

# VIII.

## National Cancer Institute

### INTRODUCTION

The National Cancer Institute (NCI), in cooperation with extramural institutions and the Fogarty International Center of the National Institutes of Health (NIH), supports international health research through bilateral agreements, grants, and contracts. The Institute supports about 3,000 intramural research scientists and staff, some 1,000 Visiting Scientists and Exchange Scientists, and about 8,000 extramural grants, contracts, and training awards. The work of outstanding scientists is supported through fellowships, cooperative projects, exchanges of personnel and materials, and workshops. During fiscal year 1999 (FY 99), NCI obligated more than \$46 million for foreign grants and contracts, the NIH Visiting Program, bilateral scientist exchanges, workshops, and international dissemination of cancer information.

NCI's international effort, coordinated by the Office of International Affairs (OIA) in the Office of the NCI Director, works in conjunction with programs at other NIH Institutes and the Fogarty International Center. Advances in cancer research result from NCI support and from support by other U.S. and foreign government agencies, industries, private nonprofit institutes, and individual philanthropists. Individual scientists initiate most of the cooperation in cancer research here and abroad, and other institutions also support international activities directly, without NCI involvement. NCI does take the initiative, however, when it is expedient to exploit a scientific opportunity. The research divisions within NCI are the Division of Basic Sciences, the Division of Clinical Sciences, the Division of Cancer Biology, the Division of Cancer Epidemiology and Genetics, the Division of Cancer Prevention, the Division of Cancer Control and Population Sciences, and the Division of Cancer Treatment and Diagnosis.

### International Workshops

One way in which OIA fosters joint research between U.S. and foreign scientists is by cosponsoring international workshops. The OIA workshops program brings together small groups of U.S. and foreign scientists who are at the forefront of their fields of research, to discuss their newest research that has not yet been published.

The U.S.-Japan Cooperative Cancer Research Program is a joint program of NCI and the Japan Society for the Promotion of Science. As is customary under the program, several workshops were held in FY 99:

- Developmental Regulators and Cancer;
  - New Rodent Models for the Analysis and Prevention of Carcinogenesis;
  - Herpesvirus and Human Cancer;
  - Progress in Immunotherapy and Gene Therapy of Cancer; and
  - Growth Signal Inhibitors and New Drugs.
- Other workshops cosponsored by OIA included the following:
- Cellular Signalling From Plasma Membrane to Nucleus (Santiago, Chile);
  - Prevention and Treatment of Pediatric Malignant Solid Tumors (Guangzhou, China);
  - Conference on Childhood Cancer (Guangzhou, China);
  - 5th Marianna Lordos Seminar (Larnaca, Cyprus);
  - 3rd International Conference on Environmental Mutagens in Human Populations (Bangkok, Thailand); and
  - 1st Annual Five-A-Day International Symposium (Washington, D.C.).

The Cancer Cell Biology Branch of the NCI Division of Cancer Biology cosponsored the 2nd North American Symposium on Skeletal Complications of Malignancy, held in Montreal, Quebec.

### Scientist Exchange and Other Training Programs

The Scientist Exchange Programs bring U.S.

and foreign scientists together for either short-term (less than 1 year) or long-term cooperation. Long-term exchanges are supported by NCI and the European Organization for Research and Treatment of Cancer (EORTC); NCI and the Japanese Foundation for Cancer Research; and the Oncology Research Faculty Development Program.

OIA sponsors the Oncology Research Faculty Development Program. This is a long-term program for young but established scientists from cancer research laboratories

**TABLE VIII-1.**

#### NCI Office of International Affairs: Exchange Scientists, Fiscal Year 1999

Country or Area	No. of	
	Visits	Months
Australia	1	2.0
Belarus	2	4.0
China	10	97.3
Colombia	2	1.8
Denmark	1	4.0
Egypt	5	26.7
Estonia	1	10.5
Gambia	1	9.0
Georgia	1	5.0
Germany	6	37.3
Greece	2	3.5
Haiti	1	11.0
Hungary	1	1.5
India	2	10.5
Israel	5	26.7
Italy	4	11.5
Japan	8	50.2
Jordan	1	12.0
Kazakhstan	1	6.5
Kenya	1	0.5
Korea	4	25.8
Mexico	1	0.3
Pakistan	1	2.5
Palestine	1	4.0
Peru	1	1.0
Poland	1	1.5
Russia	7	57.5
Saudi Arabia	1	0.3
Slovakia	1	3.0
Spain	4	16.7
Thailand	1	0.2
Turkey	4	12.5
Ukraine	3	22.5
Vietnam	2	0.4
<b>Total</b>	<b>88</b>	<b>479.7</b>

