	62	7,283	100	—	—	—	—	120,011	—	X
55	1,494	25	60	—	164	745	—	—	—	—	—	—	—	11,512	—	X
—	—	—	—	—	31	860	—	—	—	—	—	—	—	17,104	—	X
55	1,494	25	60	—	195	1,605	—	—	—	—	—	—	—	28,616	—	X
584	2,775	806	553	—	—	1,579	—	—	1,219	284	1,544	118	—	70,377	X	—
—	—	312	—	—	—	—	—	599	—	—	—	—	—	911	X	—
—	—	—	—	—	—	—	—	99	—	—	—	—	—	99	X	—
—	561	400	—	—	—	—	—	18,661	—	1,214	—	—	—	22,967	X	—
584	3,336	1,518	553	—	—	1,579	—	19,359	1,219	1,498	1,544	118	—	94,354	X	—
—	106	—	19	—	—	—	—	832	—	49	—	—	—	1,612	—	X
—	—	—	—	—	—	—	—	300	—	4,372	—	—	—	4,672	—	X
—	106	—	19	—	—	—	—	1,132	—	4,421	—	—	—	6,284	—	X
240	204	86	207	—	—	659	—	310	199	1,587	—	—	—	8,016	X	X
38	240	82	76	9	12	109	—	48	166	284	37	13	14	4,230	X	X
5	—	160	144	—	—	—	—	7,175	163	—	—	—	—	10,856	X	—
1,430	14,547	6,603	2,370	1,046	973	5,590	62	35,307	1,847	7,790	1,581	131	14	272,367	X	X

ioral, and prevention research related to maternal and child health; to support collaborative training in biomedical and behavioral research related to maternal and child health by U.S. and foreign scientists; and to establish or strengthen biomedical and behavioral research in maternal and child health and prevention centers of excellence in the home countries of trainees.

National Institute on Aging

In FY 99, the Behavior and Social Research Program, Office of Demography of Aging (ODA), National Institute on Aging (NIA), was active in encouraging and supporting production of comparable data by other nations, to continue the momentum fueled by the Denver (Colorado) G8 Summit Meeting in 1997. The last paragraph of the Denver Summit communiqué on population aging has acted as a powerful catalyst and has spurred several international organizations and some national governments to make research on population aging a higher priority in their agendas. It reads as follows:

> We agreed that it is important to learn from one another how our policies and programs can promote active aging and advance structural reforms to preserve and strengthen our pension, health, and long-term care systems. Our governments will work together, within the OECD [Organization for Economic Cooperation and Development] and with other international organizations, to promote active aging through information exchanges and cross-national research. We encourage collaborative biomedical and behavioral research to improve active life expectancy and reduce disability and have directed our officials to identify gaps in our knowledge and explore developing comparable data in our nations to improve our capacity to address the challenges of population aging into the 21st century.

ODA, a major contributor to this communiqué, highlighted current research issues related to population aging, projections, retirement, disability trends, and cross-national research opportunities and stressed the need for appropriate and comparable data. ODA has been asked to participate in preparations for the July 2000 G8 meeting in Okinawa, Japan, where it is likely that issues of aging will again be prominent and will include the implications of aging societies for health and long-term care policy.

In FY 99, as a part of joint efforts with the Institute of Biophysics, University of Linz, Austria, a scientist from the Section of Molecular and Clinical Pharmacology, Laboratory of Clinical Investigation, carried out successful experiments on double-labeled, cyan fluorescent protein at the N terminus and yellow fluorescent protein at the C terminus chimera of the human calcium channel pore-forming alpha 1C subunit prepared at NIA. For the first time, the functional expression of this chimera in tsA201 cells was demonstrated and fluorescence resonance energy transfer was observed as an enhanced fluorescence emission with the yellow fluorescent resonance energy transfers filter,

TABLE I-3.

NIH International Research and Research Training Awards by Country/Area and Mechanism, Fiscal Year 1999 (in thousands of dollars)

Country/Area	Research Grants		Research Contracts		Foreign Components of Domestic Awards		Visiting Program		Special Volunteers and Guest Researchers[b]	International Research Fellows	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	No.	Amount
Albania	—	—	—	—	—	—	1	12	—	—	—
Algeria	—	—	—	—	—	—	2	67	2	—	—
Argentina	—	—	—	—	24	1,295	26	741	3	—	—
Armenia	—	—	—	—	—	—	1	45	—	—	—
Australia	24	4,817	—	—	27	2,970	39	909	12	1	32
Austria	—	—	—	—	4	85	11	310	8	—	—
Bahamas	—	—	—	—	1	285	1	75	—	—	—
Bangladesh	—	—	—	—	4	722	5	103	1	1	37
Belarus	—	—	—	—	1	22	3	98	—	—	—
Belgium	1	150	—	—	10	502	9	241	4	—	—
Belize	—	—	—	—	1	40	—	—	—	—	—
Bolivia	—	—	—	—	1	40	—	—	—	—	—
Bosnia-Hercegovina	—	—	—	—	—	—	—	—	3	—	—
Botswana	—	—	—	—	1	23	—	—	—	—	—
Brazil	1	593	—	—	34	2,562	23	648	15	—	—
Bulgaria	—	—	—	—	1	94	11	363	—	1	37
Burkina-Faso	—	—	—	—	—	—	1	26	—	—	—
Cambodia	—	—	—	—	1	15	—	—	—	—	—
Cameroon	—	—	—	—	6	434	—	—	—	—	—
Canada	107	18,792	9	2,358	178	14,238	135	4,231	14	—	—
Chile	1	50	1	30	7	374	4	141	4	2	61
China	2	560	5	696	46	4,813	331	8,572	43	—	—
Colombia	—	—	—	—	9	445	6	182	3	—	—
Congo, the	—	—	—	—	—	—	1	16	—	—	—
Costa Rica	—	—	1	972	7	449	—	—	1	—	—
Croatia	—	—	—	—	3	124	5	166	—	—	—
Cuba	—	—	—	—	—	—	1	38	—	—	—
Cyprus	—	—	—	—	—	—	2	58	—	—	—
Czech Republic	—	—	—	—	8	175	15	404	3	1	31
Denmark	3	1,176	1	133	20	2,054	11	310	7	—	—
Dominican Republic	—	—	—	—	2	45	—	—	—	—	—
Ecuador	—	—	1	43	1	207	—	—	—	—	—
Egypt	—	—	—	—	6	166	3	30	2	1	32
Estonia	—	—	—	—	3	76	2	78	—	—	—
Ethiopia	—	—	—	—	3	142	2	77	1	—	—
Fiji	—	—	—	—	1	29	1	33	—	—	—
Finland	—	—	4	1,148	8	488	15	429	3	—	—
France	4	683	1	56	27	1,440	100	2,700	13	—	—
Gabon	—	—	—	—	2	233	—	—	—	—	—
Gambia	—	—	—	—	6	332	—	—	—	—	—
Georgia	—	—	—	—	—	—	1	32	1	1	34
Germany	3	523	3	232	31	1,963	115	3,388	54	—	—
Ghana	—	—	1	1,280	5	930	—	—	—	—	—
Greece	—	—	—	—	2	122	15	438	5	1	31
Guatemala	—	—	—	—	1	61	—	—	—	—	—
Haiti	—	—	—	—	4	646	—	—	—	—	—
Hong Kong	—	—	—	—	2	454	4	90	—	—	—
Hungary	—	—	—	—	12	566	21	670	6	1	31
Iceland	—	—	—	—	—	—	2	87	1	—	—
India	2	111	—	—	16	1,306	134	3,392	15	1	54
Indonesia	—	—	—	—	4	611	1	17	—	—	—
Iran	—	—	—	—	—	—	4	131	3	—	—
Ireland	—	—	—	—	3	735	8	213	—	—	—
Israel	14	2,110	—	—	31	2,134	58	1,839	4	—	—
Italy	3	594	4	677	34	1,559	126	3,833	44	—	—
Jamaica	—	—	1	795	4	127	1	34	—	—	—
Japan	1	300	1	136	8	960	334	9,000	100	—	—
Jordan	—	—	—	—	1	7	4	94	1	—	—
Kenya	—	—	—	—	16	1,372	3	58	—	—	—
Korea	—	—	—	—	2	100	169	4,594	22	—	—
Laos	—	—	—	—	1	88	—	—	—	—	—
Latvia	—	—	—	—	—	—	1	37	—	—	—
Lebanon	—	—	—	—	—	—	1	35	—	—	—
Liberia	—	—	—	—	1	150	1	9	—	—	—
Madagascar	—	—	—	—	1	178	—	—	—	—	—
Malawi	—	—	—	—	8	1,744	1	30	—	—	—
Malaysia	—	—	—	—	1	1,048	4	102	—	—	—
Mali	1	640	4	266	2	418	2	65	—	—	—

Senior International Fellows		National Research Service Award		
No.	Amount	No.	Amount	Totals
—	—	—	—	12
—	—	—	—	67
—	—	—	—	2,036
—	—	—	—	45
1	17	1	37	8,782
—	—	—	—	395
—	—	—	—	360
—	—	—	—	862
—	—	—	—	120
—	—	—	—	893
—	—	—	—	40
—	—	—	—	40
—	—	—	—	0
—	—	—	—	23
—	—	—	—	3,803
—	—	—	—	494
—	—	—	—	26
—	—	—	—	15
—	—	—	—	434
—	—	5	160	39,779
—	—	—	—	656
—	—	—	—	14,641
—	—	—	—	627
—	—	—	—	16
—	—	—	—	1,421
—	—	—	—	290
—	—	—	—	38
—	—	—	—	58
—	—	—	—	610
1	35	—	—	3,708
—	—	—	—	45
—	—	—	—	250
—	—	—	—	228
—	—	—	—	154
—	—	—	—	219
—	—	—	—	62
—	—	—	—	2,065
2	74	4	152	5,105
—	—	—	—	233
—	—	—	—	332
—	—	—	—	66
1	31	6	188	6,325
—	—	—	—	2,210
1	46	—	—	637
—	—	—	—	61
—	—	—	—	646
—	—	—	—	544
—	—	—	—	1,267
—	—	—	—	87
—	—	—	—	4,863
—	—	—	—	628
—	—	—	—	131
—	—	—	—	948
1	46	—	—	6,129
—	—	—	—	6,663
—	—	—	—	956
1	32	—	—	10,428
—	—	—	—	101
—	—	—	—	1,430
—	—	—	—	4,694
—	—	—	—	88
—	—	—	—	37
—	—	—	—	35
—	—	—	—	159
—	—	—	—	178
—	—	—	—	1,774
—	—	—	—	1,150
—	—	—	—	1,389

Cont'd

on excitation of the cyan chromophore. This finding allows the research team to extend the study to monitoring of the state-dependent molecular motions of distant parts of the channel protein and resulted in several publications.

The Neuroscience and Neuropsychology of Aging Program supported collaboration between Karolinska Institute, Stockholm, Sweden, and the University of Colorado Health Sciences Center, Denver. The investigators conducted studies of neural grafts and growth factors, to find methods that may be useful in treating neurodegenerative diseases. The research has identified new neurotrophic factors, the receptors for those factors, and their functional activity in the brain. The findings support the potential use of neurotrophic factors in the treatment of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

National Institute on Alcohol Abuse and Alcoholism

The National Institute on Alcohol Abuse and Alcoholism and the First Moscow Medical Academy, Russia, are working together to transfer research-based knowledge about the prevention and treatment of alcohol-use disorders into the Russian medical education system. This highly successful initiative focuses on developing faculty in the primary care specialties to improve teaching and clinical skills in the early identification and treatment of alcohol-related problems. Faculty from 18 departments of family medicine at Russian medical academies have been trained and are part of an ongoing research effort to contribute to new developments in Russian preventive medicine.

Significant progress has been made in establishing a minimum prevalence of fetal alcohol syndrome (FAS) among first-grade students in one city in the Western Cape of South Africa. The results of two screening and diagnostic efforts indicate a prevalence of 5%–7% among the 1,800 students examined. Diagnosis involves maternal interviews, neurobehavioral testing, and examination by a dysmorphologist. The screening methods developed and used will be the standard for active case studies in the United States, and the publication of research reports is in progress. Initial developmental testing of children with FAS and control subjects indicates a specific pattern of deficits and strengths. Plans have been made to strengthen and expand the testing procedures to clarify findings. The methods used and tests selected were developed by U.S. scientists expert in assessing Native American children with FAS, in collaboration with South African specialists in child development. Metabolism and genetic pilot projects to determine why some women who drink similar amounts of alcohol have affected children and some have normal children are under way.

National Institute of Allergy and Infectious Diseases

AIDS

NIAID funds the Atlantic Study, which is sponsored by the AIDS Clinical Trials Group (ACTG). Participants in this international, multicenter study include St. Pierre University, Brussels, Belgium; the University of British Columbia, Vancouver; Goethe University, Frankfurt, and Medizische Hochschule, Hannover, Germany; St. Lazlo Hospital, Gyali, Hungary; the University of Milan, Italy; the Netherlands AIDS Treatment and Education Center, Amsterdam; and the Warsaw AIDS Center, Poland. The study is a randomized, placebo-controlled, open-label trial comparing the effectiveness of two protease inhibitors with that of standard highly active antiretroviral therapy (HAART) regimens containing a single protease inhibitor.

The Esprit Project is a multinational study funded by NIAID's Laboratory of Immunoregulation and coordinated by the University of Minnesota, Minneapolis. In this 16-country study, which has 18 sites, investigators are evaluating the clinical response of HIV-positive patients treated either with interleukin 2 (IL-2), a cytokine immunostimulator, in addition to a standard HAART regimen, or with a conventional HAART regimen alone. The following countries are collaborating in this research: Australia, Belgium, Canada, England, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Poland, Portugal, Spain, Sweden, and Thailand.

The Laboratory of Immunoregulation (NIAID), the University of Washington, Seattle, the University of Alabama, Birmingham, the Institute of Clinical Research, Montreal, Quebec, San Raffaele Scientific Institute, Milan, Italy, and the University of Geneva,

TABLE I-3.

NIH International Research and Research Training Awards by Country/Area and Mechanism, Fiscal Year 1999 (in thousands of dollars)

	Research Grants		Research Contracts		Foreign Components of Domestic Awards		Visiting Program		Special Volunteers and Guest Researchers[b]	International Research Fellows	
Country/Area	**No.**	**Amount**	**No.**	**Amount**	**No.**	**Amount**	**No.**	**Amount**	**No.**	**No.**	**Amount**
Mauritius	—	—	—	—	1	79	—	—	—	—	—
Mexico	2	172	—	—	31	2,740	18	362	2	1	27
Mongolia	—	—	—	—	1	34	2	43	—	—	—
Morocco	—	—	—	—	—	—	3	98	—	—	—
Nepal	—	—	—	—	3	52	—	—	—	—	—
Netherlands	3	253	1	61	19	1,178	29	871	23	—	—
New Zealand	3	324	—	—	13	466	6	175	1	—	—
Niger	—	—	—	—	—	—	—	—	1	—	—
Nigeria	—	—	—	—	6	694	3	63	1	—	—
Norway	—	—	3	357	7	571	1	1	3	—	—
Pakistan	—	—	—	—	2	190	7	218	3	—	—
Panama	—	—	—	—	4	435	—	—	—	—	—
Papua New Guinea	—	—	—	—	2	93	—	—	—	—	—
Paraguay	—	—	—	—	—	—	1	11	—	—	—
Peru	—	—	—	—	9	1,089	4	96	—	—	—
Philippines	—	—	—	—	2	172	9	211	2	—	—
Poland	—	—	1	411	9	319	29	787	2	5	168
Portugal	—	—	—	—	5	834	3	72	4	—	—
Romania	—	—	—	—	2	80	3	105	3	2	90
Russia	—	—	1	100	36	1,254	103	3,307	14	—	—
Saint Kitts & Nevis	—	—	—	—	4	698	—	—	—	—	—
Saudi Arabia	—	—	—	—	—	—	—	—	2	—	—
Senegal	—	—	—	—	8	489	1	33	—	—	—
Serbia	—	—	—	—	—	—	4	95	1	—	—
Seychelles	—	—	—	—	1	25	—	—	—	—	—
Sierra Leone	—	—	—	—	—	—	—	—	1	—	—
Singapore	—	—	—	—	3	484	6	118	—	—	—
Slovakia	—	—	—	—	4	95	18	567	2	—	—
Slovenia	—	—	—	—	7	213	1	64	—	—	—
South Africa	1	181	—	—	15	2,098	4	114	1	3	123
Spain	2	122	—	—	12	1,777	53	1,527	14	1	32
Sri Lanka	—	—	—	—	—	—	2	72	—	—	—
Sudan	—	—	—	—	1	15	—	—	—	—	—
Suriname	—	—	—	—	1	127	—	—	—	—	—
Sweden	8	1,629	2	377	33	2,751	8	188	8	—	—
Switzerland	—	—	—	—	18	1,302	9	309	4	—	—
Syria	—	—	—	—	—	—	1	10	—	—	—
Taiwan	—	—	—	—	6	707	29	756	4	—	—
Tanzania	—	—	—	—	2	338	—	—	—	—	—
Thailand	—	—	1	55	12	2,480	6	192	3	—	—
Trinidad	—	—	—	—	3	282	1	40	1	—	—
Turkey	—	—	—	—	3	121	15	490	8	1	37
Uganda	—	—	—	—	9	3,926	—	—	1	—	—
Ukraine	—	—	—	—	1	23	8	205	2	1	54
United Kingdom	21	4,077	3	315	94	6,729	90	2,710	18	—	—
United States	—	—	—	—	—	—	162	6,969	2	—	—
Uruguay	—	—	—	—	2	33	—	—	—	—	—
Uzbekistan	—	—	—	—	—	—	1	46	—	—	—
Venezuela	—	—	—	—	5	826	3	41	—	—	—
Vietnam	—	—	1	41	2	177	2	53	—	—	—
Yugoslavia	—	—	—	—	1	51	1	35	1	—	—
Zambia	—	—	—	—	6	1,483	—	—	—	—	—
Zimbabwe	—	—	—	—	8	3,025	1	32	—	—	—
Subtotal	207	37,857	50	10,539	1,056	92,753	2,424	70,377	530	25	911
International Organizations											
EORTC	1	402	—	—	—	—	—	—	—	—	—
IARC	1	576	—	—	—	—	—	—	—	—	—
PAHO	—	—	1	426	—	—	—	—	—	—	—
UICC	—	—	1	75	—	—	—	—	—	—	—
WHO	1	1,693	3	472	—	—	—	—	—	—	—
HFSP	—	—	—	—	—	2,500	—	—	—	—	—
Subtotal	3	2,671	5	973	—	2,500	—	—	—	—	—
TOTAL	210	40,528	55	11,512	1,056	95,253	2,424	70,377	530	25	911

[a] Does not include Scholars-In-Residence Awards ($0.1 million), Int'l Training & Research Grants ($23.0 million), Minority Research Training Program ($4.7 million), part of FIC's Biodiversity Program ($0.9 million), Career Development Awards ($.3 million), Other ($.4 million), Bilateral Exchanges/Conferences ($8.0 million), and ICD Progran Support/Travel ($15.1 million). Most of the funds for these programs are expended in the United States.

Senior International Fellows		National Research Service Award		
No.	Amount	No.	Amount	Totals
—	—	—	—	79
—	—	—	—	3,301
—	—	—	—	77
—	—	—	—	98
—	—	—	—	52
—	—	—	—	2,363
2	53	—	—	1,018
—	—	—	—	0
—	—	—	—	757
—	—	—	—	929
—	—	—	—	408
—	—	—	—	435
—	—	—	—	93
—	—	—	—	11
—	—	—	—	1,185
—	—	—	—	383
—	—	—	—	1,685
—	—	—	—	906
—	—	—	—	275
—	—	—	—	4,661
—	—	—	—	698
—	—	—	—	0
—	—	—	—	522
—	—	—	—	95
—	—	—	—	25
—	—	—	—	0
—	—	—	—	602
—	—	—	—	662
—	—	—	—	277
—	—	—	—	2,516
—	—	—	—	3,458
—	—	—	—	72
—	—	—	—	15
—	—	—	—	127
—	—	—	4	4,949
2	62	—	—	1,673
—	—	—	—	10
—	—	—	—	1,463
—	—	—	—	338
—	—	—	—	2,727
—	—	—	—	322
1	49	—	—	697
—	—	—	—	3,926
—	—	—	—	282
4	108	6	190	14,129
—	—	—	—	6,969
—	—	—	—	33
—	—	—	—	46
—	—	—	—	867
—	—	—	—	271
—	—	—	—	86
—	—	—	—	1,483
—	—	—	—	3,057
17	553	22	731	213,721
—	—	—	—	402
—	—	—	—	576
—	—	—	—	426
—	—	—	—	75
—	—	—	—	2,165
—	—	—	—	2,500
—	—	—	—	6,144
17	553	22	731	219,865

[b] *Do not receive NIH funding.*

Switzerland, reported that the qualitative nature of the primary immune response to HIV infection is a prognostic indicator of disease progression, independent of the initial level of plasma viremia.

Bacterial Diseases

NIAID funds the International *Klebsiella* Study Group, which is evaluating the in vitro susceptibility of *Klebsiella pneumoniae* and the clinical outcome of bacteremia due to *K. pneumoniae* that produces extended-spectrum β-lactamase, in different geographic and institutional settings. The study group consists of 11 hospitals in seven countries: Argentina, Australia, Belgium, Canada, South Africa, Turkey, and the United States.

The University of California, San Francisco, is working with the University of Alexandria, Egypt, in a clinical trial in the Gambia and Tanzania comparing mass treatment of communities where trachoma is endemic with a single oral dose of azithromycin versus the recommended WHO 2-week administration of topical tetracycline, with a 22-month follow-up. This clinical trial will be the basis for other research studies on the epidemiology of trachoma in the communities, the molecular epidemiology of *Chlamydia trachomatis,* and measurement of tears in the eyes before and after treatment, to determine the response to antibody.

Immunology

The International Collaboration in Infectious Disease Research (ICIDR) Program at the University of Maryland, Baltimore, hosted a study of immunogenicity to an outer-membrane protein of group B meningococcus used in vaccines developed by the Finlay Institute, Havana, from bacteria from patients in Cuba and Norway. The study subjects were Chilean infants, children, and adults at risk from a heterologous epidemic strain.

The University of Virginia, Charlottesville, Federal University of São Paulo, Brazil, the University of Manchester, England, and the National University of Singapore are engaged in a multicenter study of the biological activity of recombinant group 5 mite allergens.