**TABLE VIII-2.****Foreign Scientists at NCI Under NIH Visiting Program, Fiscal Year 1999**

Country or Area	No. of Scientists
Argentina	9
Australia	13
Austria	6
Bangladesh	2
Belgium	4
Brazil	3
Bulgaria	3
Burkina Faso	1
Canada	32
Chile	1
China	95
Colombia	3
Costa Rica	1
Croatia	2
Cyprus	1
Czech Republic	4
Denmark	6
Egypt	2
Fiji	1
France	30
Germany	43
Greece	6
Hong Kong	1
Hungary	11
India	49
Iran	2
Ireland	1
Israel	13
Italy	39
Japan	124
Jordan	2
Korea	67
Latvia	1
Lebanon	1
Malaysia	1
Mexico	6
The Netherlands 16	
Norway	4
Pakistan	4
Peru	1
Poland	8
Portugal	1
Romania	1
Russia	28
Senegal	1
Serbia	1
Singapore	3
Slovakia	5
South Africa	4
Spain	22
Sweden	2
Switzerland	2
Thailand	2
Turkey	9
Uganda	1
Ukraine	1
United Kingdom 15	
Venezuela	2
Taiwan	10
<b>Total</b>	<b>729</b>

in developing countries, designed to prepare these scientists for independent careers as investigators and for leadership positions

in cancer research in their country. Foreign cancer research institutes nominate a limited number of scientists to the OIA selection committee. Each year, up to 16 candidates are accepted in NCI-supported laboratories. The cost is shared by NCI and the sponsoring laboratory.

During FY 99, OIA shared the costs of supporting 88 Exchange Scientists from 34 countries, for a total of 479.7 person-months, through the short- and long-term exchange programs. The distribution of these scientist exchanges for FY 99 is shown in Table VIII-1.

In addition to the Exchange Scientists supported by OIA, 729 foreign scientists visited NCI laboratories under the NIH Visiting Program (Table VIII-2). NCI also contributed to the funding of more than 100 short-term International Cancer Technology Transfer Fellowships, a program administered by the International Union Against Cancer (UICC).

Each year, individuals from a number of foreign countries participate in the Cancer Prevention and Control Academic Course, offered by the Division of Cancer Prevention. In FY 99, participants included representatives from Argentina, Brazil, China, Colombia, Côte D'Ivoire, France, Hungary, Korea, Mexico, Peru, Poland, Romania, Turkey, and Vietnam.

#### **Cancer Registration in Developing Countries**

Population-based cancer registries collect information on all cases of cancer in a defined geographic area, to estimate cancer incidence rates in the general population by variables such as gender, age, cancer site, and stage of disease. The establishment of cancer registries is a critical first step in public health planning, assessment of facility and manpower needs, research, and establishment of effective cancer control programs.

OIA sponsored attendance of personnel from developing countries at courses on cancer registration and genetic counseling, conducted by the International Agency for Research on Cancer (IARC), and at a course on cancer registration, held at Emory University, Atlanta, Georgia. OIA also sponsored two courses on cancer pain control, held in Santa Cruz, Bolivia, for participants from all over Latin America.

In cooperation with the Middle East

Cancer Consortium, OIA has sponsored cancer registry training programs in Bethlehem, Israel (West Bank), and Amman, Jordan. Training programs have also been held in Santa Cruz, Bolivia; Shanghai and Beijing, China; and Trivandrum, India. The course in Bolivia was attended by participants from Argentina, Bolivia, Brazil, Colombia, Costa Rica, the Dominican Republic, Mexico, and Peru. OIA has also sponsored participants from several developing countries for the annual meeting of the International Association of Cancer Registries (Lisbon, Portugal). In addition, OIA is providing assistance to develop infrastructure at cancer registries in Nigeria, Swaziland, Yemen, and Zimbabwe.

NCI's Surveillance, Epidemiology, and End Results Program participates with an international team working to revise and update the *International Classification of Diseases for Oncology*.

#### **Cancer Information Dissemination Electronic Access**

International dissemination of information on cancer research and treatment is a high-priority activity for NCI. In 1990, OIA began information dissemination projects at cancer centers in developing countries, to provide access to the latest published cancer research literature and treatment information through the NCI databases CancerLit and PDQ (Physician Data Query). NCI provided free subscriptions to these two databases on compact disk for a limited time, and the host institute provided the necessary computer hardware. By 1994, more than 50 information dissemination sites were in operation worldwide. With increasing availability of the Internet to access these databases, the compact disk program was discontinued in 1995.