Parasitic Diseases

The Tropical Medicine Research Center (TMRC) at the Research Institute of Tropical Medicine/Manila (Philippines), together with Case Western Reserve University, Cleveland, Ohio, Brown University, Providence, Rhode Island, Nanjing Medical University and Sichuan Institute of Parasitic Diseases, China, Kenya Medical Research Institute, Nairobi, and WHO, Geneva, Switzerland, participated in a double-blind, placebo-controlled study of concurrent administration of albendazole and praziquantel in African and Asian rural school children infected with *Schistosoma mansoni, Schistosoma haematobium,* or *Schistosoma japonicum* and other intestinal helminths. The study concluded that the two drugs could be administered concurrently by teachers. The regimen had no effect on trichuriasis and ascariasis rebounded to pretreatment levels in 6 months, but reductions in schistosomiasis and hookworm infection were sustained. A significant reduction in anemia and increase in hemoglobin were observed in children receiving praziquantel. The study provides the basis for safe and cost-effective deworming campaigns for school children in rural Africa and Asia with mixed helminth infections and should result in a significant increase in hemoglobin levels in this population.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Researchers at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), working with researchers at nine institutions, have discovered gene mutations that define a new group of inflammatory diseases. The collaborating institutions are The New Children's Hospital, Westmead, New South Wales, Australia; Women's and Children's Hospital, North Adelaide, South Australia; St. Bartholomew's and the Royal London Hospital, Whitechapel, London, and the University of Nottingham, England; Helsinki University Central Hospital, Finland; National University of Ireland, Cork; Harvard Medical School, Boston, Massachusetts; the University of Texas, Houston; and the University of Vermont College of Medicine, Burlington. This discovery marks the first time that mutant tumor necrosis factor (TNF) receptor has been tied to an inherited disease.

The NIAMS researchers and their colleagues discovered genetic mutations on chromosome 12 that underlie a newly rec-

TABLE I-4.

NIH International Research and Research Training Awards, Fiscal Years 1950–1999 (in thousands of dollars)

		Research Grants		Research Contracts		Foreign Components of Domestic Awards		Special Foreign Currency Program (Public Law 480)		Training Grants	
Fiscal Year	Total	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
1950	391	20	219	—	—	—	—	—	—	—	—
1951	412	28	210	—	—	—	—	—	—	—	—
1952	495	22	257	—	—	—	—	—	—	—	—
1953	495	24	245	—	—	—	—	—	—	—	—
1954	497	15	145	—	—	—	—	—	—	—	—
1955	470	14	111	—	—	—	—	—	—	—	—
1956	683	18	190	—	—	—	—	—	—	—	—
1957	1,808	61	824	—	—	—	—	—	—	1	13
1958	2,777	92	1,307	—	—	—	—	—	—	1	17
1959	5,425	170	2,997	—	—	—	—	—	—	2	30
1960	8,492	307	5,249	3	90	—	—	—	—	3	39
1961	12,692	563	8,999	2	118	—	—	—	—	7	251
1962	22,770	811	13,410	8	181	5	2,093	20	2,765	13	380
1963	24,067	981	14,956	5	182	7	2,093	16	1,517	16	536
1964	25,590	932	13,759	13	429	6	2,484	19	3,328	17	544
1965	23,514	801	11,467	22	867	6	2,491	25	3,026	22	615
1966	21,653	718	10,010	29	901	5	2,423	22	2,182	18	559
1967	20,068	624	8,509	27	1,037	5	2,360	27	3,559	15	506
1968	20,525	480	6,424	35	1,325	5	2,360	42	5,459	16	449
1969	19,985	325	4,481	32	1,369	5	2,294	44	7,312	11	187
1970	15,627	170	2,968	34	1,805	4	2,070	39	4,503	4	6
1971	21,844	120	2,489	41	2,319	5	2,285	79	10,149	—	—
1972	19,762	113	2,449	65	5,337	4	2,399	24	2,894	—	—
1973	19,874	116	2,905	86	6,508	4	2,244	21	2,706	—	—
1974	23,020	119	3,360	105	8,381	4	2,360	13	1,544	—	—
1975	31,867	130	3,917	120	13,790	4	2,411	24	3,257	—	—
1976	34,457	138	5,128	134	12,525	4	2,400	18	2,934	—	—
1977	40,719	149	6,532	135	15,173	4	2,400	25	4,484	—	—
1978	42,829	162	7,502	139	15,107	4	2,117	16	4,199	—	—
1979	47,333	191	10,042	117	14,759	13	4,699	9	1,298	—	—
1980	45,179	206	11,139	93	12,932	10	2,756	9	612	—	—
1981	46,622	237	13,223	61	9,672	10	2,585	20	911	—	—
1982	45,598	212	13,336	53	10,608	8	2,384	19	1,424	—	—
1983	46,023	214	14,079	37	6,597	9	2,741	14	945	—	—
1984	60,227	191	15,708	43	11,094	9	2,870	39	6,128	—	—
1985	59,047	220	15,466	55	8,767	10	2,998	47	4,560	—	—
1986	58,385	219	16,723	63	9,276	9	2,933	29	998	—	—
1987	71,193	242	22,150	55	11,658	9	3,019	63	1,848	—	—
1988	78,028	256	26,405	52	13,338	9	2,336	59	622	12	3,912
1989	90,710	259	27,627	50	14,733	142	9,723	21	2,329	14	4,322
1990	95,819	220	26,828	57	11,337	188	13,015	24	1,290	14	4,733
1991	116,954	213	27,406	48	16,623	252	15,423	21	1,332	14	5,142
1992	142,792	210	29,270	51	24,028	337	21,306	19	2,718	14	5,178
1993	154,938	240	35,928	43	16,715	450	23,504	22	1,493	17	5,114
1994	166,169	231	33,254	59	17,647	481	27,430	25	1,493	41	13,505
1995	171,389	202	31,043	60	15,063	527	34,061	29	1,534	62	17,602
1996	178,658	184	32,818	65	14,285	572	41,284	20	978	67	19,085
1997	186,200	168	33,885	49	11,258	894	54,183	21	1,511	82	17,818
1998	199,555	183	33,308	38	9,968	869	65,425	20	1,278	89	20,838
1999	247,603	210	40,528	55	11,512	1,056	95,253	0	0	95	27,639

[a]*Table I-4 includes only those categories in Table I-2 that constitute research and research training awards.*

ognized group of inherited inflammatory disorders, including familial Hibernian fever. The disorders, collectively known as TNF receptor–associated periodic syndrome (TRAPS), are characterized by long, dramatic episodes of high fever, severe pain in the abdomen, chest, or joints; skin rash; and inflammation in or around the eyes. Some patients also develop amyloidosis, a potentially fatal disease in which a blood protein is deposited in vital organs.

The mutations, reported in *Cell* (April 2, 1999), involved a cell-surface receptor for the inflammatory protein TNF. Patients from seven families with TRAPS symptoms exhibited the mutations. Normally, the TNF receptor plays a role in the body's defenses against infectious and foreign agents. The

Visiting Program		Special Volunteers and Guest Researchers[b]	International Research Fellows		Scholars-in-Residence		Senior International Fellows		National Research Service Awards	
No.	Amount	No.	No.	Amount	No.	Amount	No.	Amount	No.	Amount
1	—	—	36	135	—	—	—	—	11	37
5	29	—	37	127	—	—	—	—	13	47
7	42	—	36	119	—	—	—	—	20	78
6	42	—	13	41	—	—	—	—	36	168
17	115	—	2	1	—	—	—	—	54	236
26	165	—	—	—	—	—	—	—	48	194
42	270	—	—	—	—	—	—	—	56	224
76	518	—	—	—	—	—	—	—	86	453
110	785	—	16	102	—	—	—	—	99	566
128	1,097	—	67	467	—	—	—	—	128	834
138	1,035	—	68	501	—	—	—	—	230	1,577
149	869	—	—	—	—	—	—	—	251	1,780
190	1,052	—	90	681	—	—	—	—	279	2,207
200	1,203	—	172	1,199	—	—	—	—	310	2,381
179	1,434	—	183	1,199	—	—	—	—	296	2,413
156	1,172	—	166	1,199	—	—	—	—	342	2,678
139	1,194	—	166	1,197	—	—	—	—	397	3,188
129	1,157	87	176	1,200	—	—	—	—	211	1,740
149	1,405	95	151	1,379	—	—	—	—	188	1,724
138	1,299	93	168	1,409	5	130	—	—	222	1,504
178	1,628	53	137	1,027	5	119	—	—	185	1,101
188	2,070	100	130	1,077	6	141	—	—	167	1,314
259	3,108	118	163	1,588	8	182	—	—	214	1,806
290	3,763	134	110	777	12	228	—	—	143	742
351	4,506	145	127	1,489	13	219	—	—	129	1,162
494	5,946	157	107	1,370	8	163	—	—	115	1,014
676	7,948	180	137	1,605	8	150	42	717	75	1,050
740	8,404	159	126	1,636	16	362	50	906	59	823
804	9,469	205	128	2,094	12	253	64	1,203	75	1,065
830	11,159	229	134	2,413	11	272	75	1,680	72	1,009
909	12,445	266	132	2,263	20	715	52	1,227	54	1,090
976	14,568	355	136	3,450	18	456	32	673	58	1,084
979	15,722	381	153	3,061	20	485	29	593	59	985
1,128	16,953	390	101	2,689	8	357	41	926	43	756
1,176	19,654	396	87	2,357	12	565	53	1,240	34	611
1,288	21,882	479	104	2,794	10	402	45	1,165	48	1,013
1,391	23,659	551	101	2,727	14	446	40	868	34	755
1,465	27,796	538	103	2,767	6	279	47	921	36	755
1,507	31,539	410	97	2,664	11	329	44	998	39	797
1,470	32,106	623	91	2,472	12	381	38	926	34	794
1,555	37,650	666	146	3,963	8	188	41	833	36	903
1,680	44,525	684	157	4,136	7	478	39	1,077	33	812
1,866	53,257	635	146	4,518	7	680	49	1,235	26	602
2,171	66,105	669	124	3,835	5	618	53	1,179	19	447
2,199	68,518	627	74	2,289	6	650	42	861	23	522
2,152	67,960	630	55	1,759	13	665	44	1,124	23	578
2,174	67,059	660	39	1,306	7	536	24	777	21	520
2,210	64,192	622	39	1,316	2	563	26	904	22	570
2,232	66,290	621	32	1,104	1	249	21	611	21	484
2,424	70,377	530	25	911	1	99	17	553	22	731

[b]*Do not receive NIH funding.*

mutant receptors are thought to predispose individuals to severe inflammation, which can be triggered by emotional stress or minor trauma or which can occur for no apparent reason.

These results are a very important contribution to better understanding of the role of the TNF pathway in disease. The findings may lead to additional therapies, targeted at the cellular level, for many immunologic and inflammatory disorders.

National Cancer Institute

International Consortia

In 1996, the Ministers of Health of Cyprus, Egypt, Israel, Jordan, and the Palestinian Authority formed a historic partnership, with the official signing of the Middle East Can-

cer Consortium (MECC) agreement. The National Cancer Institute (NCI) played a major role in orchestrating the agreement. The aims of MECC are to increase knowledge about cancer and to decrease its burdens for the people of the Middle East. In a region where few countries maintain cancer registries, especially population-based registries, and where cancer statistics are scarce, MECC's main areas of focus include cancer surveillance, information, and education. The consortium also concentrates on training, basic research, enhancement of public health and patient care, quality control, and international communications.

In Belfast, Northern Ireland, a Memorandum of Understanding has been signed by representatives of Northern Ireland, the Republic of Ireland, and the United States—heralding cooperation to enhance cancer research and treatment in Ireland. In Ireland, the incidence and mortality rates for cancer are among the highest in the Western world, and trinational collaboration is intended to address this problem. Initial projects will focus on the coordination of tumor registries, the development of informatics to support coordinated clinical trials, and training and scholarship programs for scientists in the cancer research programs of partner institutions. The Directors of the NIH and NCI, as well as leading NCI scientists in the fields of cancer surveillance and cancer treatment, participated in the All-Ireland Conference, in Belfast, in October 1999, in an exchange of information among scientists of the three countries.

Cervical Cancer

Worldwide, cervical cancer is the second or third most common cancer among women, after breast cancer. In some developing countries, cervical cancer is the most common cancer. About 400,000 new cases are diagnosed each year, predominantly among the economically disadvantaged, in both developing and industrial nations. Cervical cancer is very treatable, but only if diagnosed in its early stages. Thus, determination of risk factors and development of new detection methods are important. The primary risk factor for cervical cancer is infection with certain types of the human papillomavirus (HPV). Large studies have found HPV in more than 93% of cases of cervical cancer. Because most women infected with HPV do not develop cancer, however, researchers are looking at cofactors that may work with HPV to promote carcinogenesis.

Immunologic and other cofactors are the focus of a large NCI study in Guanacaste Province, Costa Rica, a region with high incidence of cervical cancer. Investigators have screened about 10,000 women to obtain data on the incidence and prevalence of HPV infection and on cofactors that increase the risk of cervical cancer. The follow-up study is now in its 7th year. This project is also evaluating some new technologies for highly sensitive detection of HPV infection as a means of early diagnosis of cervical cancer. In related research, scientists in the NCI Division of Basic Sciences have initiated the development of vaccines directed against infection with HPV. Results from these studies and early-phase clinical trials have led to the decision to go forward with a clinical trial in a large study population in Costa Rica.

Renal Carcinoma

Until recently, relatively little attention was paid to the genetics and histology of renal carcinomas. Improved understanding of the genetic basis of human renal carcinoma has come from studies of families with an inherited predisposition to develop this disease. Researchers in NCI's Laboratory of Immunobiology, Division of Basic Sciences, are studying the genetic basis of three of its inherited forms: von Hippel-Lindau disease, hereditary papillary renal carcinoma, and renal carcinoma associated with the chromosome 3;8 translocation. They have identified families in which multiple members have renal oncocytoma. These families have provided a foundation for studies aimed at defining genes involved in the pathogenesis of renal oncocytoma. There has been international collaboration to include clinical populations from Canada, Hungary, and Italy.

National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) participated in the HIVNET 012 Prevention Trials of nevirapine, which demonstrated in clinical trials that a two-dose, oral regimen of the agent, given once to HIV-infected pregnant women at the onset of labor and once to the infants at 48 hours of life, resulted in a remarkable 50% reduction in the risk of perinatal HIV transmission. The interpretation and application of these study results may produce a safe, cost-effective, feasible regimen for reduction of vertical transmission of HIV in some developing countries.

NICHD has supported a study of mother-to-child transmission of HIV in Kenya for more than one decade. Investigators recently reported data from their Nairobi-based study of breast-feeding in HIV-infected women. This randomized clinical trial examined the impact of formula feeding compared with exclusive breast-feeding on the transmission of HIV from infected mothers to their offspring. The investigators found that 37% of breast-fed infants were infected with HIV, compared with only 21% of formula-fed infants. The study report emphasized the prominent role of breast-feeding in vertical HIV transmission. Investigators from this team also have demonstrated a relationship between the presence of genital human immunodeficiency virus type 1 (HIV-1) DNA and vertical transmission. This association is independent of plasma levels of viral HIV-1 RNA. With continuing NICHD support, this group of investigators will determine the effect of cytotoxic T lymphocytes in breast milk on transmission of HIV-1 from infected mothers to their breast-fed infants in Nairobi. NICHD's uninterrupted, long-term support of this international team has resulted in substantial contributions to the understanding of HIV transmission, the training of Kenyan scientists, and the strengthening of in-country research capacity.

In an international study that brought together researchers from Canada, Europe, and the United States, there was a significant reduction in the rate of HIV transmission from mother to infant for women who delivered via cesarean section before the onset of labor and rupture of membranes. These findings have formed the basis of recommendations by the American College of Obstetricians and Gynecologists on the utility of elective cesarean section in the reduction of vertical HIV transmission.

Using knowledge of how insulin works at the cellular level, an NICHD-supported team of investigators developed an experimental treatment for polycystic ovary syndrome (PCOS) that is based on a naturally occurring

component of the cells' signaling system. With funding from a Small Business Innovation Research grant, the team studied 44 women in Venezuela with PCOS. The research team tested the hypothesis that, because the insulin resistance in PCOS seems to be due to a deficiency of inositol, the syndrome could be overcome by administering inositol as a drug. The researchers found that D-*chiro*-inositol lowered plasma levels of insulin and testosterone. Significantly, 86% of treated women ovulated, compared with 27% of those who received placebo. It is exciting that the idea for this treatment came from understanding the cell biology of insulin's action in promoting ovarian steroid production. This promising result from research by a small business is being expanded as a multicenter clinical trial.

National Institute on Deafness and Other Communication Disorders

The Division of Intramural Research of the National Institute on Deafness and Other Communication Disorders continues to support an international consortium with the purpose of expediting the discovery of genes responsible for hereditary hearing impairment. The consortium encompasses research on nonsyndromic and syndromic forms of hereditary hearing loss, such as Waardenburg syndrome and Usher syndrome. Scientists from countries including Belgium, Colombia, Finland, France, Germany, Israel, Japan, Norway, South Africa, and the United Kingdom, as well as scientists throughout the United States, continue their efforts to map the genes responsible for syndromic and nonsyndromic hereditary hearing impairment. Almost 60 genes have been identified for recessive and dominant nonsyndromic hereditary hearing impairment in families from Colombia, India, Indonesia, Israel, Lebanon, Newfoundland, Pakistan, Tunisia, and the United States, including Puerto Rico. The collaborative efforts fostered by the consortium have been instrumental in identifying a large number of the genes responsible for hereditary hearing impairment and in advancing the understanding of these disorders.

National Institute of Dental and Craniofacial Research

Intramural Research

Animal Model for Bone Studies

In FY 99, a team of investigators in Canada, Denmark, and Italy and researchers in the Matrix Metalloproteinase Unit and the Craniofacial and Skeletal Diseases Branch of the National Institute of Dental and Craniofacial Research (NIDCR) collaborated to generate a knockout mouse deficient in membrane type1 matrix metalloproteinase (MT1-MMP). This family of enzymes is believed to play a major role in cellular development and remodeling processes. The essential nature of the gene became manifest when the scientists characterized the phenotype of the MT1-MMP–deficient mouse. The animal exhibited dwarfism, osteopenia, arthritis, and connective tissue disease resulting from reduced turnover of collagen. This animal model will be used to determine whether the membrane-associated matrix metalloproteinase (MMP) produces these effects independently or exerts effects on other MMPs. The scientists reported this significant finding in *Cell,* in October 1999.

Genes for Taste Receptors

Also during FY 99, two investigators from the United Kingdom, working in NIDCR's Oral Infection and Immunity Branch, discovered and sequenced the first genes for taste receptors. These receptor proteins (TR1 and TR2) are responsible for recognition of sweet and bitter substances. The transmembrane proteins, which signal via a G protein pathway, share only 40% homology, a finding that highlights the selectivity of each receptor. TR1 is associated with fungiform papillae, which are scattered, knob-like projections on the tongue, whereas TR2 is associated with circumvallate papillae, which are the largest projections, arranged in a "V" pattern at the front of the tongue. The investigators have provided a vital tool for tracing the development and migration of taste receptors and an approach to discovering related genes. This important discovery was published in *Cell,* in February 1999; the report was selected as the lead article, and a figure from the article was displayed on the cover.

Office of International Health

Three themes for NIDCR's international activities during FY 99 were globalization, research networks, and funding partnerships. To globally link scientists from industrial and developing countries in collaborative research teams, NIDCR's Office of International Health (OIH) and Division of Extramural Research issued, in March 1999, a Request for Applications for 2-year International Collaborative Oral Health Research (ICR) planning grants. These grants, which are a significant innovation at NIDCR and the NIH, will support the planning of scientifically meritorious biomedical, epidemiologic, and behavioral research that requires international attention. To foster research networks, NIDCR promoted collaborative research in priority areas of the ICR agenda. One of these areas is craniofacial anomalies. During FY 99, NIDCR hosted two major, successful international meetings, to probe the molecular basis of these disorders and to develop strategies for preventing cleft lip and palate. In addition, OIH staff emphasized the need for research networks at other international meetings, and the Director, NIDCR, addressed research needs in a keynote lecture presented at the 6th European Craniofacial Congress, in Manchester, England. Partnerships in funding are essential for supporting broad-scale international research. During FY 99, OIH prepared a strategic implementation plan for network development and initiated preliminary and exploratory discussions with public, private, and nonprofit organizations in the United States and worldwide. Partnerships in funding will enable NIDCR to leverage its own research dollars to accomplish research goals for the benefit of all.

National Institute of Diabetes and Digestive and Kidney Diseases

The Laboratory of Bioorganic Chemistry of the National Institute of Diabetes and Digestive and Kidney Diseases is responsible for numerous scientific advances stemming from its international activities. These advances include the following:

- elucidation of the structure of biologically active alkaloids from amphibians, birds, and insects (specimens supplied by scientists in Argentina, Brazil, Chile, Costa Rica, Madagascar, Mexico, New Guinea, Panama, and Venezuela);

■ illumination of routes and mechanisms of metabolism that lead to carcinogenic activity, as shown in studies of polycyclic aromatic hydrocarbons and their aza analogues (collaboration with researchers in Australia, Germany, and Northern Ireland);

■ insights into structural modifications affecting activity at receptors for peptide, histamine, and adenosine triphosphate, as well as adenosine muscarinic and adrenergic receptors (cooperation with investigators in countries including Germany, Israel, Sweden, and the United Kingdom); and

■ synthesis of a series of perfluoroalkylpyrimidines to be used as affinity labels for viral enzymes and for pyrimidine reductase (joint research with scientists in Japan).

National Eye Institute

Chile, China, and Nepal

Using a common protocol and examination methods, the National Eye Institute (NEI) has been working with three institutions in conducting a population-based survey of childhood refractive error and vision impairment. Surveys were carried out in La Florida (a suburb of Santiago), Chile, in collaboration with Pontifica Universidad Catolica de Chile; in Shunyi County (outside Beijing), China, in collaboration with the Peking Union Medical College Hospital; and in eastern Nepal, in collaboration with Foundation Eye Care Himalaya. Findings have demonstrated wide variations among these countries, in the prevalence of refractive error in school-age children. This work, which was funded in collaboration with WHO, will be reported as four articles in a single issue of a leading ophthalmology journal.

India

The NEI Director and Associate Director for Applications of Vision Research have continued to participate as consultants to the World Bank in developing and evaluating, with the government of India, the Indian National Blindness Control Project. They have provided technical and analytic assistance in two surveys of the prevalence of blindness and outcomes of cataract surgery. Collaborations are continuing with the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, and the Aravind Eye Hospital, Madurai, to analyze data and report findings of surveys.

The Director and Associate Director have continued to work during FY 99 with physician-scientists at the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, to develop and evaluate a questionnaire on vision function and quality of life that would be suitable for administration across subpopulations within India. The research follows a protocol that is used in the United States for development of NEI's Visual Functioning Questionnaire, including the use of patient focus groups to collect information on the variety and extent of day-to-day, vision-related problems faced by the visually impaired. Researchers at the London School of Hygiene and Tropical Medicine, England, who are studying quality of life are also participating in this endeavor in applied research.

Intramural scientists from the Laboratory of Mechanisms of Ocular Diseases have collaborated with colleagues at the Centre for Cellular and Molecular Biology, Hyderabad, to study aging-related modifications to lens crystallins. Cataract typically occurs at an earlier age and is more heavily pigmented in subjects in India than in those in the United States. To elucidate the molecular mechanisms underlying this difference in color, the scientists are comparing the fluorescence spectra for healthy, intact lenses from subjects in India over a wide range of ages with the spectra for eye-bank lenses from age-matched subjects in the United States. The lenses from Indian subjects contain substantially greater amounts of pigmented fluorescent compounds than those from U.S. subjects. These compounds, through their ability to function as photosensitizers, may contribute directly to cataractogenesis.

Another joint effort is the study of the proteins in cataract in Indians. In an attempt to elucidate processes that may contribute to the early onset and high incidence of cataract in India, researchers are comparing the crystallin properties of cataractous lenses from Indians with those of healthy or cataractous lenses from age-matched, eye-bank donors in the United States. The different forms of crystallins that have been identified are being further characterized to determine the mechanisms involved in the expression and formation of these proteins in cataract.

In addition, molecular geneticists at NEI have initiated gene-linkage studies with scientists at Osmania University and the L. V. Prasad Eye Institute, Hyderabad. Participants in these studies are members of selected families with hereditary cataracts. The prevalence of consanguineous marriages in this region of India greatly increases the likelihood of recessive cataract phenotypes. A geneticist from Osmania University, who was trained at NEI in relevant techniques, has returned to Hyderabad to establish a laboratory, so that gene-linkage analysis in individuals with suitable pedigrees can be performed in India. In one family, the cataract trait has been linked to a particular chromosome, and a potential candidate gene has been identified.

An NEI-supported, randomized clinical trial at the Aravind Eye Hospital, Madurai, has been completed. In this study, treatment using intracapsular cataract surgery plus eyeglasses for the resulting aphakia was compared with treatment using extracapsular cataract extraction plus implantation of an intraocular lens. The trial's primary purpose was to compare intraoperative complications, postoperative complications, and visual acuity outcomes by 1 year after the operation. A randomly selected subgroup of these patients was examined 4 years after surgery, to investigate the incidence of opacification of the posterior capsule. Findings have demonstrated a relatively low incidence among the study population.

United Kingdom

The United Kingdom Prospective Diabetes Study is a multicenter, randomized clinical trial to determine whether improved control of blood glucose levels or blood pressure in non–insulin- dependent diabetes mellitus (type 2 diabetes) reduces morbidity and mortality. Starting in 1977, 5,102 patients with newly diagnosed type 2 diabetes were treated with diet therapy for 3–4 months. Patients who remained asymptomatic but had high blood glucose levels were then randomly assigned to diet therapy or to treatment with sulfonylurea, insulin, or metformin. In a factorial design, a randomized trial of strict control of blood pressure was carried out in 1,148 patients with type 2 and hypertension. Patients were assigned to treatment of hypertension with angiotensin-converting enzyme inhibitors or β-blockers or to less tight control of hypertension. All patients' eyes are photographed every 3

years to assess development and progression of diabetic retinopathy. The median duration of follow-up is 12 years.

Scientists at the Laboratory of Molecular and Developmental Biology are working with investigators at Baylor College of Medicine, Houston, Texas, and the Imperial Cancer Research Fund, London, England. These scientists are targeting the expression of the FGF3/int2 gene to the lens. This work will allow researchers to characterize the fibroblast growth factor (FGF) receptors that FGF3 interacts with and the role of secreted FGFs in differentiation in the lens.

Researchers in the Laboratory of Sensorimotor Research, together with a former colleague who is now at the University of St. Andrews, Fife, Scotland, are studying the ability of human subjects to use cognitive information to modify an already programmed saccadic eye movement to a new visual location.

National Institute on Drug Abuse

Canada

Long-term Use of Methamphetamine

The National Institute on Drug Abuse (NIDA) is supporting an investigator at Clarke Institute of Psychiatry, Toronto, Ontario, in research to identify changes in the brain of long-term users of methamphetamine, as well as other drugs that might be responsible for the behavioral and possible neurotoxic consequences of long-term drug exposure. In preclinical studies, the principal investigator explored the mechanisms of methamphetamine neurotoxicity. He examined binge use of methamphetamine versus long-term, daily administration and found that bingeing was associated with a regionally specific reduction of glutathione, an antioxidant that protects neural cells from oxidative stress, which can lead to neurotoxicity. This finding suggests that medications designed to increase glutathione might protect against oxidative damage brought about by drugs of abuse.

In a clinical study in FY 99, the investigator measured the activity of choline acetyltransferase, a marker enzyme for cholinergic brain cells, in brains obtained at autopsy of long-term users of one or more of the drugs cocaine, methamphetamine, and heroin. His studies revealed that 2 of 12 methamphetamine users, who had the highest brain-blood drug levels at autopsy, had a severe depletion (up to 94%) of this enzyme in different brain regions (cerebral cortex, striatum, and thalamus). He reported that the neurochemical data suggest that damage to cholinergic brain neurons is not typical for long-term use of cocaine, methamphetamine, or heroin, but that exposure to very high doses of methamphetamine could damage this neuronal system and lead to impairments of cognitive function.

Prenatal Exposure to Cannabis and Tobacco

A study on Prenatal Cannabis and Cigarette Exposure—Outcomes in Adolescents and Young Adults, with Carleton University, Ottawa, Ontario, was in the 12th year of a 15-year project in FY 99. One of only two such cohort studies in the United States and Canada, this critical project examines health and development outcomes after prenatal exposure to marijuana. The children in this sample, with follow-up since birth, are now 16½–19½ years old. Consequently, this research affords immense opportunity to acquire previously unattainable information, including new knowledge on initiation and patterns of drug use for adolescents and young adults who were exposed to illicit drugs in utero.

Specific observations for children 9–12 years old include the finding that maternal use of marijuana during pregnancy is associated with markedly different child outcomes than is maternal use of tobacco during pregnancy. Childhood outcomes of prenatal exposure to marijuana appear to be consistent with findings in the literature on outcomes in adult, nonpregnant, long-term users of marijuana and on the neurophysiological effects of marijuana in animals. These effects in animals relate to the distribution of cannabinoids and cannabinoid receptors in the nervous system, which implicates the frontal region of the brain. Furthermore, together with observations made when the children were younger, results at 9–12 years of age suggest that prenatal marijuana exposure may influence specific aspects of executive function. Preliminary findings for children 13½–16 years old also indicate a clear association of prenatal marijuana with later executive function, rather than with more general measures of cognition such as IQ (intelligence quotient). In contrast, the effects of maternal cigarette use during pregnancy seem to relate to behaviors involving auditory processing and measures of general intelligence in children. The researchers are continuing to study these differential outcomes.

Croatia

A scientist from Ruder Boskovic Institute, Zagreb, was trained in opioid immunopharmacology with support from a NIDA INVEST (International Visiting Scientists and Technical Exchange) fellowship. The scientist reported that κ opioid receptors are expressed on mouse lymphocytes and on modified cell lines. The purpose of the investigation is to study the regulation of calcium by opioids to determine whether the κ opioid receptor on cells of thymoma cell lines downregulates calcium and desensitizes when the cells are cultured in the presence of a κ opioid agonist. She studied the effects of the synthetic κ opioid U50488 on calcium transport into these mouse thymoma cells, which selectively express the κ opioid class of receptors. Calcium transport into these cells was not affected by the κ opioid agonist U50488 alone or in the presence of the plant lectins, phytohemagglutinin and concanavalin A, which are used to stimulate red blood cells. These findings were published in the *International Journal of Immunopharmacology* in FY 99. The studies reported here are a part of the overall effort of this laboratory to clarify the role of opioids in immune function. This scientist will now be able to continue her research in Croatia with a better understanding of the function of opiates in disease processes such as AIDS.

National Institute of Environmental Health Sciences

Healthy Babies Delivered by Mothers With Malformations

Researchers at the National Institute of Environmental Health Sciences (NIEHS) have found that more than 96% of babies delivered by women with malformations are healthy, according to a recent study based on the Norwegian Medical Birth Registry. The Norwegian registry is a unique resource, linking medical and birth records through personal identifiers. Researchers from NIEHS and the registry collaborated in an analysis that showed that mothers with defects had

only a slightly higher chance than healthy women of having a baby with malformation. The risk in offspring was higher for the same defect carried by the mother but no higher for any other defects.

Biokinetics of Lead in Human Pregnancy

The Biokinetics of Lead in Human Pregnancy study recruits women of childbearing age who are recent immigrants to Australia from Central and Eastern Europe and whose isotopic signature of lead is different from that in Australians. The women are assigned to treatment or control groups, and then they contribute quarterly blood samples until conception. This study tests the hypothesis that administration of calcium supplements during pregnancy and lactation lessens the pregnancy-related mobilization of lead from skeletal stores. It is the first study of this type to test theoretical treatments for lead poisoning in utero.

Women must be recent immigrants from specific European regions with populations known to have ratios of lead isotopes sufficiently different from those in Australians for detection of changes during pregnancy and lactation. The different isotope ratios distinguish between environmental lead and "old" lead in bone stores. After conception, in addition to the calcium supplementation, the study involves monthly blood and urine samples, environmental samples from the home, and diet studies; for 6 months after delivery, the study requires samples of breast milk, blood, and urine. To date, there are seven women in the study, and three women have become pregnant and are due to give birth in April 2000. The study enrollment goal is 15 women who become pregnant.

This investigation was approved by all the local Australian Institutional Review Boards, and those institutions were granted Single Project Assurances from the Office for Protection From Research Risks, NIH, in August 1999, before enrollment of any study subjects. Concurrent with award of these grants, the Project Office made a field site visit to discuss and clarify issues of recruitment, informed consent, records management, and fieldwork protocols.

National Institute of General Medical Sciences

First Structural Determination of a Yeast Mannosidase

A study supported by the National Institute of General Medical Sciences at McGill University, Montreal, is focusing on understanding the structure and function of two enzyme families—the class I α 1-2 mannosidases and α 1,2-mannosyltransferases. Assembly of *N*-linked glycoproteins, the most abundant class of cellular glycoproteins, requires the cotranslational transfer of oligosaccharide chains, synthesized on dolicholphosphate carrier molecules, to appropriate Asn-X-Ser/Thr sites of growing polypeptide chains in the lumen of the endoplasmic reticulum and Golgi apparatus of cells. Subsequently, these glycoproteins are processed in the Golgi apparatus. The extent of this processing is determined by the *N*-glycan α mannosidase family of enzymes. Appropriate oligosaccharide processing appears to be necessary for proper protein folding, as well as protein stability, biological activity, and cell-to-cell interactions, including bacterial, viral, and parasitic infection; cellular adhesion; and metastasis. The essential class I mannosidase enzymes are highly conserved from yeast to man, which makes them potential therapeutic targets for antimetastatic and antiviral agents. Similarly, the mannosyltransferase enzymes are found in yeast, where they are essential for cell wall biosynthesis and thus are targets for antifungal agents. Structures for these enzymes are therefore key to development of effective therapeutic agents. The researcher previously provided the first report of the crystallization of a glycosidase of *N*-glycan biosynthesis, and she has now solved the structure of this yeast mannosidase. This researcher presented her findings for yeast α 1-2 mannosidase at the meeting of the American Crystallographic Association, in Buffalo, New York, on May 22–27, 1999.

Crystallographic Studies of Ribosomal Particles

A scientist at the Weizmann Institute, Rehovot, Israel, has made important progress in elucidating, by x-ray crystallography, the structure of the small ribosomal subunit at the highest resolution yet achieved, 4.5 Å. This structure has revealed a number of key ribosomal features, including the site where protein biosynthesis is initiated, as well as clear views of the RNA molecules that are required for this fundamental cellular process. The scientist was able to obtain snapshots of protein biosynthesis in the "activated state" by triggering protein biosynthesis and by then flash freezing the crystals to –185°C. The high degree of resolution was achieved by preparing heavy atom derivatives of the ribosome subunit. The resultant image was constructed from twice the diffraction data collected elsewhere on this structure. The scientist's findings are the result of almost 20 years of pioneering research on the structure of the ribosome.

DNA–Protein Complex of *Bacillus subtilis* Bacteriophage

An investigator at Universidad Autonoma, Madrid, Spain, is studying the mechanism of protein-primed DNA replication in the bacteriophage phi29 of *Bacillus subtilis*. The long-term objective of this research is to find specific ways to interfere with the initiation of viral DNA replication. Disease-producing viruses such as adenovirus and hepatitis B virus replicate by using similar protein-priming mechanisms.

National Heart, Lung, and Blood Institute

Three highlights of international activities of the National Heart, Lung, and Blood Institute (NHLBI) in FY 99 reflect the increasing globalization of international activities: (1) development of the Pan American Hypertension Initiative (PAHI), (2) the Global Initiative for Asthma (GINA), and (3) initiation of discussions of a Middle East Hypertension Initiative (MEHI).

Pan American Hypertension Initiative

Hypertension is the most prevalent cardiovascular disease in the Americas, affecting approximately one in four adults (about 140 million people). In the Americas, as in most nations, hypertension control rates are very poor. Throughout most of the world, fewer than one-fourth of hypertensive patients are adequately controlled. As a result, many people suffer from heart attacks and strokes and die prematurely. To address this challenge in the Americas, PAHO and NHLBI have jointly proposed PAHI. The purpose of PAHI is to advance knowledge and to facilitate action toward the prevention and con-

trol of high blood pressure in the Americas.

PAHI was issued as a call to action at the conclusion of the conference on Global Shifts in Disease Burden: the Cardiovascular Disease Pandemic. This conference, held in May 1998 at PAHO Headquarters in Washington, D.C., was cosponsored by PAHO, WHO, NHLBI, and FIC. In follow-up of the conference, NHLBI hosted a planning meeting on Translating Science Into Action, at the NIH, in Bethesda, Maryland, in March 1999. The participants included representatives from Argentina, Barbados, Brazil, Canada, Chile, Cuba, Mexico, the United States, and Uruguay, and international and regional scientific organizations. The goals of this meeting were to set priorities for actions to reduce the burden of hypertension in the Americas and to identify areas of mutual interest and cooperation among institutions and organizations represented at the meeting.

The planning meeting culminated in the development of a joint PAHI statement that outlines proposed activities for the future. To date, six international organizations |have endorsed this statement, in addition to PAHO, NHLBI, and delegates to the March 1999 meeting. The international organizations include the World Hypertension League, the Inter-American Society of Hypertension, the Pan American Network of CARMEN Programs (Comprehensive Intervention Programs to Reduce Risk Factors for Non-Communicable Diseases), the Inter-American Society of Cardiology, the Inter-American Heart Foundation, and the Latin American Society of Nephrology and Hypertension. These partners have indicated their willingness to collaborate in this important international initiative to improve the health of the people of the Americas.

Global Initiative for Asthma

NHLBI, WHO, and experts from a number of countries also collaborate on a joint initiative to address asthma as a serious global health problem. Asthma is estimated to affect more than 150 million people worldwide, and there is evidence that prevalence is on the increase in children in most countries. GINA was established by WHO, NHLBI, and the European Respiratory Society to decrease morbidity and mortality by the development and implementation of an optimal strategy for the management and prevention of asthma.

Asthma is a chronic condition characterized by a narrowing of the bronchial tubes, swelling of the bronchial tube lining, and mucous secretion that can block the airway, making breathing difficult. The prevalence of asthma can be as high as 30% among certain populations, and internationally, cases have more than tripled in the last 10 years. In the United States, between 1990 and 1994, the number of people reported to have asthma increased from 10.4 to 14.6 million, including approximately 5.0 million children.

In December 1998, NHLBI, the American Academy of Allergy, Asthma, and Immunology, the American College of Chest Physicians, and the American Thoracic Society launched a global plan to cut childhood asthma deaths by 50% by 2005. Other international supporting organizations include the European Academy of Allergology and Clinical Immunology and the International Union Against Tuberculosis and Lung Disease. This global effort was announced on the eve of the first World Asthma Day, on December 11, 1998. The theme was Help Our Children Breathe. In announcing the global plan, the chairman of GINA called on parents, physicians, public authorities, and national organizations to work together.

Middle East Hypertension Initiative

NHLBI has collaborated with individual countries in the Middle East for a number of years to address the increasing prevalence of cardiovascular disease. Toward the end of FY 99, the Institute invited hypertension experts from the Middle East to join with U.S. experts for an exploratory meeting to be held in Amman, Jordan, in December 1999, to address the problem of hypertension. Representatives from Egypt, Israel, Jordan, Lebanon, the Palestinian Authority, and the United Arab Emirates accepted the Institute's invitation.

In previous NHLBI collaboration with Egypt, research funded by the Institute, the Egyptian Ministry of Health, and the U.S. Agency for International Development (USAID) demonstrated that hypertension is a serious problem in the Egyptian population. Other countries in the Middle East have also reported high rates of hypertension. Hypertension is a major risk factor for coronary heart disease, stroke, premature death, and renal failure, making the prevention and control of hypertension an important health priority for the region.

The purpose of the December 1999 meeting in Jordan is to explore the interest in developing a joint MEHI and plans for future collaboration to reduce the risk of cardiovascular disease. Discussions will be held on a common protocol to estimate the prevalence of hypertension in Middle Eastern nations. It is anticipated that the ability to compare prevalence rates among countries will stimulate sharing of hypertension prevention, intervention, and evaluation strategies and will become the basis for developing national education campaigns designed to improve cardiovascular health in nations of the Middle East.

National Human Genome Research Institute

Progress on Human Genome Project

The Human Genome Project (HGP) is an international research effort to characterize the human genome and the genomes of selected model organisms through complete mapping and sequencing of the DNA. The goals of the project are to develop technologies for genomic analysis; examine the ethical, legal, and social implications of research in human genetics; and train scientists to use the tools and resources developed through the HGP to pursue biological studies that will improve human health. Begun in October 1990, the HGP is funded in the United States by the National Human Genome Research Institute (NHGRI) and the U.S. Department of Energy. After the success of the pilot phase in March 1999, an international consortium launched the full-scale effort to sequence the estimated 3 billion base pairs that make up the human genetic instruction book. With the United States taking the lead and with important participation by China, France, Germany, Japan, and the United Kingdom, the consortium expects to produce at least 90% of the human genome sequence in a "working draft" form by the spring of 2000, years earlier than initially expected.

On November 17, 1999, the consortium deposited the 1 billionth base pair of the human genome sequence into the public databases such as GenBank. Achieving this important milestone marks the success of

the transition from the pilot phase to full-scale production sequencing. This international effort is distinguished from private-sector efforts in its commitment to free public access to sequence data, without restrictions on use, and in its assurance of a finished product that has exhausted all available technologies for sequencing difficult regions of the genome. The updated status of the HGP can be monitored at the Web site http://www.ncbi.nlm.nih.gov/genome/seq/.

First Chapter of Human Genetic Instruction Book Deciphered

An international team of researchers achieved a historic scientific milestone by unraveling, for the first time, the genetic code of an entire human chromosome. The sequence of the 33.5 million base pairs that make up the DNA of chromosome 22 was deciphered by researchers at Washington University, St. Louis, Missouri; the University of Oklahoma, Norman; the Sanger Centre, near Cambridge, England; and Keio University, Tokyo, Japan. The sequencing of the DNA of chromosome 22 was conducted as part of the international HGP. All of these extremely high-quality data are freely available in public databases for scientists to use without the constraints of secrecy agreements, patents, or fees. Chromosome 22 was the first of 23 human chromosome pairs to be deciphered, partly because of its relatively small size and its association with several diseases. Research now will focus on determining what information can be deduced from these data. Sequencing and mapping efforts have already revealed that chromosome 22 is implicated in the workings of the immune system, congenital heart disease, schizophrenia, mental retardation, birth defects, and several cancers including leukemia, but many more secrets will be discovered in this decoded text. The results of this work will give scientists insights into the way genes are arranged along the DNA molecule and will pave the way for major advances in the diagnosis and treatment of disease.

Until now, scientists were uncertain about whether an entire human chromosome could be sequenced in this manner. For example, they did not know whether insurmountable problems would prevent assembly of their sequencing data. The presence of a small number of unclonable gaps (10) was not unexpected, but the scientists adhered to the standards that a chromosome should not be considered "essentially complete" (1) until the DNA sequences of regions that can be cloned and sequenced with current technology have been determined to high accuracy (less than one error in 50,000 base pairs) and (2) until the sizes of any remaining gaps have been determined.

Single Nucleotide Polymorphisms: New Tools for Tracing Inherited Disease

The DNA of any two individuals is 99.9% identical. The 0.1% difference represents genetic variation that can lead to differences in the risk of developing various diseases. Some diseases (e.g., cystic fibrosis and Huntington's disease) result from differences in the DNA sequence of single genes. However, many common diseases (e.g., diabetes, cancer, heart disease, psychiatric disorders, and asthma) are influenced by complex interactions among multiple genes and by nongenetic factors, such as diet, exercise, smoking, and exposure to toxins. A catalog of the sites in the genome where the DNA sequence differs among individuals will help in the effort to discern the genetic signals associated with a disease, amid the noise from other influences on the disease.

Led by NHGRI, the NIH organized the establishment of the DNA Polymorphism Discovery Resource, which consists of 450 DNA samples obtained under strict ethical guidelines from anonymous, unrelated U.S. residents of diverse ethnic backgrounds. This resource is now the major source in the search for DNA variants known as single nucleotide polymorphisms (SNPs). In the next 2 years, NIH-supported researchers expect to find about 200,000 SNPs. This effort is complemented by a similar effort in the private sector. The SNPs Consortium consists of 10 large pharmaceutical companies, Motorola, and the Wellcome Trust, which are collaborating to identify an additional 310,000 SNPs and to regularly deposit the information into the public SNP database.

Armed with a robust catalog of SNPs, researchers can then study persons with or without particular diseases to discover the variants related to differences in disease risk and response to therapy. The large number of genetic variants will help researchers to identify disease-related genes, especially those for common diseases, with the goal of understanding the causes of the diseases. Association of variants with a disease will facilitate development of diagnostic tests and provide targets for further study to understand the biological processes underlying health and disease. This understanding in turn will fuel development of improved prevention and treatment strategies. Because genetic variants contribute to individual differences in response to drugs, the identification and understanding of these variants will allow physicians to choose the most effective drug on the basis of a patient's particular variants.

National Institute of Mental Health Center for Mental Health Research on AIDS

Prevention Program

Prevention remains a critical priority of the National Institute of Mental Health (NIMH) Center for Mental Health Research on AIDS, in efforts to curtail the AIDS epidemic that is emerging worldwide. Few epidemics are stopped by treatment, and treatment certainly is the more expensive route. However, it is possible to mobilize behavioral prevention within a community, to address the major factors associated with the rapid development of an epidemic. NIMH has made a commitment to the development of an international prevention program for HIV and sexually transmitted diseases (STDs). The bidirectional goals for this program are (1) to extend the generalizability of research findings to international settings; (2) to identify assumptions and cultural issues in prevention programs; and (3) to understand the situational determinants and dynamics of AIDS prevention in multicultural settings.

International Research Studies

NIMH Collaborative HIV/STD Prevention Trial. The AIDS epidemic remains largely out of control in many areas of the world, particularly in developing countries with few economic resources, where there are large increases in HIV incidence. Rapidly increasing STD rates are also a widespread concern, because STDs can lead to infertility and increased risk of HIV. Approaches that change behavior one person at a time cannot be implemented rapidly enough to avert an epidemic. However, community-level interventions to achieve behavioral change

have the potential to reach large numbers of people, to reinforce individual behavior change, and to be cost-effective and feasible, even in areas with limited resources.

The NIMH Collaborative HIV/STD Prevention Trial is a two-arm, randomized, community-level trial in five countries—China, India, Peru, Russia, and Uganda. This project will be the first international test of a community-level prevention program. The trial uses the Popular Opinion Leader program, which is based on the theory of diffusion of innovations through popular opinion leaders in the community. The intervention engages these leaders to serve as agents of behavior change to friends and neighbors in their community. The prevention program is expected to strengthen norms of safer sexual behavior and encourage risk reduction among at-risk populations.

The pairs of collaborating institutions conducting this trial in foreign countries are (1) the University of California, Los Angeles, and the Chinese Academy of Preventive Medicine, Beijing; (2) Johns Hopkins University, Baltimore, Maryland, and the YRG Centre for AIDS for Research and Education (CARE), Madras, India; (3) the University of California, San Francisco, and Cayetano Heredia University, Lima, Peru; (4) the Medical College of Wisconsin and St. Petersburg State University and Biomedical Center, St. Petersburg, Russia; and (5) Columbia University, New York City, New York, and Makerere University, Rakai, Uganda.

Brazil. Two NIMH-supported investigators are conducting HIV studies in Brazil. One investigator, from Columbia University, New York City, is studying the use of combination antiviral therapies in the developing world. Brazil is the only developing country that makes drugs for combination therapies widely and freely available for persons who are HIV seropositive, and little is known about adherence to treatment protocols or the behavioral consequences of these therapies. The aims of this study are to measure adherence to protocols for combination therapies in developing countries and to examine the relationship between administration of combination therapies and safer sexual behaviors and better quality of life in persons with HIV/AIDS. Another high-priority study in Brazil, conducted by an investigator at the University of California, San Francisco, will determine the frequencies of drug-resistant HIV subtypes present in persons recently infected with HIV and the behavioral and social factors associated with transmission of drug-resistant HIV subtypes. These data are critical to design of culturally appropriate HIV prevention programs.

Dominican Republic, Mexico, and Puerto Rico. A researcher from the University of Puerto Rico is conducting a multisite study in the Dominican Republic, Mexico, and Puerto Rico, focusing on the role of men in HIV/AIDS prevention with women. The specific aims of the study are to explore the social and cultural context of HIV risk behaviors in men, in efforts to develop interventions for male partners in prevention programs. In addition, an investigator at the National Development and Research Institute, New York City, New York, is working with a Mexican investigator to replicate a preventive intervention for parents and their children. The prevention program teaches parents how to talk about sexual behavior and AIDS with their children who are not yet sexually active. The goals of this study are to overcome AIDS stigma in young children and to delay the initiation of sexual activity in the children.

India. NIMH has made a major commitment to support intervention research to encourage behavioral change to prevent the spread of HIV in India. NIMH researchers are conducting four projects there. Researchers at Johns Hopkins University, Baltimore, and YRG CARE are implementing the NIMH Collaborative HIV/STD Prevention Trial, in Madras. Investigators at the University of California, Los Angeles, and the Indian Council on Medical Research are conducting a study to identify HIV/STD risk factors for Indian women in order to develop an intervention that will integrate disease prevention and reproductive health, for use in clinics. Also, the first randomized clinical trial of an intervention for women in Calcutta will be conducted jointly by a researcher from the University of California, Los Angeles, and the Indian researcher who developed this comprehensive AIDS prevention program using empowerment for women. In addition, an investigator at the University of Syracuse, New York, is collaborating with an investigator at the National Institute of Mental Health and Neurosciences, Bangalore. The investigators will adapt and test an HIV/STD prevention program for persons who have serious mental illness.

Indonesia. A study by a researcher at the University of Michigan, Ann Arbor, is evaluating the effectiveness of two long-term HIV prevention programs for women in Bali. Interviews are being conducted to collect qualitative and quantitative data to elucidate the dynamics of HIV transmission in this vulnerable population. The presence of STDs is being evaluated at baseline and at 6, 12, and 18 months later. The results from this project can be used to develop long-term intervention programs for high-risk populations in developing countries.

South Africa. An investigator at Columbia University, New York City, will collaborate with mental health care providers in South Africa to develop and implement HIV prevention programs among persons with severe mental illness. The study is being performed in collaboration with a large public psychiatric institution in KwaZulu, Natal province, which has the highest HIV seroprevalence in South Africa. The goals are (1) to train mental health care providers in South Africa in basic knowledge of HIV/AIDS and in communication with patients about sexual issues and stigma and (2) to develop and adapt interventions for HIV prevention for persons with severe mental illness.

Zimbabwe. Zimbabwe is the site of two studies focused on populations at risk for HIV: orphans and patrons of beer halls. A small study of orphans of parents who died of AIDS is being conducted in Mutare by the AIDS Orphan's Project, a private African foundation, and in New York City, New York, by a researcher from Einstein College of Medicine. The aims of this study are (1) to document the extent to which children have taken on adult responsibilities when parents with AIDS are ill and (2) to describe educational, health, mental health, and developmental consequences for children who assume these caregiving roles. These data will be used to develop an intervention to prevent negative psychological and behavioral sequelae in these children.

Municipal social halls are a major feature of the social life of men living in Harare, and social halls are the setting for the high transmission rates of HIV/STDs. Frequent attendance at social halls in Harare is also a

strong predictor of HIV seroconversion. Researchers from the University of California, San Francisco, are conducting the first study of HIV seroprevalence in male patrons of social halls in sub-Saharan Africa and are obtaining data on behavior risk that can be used to develop an intervention to prevent HIV transmission in this setting.

Revision of *International Classification of Impairments, Disabilities, and Handicaps*

Throughout FY 99, the International Task Force on Mental Health and Addictive, Behavioral, Cognitive, and Developmental Aspects of the *International Classification of Impairments, Disabilities, and Handicaps (ICIDH)* actively contributed to the revision process for the WHO *ICIDH*. The charge of the International Mental Health Task Force continued to be focused on (1) the mental health aspects of the *ICIDH* revision, the unique contributions of mental functions and structure for which the task force has responsibility, and (2) the impact of mental disorders on performance of activities and participation in society.

During FY 99, the field trials of the beta-1 version of *ICIDH-2* were completed, analyses of the five mandatory components were conducted by WHO, and the revised version, *ICIDH-2* beta-2, was published. The International Mental Health Task Force played a leading role in the revision process, especially in developing operational definitions of mental functions and of the activities that most characteristically reflect the limitations experienced by people with mental disorders, such as those related to work and social relations.

ICIDH-2 beta-2 was published in July 1999. The International Mental Health Task Force collaborated with WHO to conduct a pilot training for the beta-2 field trials in August. The task force also undertook to translate *ICIDH-2* beta-2 into six languages: Tamil and Hindi (India), Yoruba (Nigeria), Russian, Spanish, and Turkish.

The translation of *ICIDH-2* beta-2 into Spanish was conducted with use of an innovative method. Because Spanish languages and cultures are diverse across the many Spanish-speaking countries, it became necessary to develop a consensus on the version that would be acceptable and practical for all. To accomplish this, La Red de Habla Hispana en Discapacidades (La RHHD), with major support from NIMH, convened two meetings. At the first meeting, which was held in Santander, Spain, in 1998, the method of translation was developed, and responsibilities were identified for each of the participating countries. Initial translation was conducted by a core group in Spain, and each chapter and section was then sent to chapter leaders in different countries for correction, modification, and further circulation. Field trial materials were also translated in this fashion.

A second meeting of representatives of NIMH and La RHHD was held with members of the Ministry of Health, Santiago, Chile, in September 1999. The purposes were (1) to plan a meeting to train all members of La RHHD to conduct field trials and (2) to develop a network of potential users of *ICIDH-2* in Chile. One aspect of this meeting was to solidify the liaison and harmonize the revision process with a second Spanish-language network in Latin America (La Red de Discapacidade y Rehabilitación), which had been convened by PAHO and also worked on the revision of *ICIDH*.

Both the formal training for and the conduct of the *ICIDH-2* beta-2 field trials are planned as FY 00 activities. With the foundation laid by the International Mental Health Task Force and its collaboration with La RHHD, at least 22 countries are actively participating in the revision process and the field trials. During FY 99, in addition to support for the meetings described here, NIMH contributed funding as seed money for the conduct of the field trials for both the International Mental Health Task Force and La RHHD.

Russia

After the development of programs to treat depression in primary health care settings in four Russian cities (Dubna, Moscow, Tomsk, and Yaroslavl) in FY 98, the Health Committee of the U.S.-Russia Joint Commission on Economic and Technological Cooperation proposed a merger of several related programs. The program for treatment of depression in primary care settings was merged with other primary care programs directed at treatment of chronic medical conditions, such as hypertension, asthma, and diabetes mellitus. This component of the commission's Health Committee, entitled Access to Quality Health Care, came under the purview of the Director of the Agency for Health Care Research and Quality, who serves as the point of contact for the Secretary of the U.S. Department of Health and Human Services (DHHS) with the Russian Minister of Health. The overall Health Committee is cochaired by the Secretary of DHHS and the Russian Minister of Health.

A major objective of merging the activities was to facilitate a greater coordination of management of chronic disease in primary health care settings. Hence, the Health Committee sponsored a primary care site in Tula, Russia, and a primary demonstration project to improve treatment of hypertension was selected to exchange its expertise in managing this chronic condition with one of the Moscow-based primary care sites treating depression. Facilitating all of these activities was a contribution from USAID, to purchase and equip eight laptop computers for use in administering a computer-assisted diagnostic assessment interview for mental disorders—the *Composite International Diagnostic Interview,* which was developed by WHO. On the basis of its extensive USAID-sponsored work in Russia, the American International Health Alliance was of great assistance in facilitating the purchase and equipping of these computers for use in Russian-language settings. The computers are also useable for data management of demonstrations at each site and Internet-based communication of results to the coordinating center at the Moscow Research Institute of Psychiatry. Implementation of a joint protocol for treatment of hypertension or depression in each site, with monitoring of patients by a common nurse-coordinator, is expected in FY 01.

National Institute of Neurological Disorders and Stroke

Repair of Severed Nerve Fibers in Animal Model of Spinal Cord Injury

Traumatic injuries to the brain, spinal cord, and peripheral nerves often involve severing or crushing of axons—nerve fibers that transmit the electrochemical signals of the nervous system, which are the basis for sensory and motor activity. Such injuries disrupt axonal conductance, so that this critical cellular communication is no longer possible. They can cause severe disorders, ranging from muscle weakness to paralysis and ab-

normal sensation or no sensation. Interruption of life functions as a result of such injuries affects millions of persons in the United States every year, and these injuries are a leading cause of disability in both children and adults.

After interruption of axonal connections, some amount of regeneration can take place. The regrowth of axons is slow and inefficient, however, and reformation of the circuitry needed for return of normal function remains a goal of research.

Grantees of the National Institute of Neurological Disorders and Stroke (NINDS), collaborating with investigators from the Swiss Federal Institute of Technology and the University of Zürich, Switzerland, have taken a different approach to the problem of nerve injury. Rather than attempt to enhance regeneration, they seek to heal the damaged axons. They have developed and tested a procedure to "glue" the severed ends of the axons back together. Their in vitro technique uses calcium-free solutions of polyethylene glycol (PEG) to rapidly induce fusion of the ends of severed axons from rat sciatic nerve. Physiological measurements indicate that the resealed axons transmit action potentials. In vivo studies showed that PEG alone would fuse axons, but the natural movement of the animal disconnected the repaired nerves. To ensure a more permanent seal, the investigators incorporated PEG into a hydrogel that bound to surrounding tissues and held the axons together.

The potential to reseal or reattach injured axons, which prevents the axons from degenerating, opens a new avenue of therapy for spinal cord and peripheral nerve trauma.

Blood Test to Detect Curable, Dangerous Cause of High Blood Pressure

High blood pressure (hypertension) has many possible causes. Rarely, hypertension results from a benign tumor of the adrenal gland, a key gland that sits atop each kidney. The tumor, called pheochromocytoma, releases potent biochemicals such as adrenaline into the bloodstream. Although rare, these tumors are important in clinical medicine. Whereas most cases of hypertension require long-term treatments, surgical removal of this type of tumor can cure the hypertension. Diagnosis and surgical removal are also important because this tumor, in response to seemingly mild stressors, can secrete adrenaline or other potent related biochemicals into the bloodstream, and these catecholamines can produce catastrophic consequences such as heart attack and sudden death. None of the available blood tests have been sufficiently sensitive to detect pheochromocytoma in all patients. NINDS scientists are collaborating with a scientist from St. Radboud University Hospital, Nijmegen, the Netherlands, to develop a method to measure, in human plasma, breakdown products of catecholamines from cells in the adrenal gland. Planned studies will attempt to elucidate specific genetic mutations that predispose persons to develop disorders associated with pheochromocytoma. Understanding how different mutations cause different tumor cell types will lead to better understanding of tumorigenesis and spur development of new and improved approaches for diagnosis and treatment of pheochromocytoma.

National Institute of Nursing Research

A grantee supported by the National Institute of Nursing Research (NINR) is conducting field research in Matlab, Bangladesh, on a public health intervention to prevent or reduce the incidence of cholera in areas where people must depend on groundwater after natural disasters such as flooding. The research involves a simple filtration method that uses widely available sari cloth to filter household water. The intervention is based on earlier studies that found sari cloth effective in reducing the number of plankton associated with *Vibrio cholerae* in surface water to below the infectious level that causes cholera. Investigators are evaluating the effective use of the techniques by villagers, including whether the number of *V. cholerae* cells in water and the incidence of cholera are reduced.

Another NINR grant involves a 10-site, randomized-control study in Canada and the United States. The research is designed to reduce the unacceptably high rates of birth by cesarean section in these two countries. Earlier studies conducted on a smaller scale showed that the amount of "labor support" by caregivers during active labor can influence the rates of cesarean delivery and other adverse events related to childbirth. The elements of labor support being studied include companionship, attention to emotional needs, and comfort. The researchers are evaluating the results of two types of nursing care on women in labor—continuous support and the usual intermittent nursing care. They are comparing the effects of these types of care on rates of cesarean delivery and forceps delivery and requirements for pain reduction, particularly for administration of epidural anesthesia. Cost-effectiveness is also being addressed. The findings will contribute knowledge about the effectiveness of labor support for a variety of events related to childbirth, such as prolonged hospital stay and postpartum depression. The results of this study are expected to inform policy decisions about the staffing of hospital delivery suites.

A research project supported by NINR hospital restructuring, which is widespread in Europe and the United States. The study provides the opportunity to evaluate restructuring modifications and recommend changes to improve health care for hospitalized patients. There is little scientific evidence on the best approaches to restructuring hospitals or the effect of specific approaches on outcome for patients. This research involves hospitals in Canada, England, Scotland, and the United States, which are in different stages of restructuring. Investigators are evaluating the effects of organizational changes, including variations in nurse staffing, on patient outcomes. Also under study are the effects of nurses' personal control over nursing practice and their relationship with physicians. The investigators are also analyzing hospital mortality rates, complication rates, and rates of unsuccessful resuscitation, as well as organizational barriers to timely use of critical clinical interventions.

NINR funds U.S. training fellowships for five predoctoral students performing relevant dissertation research. These studies involve

- ascertaining the prevalence and mental and physical health outcomes of domestic violence in Chinese women in China and the United States;
- testing a hypothesis that chronic infection with the hepatitis C virus is a risk factor for development of B-cell non-Hodgkin's lymphoma, in collaboration with the National Cancer Institute of Egypt;
- improving infant nutrition to prevent

stunting of growth and nutritional deficiencies, in Trujillo, Peru;

- understanding and management of cancer, including therapeutic options and cultural variables, in Peruvian Amazonia; and
- understanding the cultural context of sickle cell disease and its pain from the perspectives of the individual, the family, and the community, in Eastern Saudi Arabia.

National Library of Medicine

The year 1999 saw continuing leadership by the National Library of Medicine (NLM) in several areas of international work:

- furthering of global Internet connectivity;
- expansion of the DOCLINE program to include libraries in Africa, Internet connectivity, and access to information for malaria researchers in Africa; and
- the first meeting of international partners after the Board of Regents' approval of the long-range plan for international programs.

Future directions of NLM's international programs received substantial attention as a new long-range plan was approved by the NLM Board of Regents and plans for implementation began.

Internet communications connectivity and access to information resources by malaria research scientists in Africa are part of the Multilateral Initiative on Malaria—a major multilateral initiative undertaken in collaboration with NIAID, FIC, and the Office of the Director of NIH.

Other international activities were carried out with individual countries and governmental and nongovernmental organizations. Information management training was provided to colleagues from abroad, numerous professional visitors were received from around the world, and publications were exchanged with libraries in other countries.

National Center for Complementary and Alternative Medicine

As part of its responsibilities as a WHO Collaborating Center in Traditional Medicine, the National Center for Complementary and Alternative Medicine (NCCAM) provided substantial input into draft WHO Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. These guidelines will be discussed and made final at a WHO meeting in Hong Kong, China, in April 2000. The general objectives of the guidelines are as follows:

1. to harmonize certain important and acceptable definitions in the field of traditional medicine;
2. to summarize key issues focusing on methods for research on and evaluation of traditional medicine;
3. to improve the quality of research in the field of traditional medicine and complementary and alternative medicine and to enhance the value of research outcomes; and
4. to provide additional appropriate and acceptable evaluation methods to facilitate establishment of regulation and registration in the field of traditional medicine.

International Meetings

The Office of Alternative Medicine, the precursor of NCCAM, cosponsored the International Cochrane Colloquium in Baltimore, Maryland, in October 1998. At this meeting, NCCAM staff presented a report on the Use of Systematic Reviews in Alternative and Complementary Medicine.

NCCAM staff attended the Symposium on Alternative and Complementary Medicine, sponsored by Harvard Medical International, at the Asian Medical Center, in Seoul, Korea, in July 1999. Staff are also serving as guest editors for a supplement on the meeting that is to be published in the *Journal of Alternative and Complementary Medicine*.

In addition, staff presented a report entitled Research Development in Traditional Medicine at the WHO International Symposium on Traditional Medicine, in Kobe, Japan, in November 1999. The report will be published in a WHO bulletin for the Asian region.

National Center for Research Resources

The National Center for Research Resources supports the Cambridge Crystallographic Data Centre, England, which builds and maintains the Cambridge Structural Database, the largest searchable database of crystal structures that have been determined by biomedical researchers. This database contains crystal structure information for more than 190,000 organic and metal organic compounds and is the only available file of x-ray crystallographic coordinates for compounds of low molecular weight. The Cambridge Crystallographic Data Centre distributes the database and software to more than 600 academic and commercial users worldwide.

Center for Information Technology

In FY 99, Center for Information Technology (CIT) scientists and engineers collaborated extensively with scientists from Australia, Canada, China, France, India, Israel, Japan, Jordan, New Zealand, Northern Ireland, Republic of Ireland, Russia, Spain, and Switzerland. In addition, visitors from many Asian, European, and Middle Eastern countries interacted with CIT staff.

CIT has assumed a major role in assisting NCI in bringing the latest advances for the diagnosis and treatment of cancer to both Ireland and Jordan through its TELESYNERGY Medical Consultation WorkStation initiative. This multimodality medical teleconferencing environment is unique because of its ability to provide a synchronized, image-oriented environment to many participants at geographically distant sites.

Hospitals in Belfast, Northern Ireland, Dublin, Republic of Ireland, and Amman, Jordan, are slated to have TELESYNERGY systems installed during FY 00. NCI physicians and the participating hospitals' staff members will be able to participate in clinic rounds, examine patients directly, review radiologic and ultrasound data, and examine microscopic samples obtained through biopsy.

It is expected that research protocols and educational programs will benefit from this high-performance, bidirectional, image-oriented communication technology.

Center for Scientific Review

The Center for Scientific Review (CSR), formerly the Division of Research Grants, is the central receipt point for approximately 40,000 grant applications submitted to the Public Health Service each year. The Center provides the review for scientific and technical merit for most of the applications submitted to the NIH. This review is accomplished through more than 140 study sections clustered by scientific area into approximately 20 integrated review groups. Review meetings of research scientists from outside the NIH are convened by scientific

review administrators of CSR to provide expertise in biomedical and behavioral research. These experts conduct rigorous and equitable review of the merit of applications for support for research and research training. In addition, CSR continues to cooperate actively with organizations in other countries that have an interest in identifying and supporting high-quality, health-related research.

In FY 99, CSR hosted two delegations of scientists from China representing engineering and physical and health sciences and many international visitors who came to study the referral and peer review procedures and recent innovations that have been introduced to improve, expedite, and streamline the processes. These visitors were from Germany, Japan, Kazakhstan, Korea, and Uzbekistan.

Warren Grant Magnuson Clinical Center

During FY 99, the Warren Grant Magnuson Clinical Center staff presented research findings at numerous international conferences on subjects such as the ethics of international clinical research; hepatitis C viral infection; laboratory errors; use of magnetic resonance imaging in multiple sclerosis; infection control; effects of low-level radiation exposure; palliative care and pain management; medications for treatment of AIDS; compliance of AIDS patients with therapy regimens; and analysis of human movement.

Staff also were involved in the formulation and distribution of investigational medications and in collaborations with international researchers in diverse fields of clinical investigation.