The increasing availability of electronic telecommunications networks, even in many countries with an otherwise poor communications infrastructure, is revolutionizing the means by which individuals can access biomedical research and treatment information. The MEDLINE database of the National Library of Medicine is freely available on the Internet, either on the Grateful Med system (<http://igm.nlm.nih.gov>) or via PubMed (<http://www.ncbi.nlm.nih.gov/PubMed/>). Most of the PDQ database is available in English and Spanish via

the World Wide Web site, CancerNet (<http://cancernet.nci.nih.gov>). The entire CancerLit bibliographic database is available through the CancerNet Web site. In a typical month in 1999, 220,000 user sessions were logged on this site, and about 10% of the users were from outside the United States and Canada.

PDQ information summaries on cancer prevention, screening, treatment, and supportive care can also be obtained from CancerFax, an automatic fax-back service, and CancerMail, an electronic mail (e-mail) service. The summaries on treatment and supportive care are also available in Spanish, either directly from NCI or from the University of Chile, Santiago. These services also offer monthly CancerLit searches on selected cancer topics. The NCI Liaison Office in Brussels, Belgium, collects information on clinical protocols from Europe for the PDQ database. PDQ is distributed by EORTC through EuroCODE, an electronic communication network for European oncologists.

To use CancerFax, the telephone on a fax machine is used to call 1-301-402-5874, and recorded instructions are followed to retrieve documents. To access CancerMail, users send e-mail messages containing codes for desired documents to the NCI computer and receive the requested information in return. A contents list can be obtained by sending e-mail to [cancermailicc.nci.nih.gov](mailto:cancermailicc.nci.nih.gov) with the word "help" as the message. CancerMail information also is available via the Internet on a number of gopher servers, Web servers, and other secondary distribution sites.

### Print and Audiovisual Materials

With the American Cancer Society and the Pan American Health Organization (PAHO), OIA cosponsored the production of a Spanish-language edition of the American Cancer Society *Textbook of Clinical Oncology*, which is being distributed free to many of the major medical libraries in Spanish-speaking countries and is being sold at a subsidized rate to medical practitioners there.

In collaboration with the American Health Foundation of New York and PAHO, OIA is cosponsoring the development of a Spanish edition of the elementary school (kindergarten through grade 6) health education program "Know Your Body," for use both in U.S. Latino schools and in foreign schools where Spanish is spoken. A translation into Polish is in process, and transla-

tions into other languages are planned. OIA previously supported an Israeli Health Education Scholar at the American Health Foundation, thus facilitating the introduction of a Hebrew and an Arabic version of "Know Your Body" into Israeli and Palestinian schools.

NCI has many collaborative research agreements with IARC. One agreement addresses the identification of agents and exposures that may pose a carcinogenic risk to humans. Monographs containing the results of risk evaluations are published by IARC as individual volumes.

NCI is providing memberships in its Information Associates Program to approximately 45 libraries in foreign cancer centers or medical schools in Africa; Asia, including the Near East; the Caribbean; Central and Eastern Europe; and Latin America. This Program, developed by the International Cancer Information Center, provides subscriptions to the *Journal of the National Cancer Institute (JNCI)* and *JNCI Monographs*; access to the PDQ database and to CancerLit digests of citations and abstracts via electronic bulletin board or Internet connection; and a variety of other cancer information services.

Distribution of a "Cancer Seminars" series on videotape is continuing. Copies of these lectures are available to libraries of 110 foreign cancer institutes, giving young foreign scientists the opportunity to access the latest findings in cancer research. Recent lectures include the following:

- Immune Response to Self and Mutated Human Cancer;
- Contemplating the Completion of the Human Genome Sequence;
- The Use of Tumor Necrosis Factor in the Treatment of Cancer;
- Transcriptional Coactivators in Virus Infection and Cancer;
- Cancer Drug Discovery: Rationalizing Empiricism;
- General Motors Cancer Research Foundation: Lectures by the 1999 Laureates;
- The Etiology and Pathobiological Consequences of p53 Mutations in Human Cancer;
- Gene Discovery in Breast Cancer;
- Consequences and Mechanisms of Loss of TGF- $\beta$  (tumor growth factor  $\beta$ ); and
- Responsiveness in Carcinogenesis.

### Clinical Trials and Preclinical Drug Development

NCI facilitates international cooperation in clinical trials involving U.S. industry, which sometimes contributes pharmaceutical agents for such trials at no cost to the U.S. Government or foreign collaborating institutions. For example, clinical trials are being conducted in parallel in the United States and at the Russian (former All-Union) Cancer Research Center, Moscow, for the treatment of colon, colorectal, and breast cancers. Patients in these trials are receiving donated leucovorin or granulocyte colony-stimulating factor.

### NCI Liaison Office

The NCI Liaison Office coordinates the Institute's research and treatment programs in Europe through a formal trilateral agreement with EORTC and the Cancer Research Campaign (CRC) of the United Kingdom. The Liaison Office is involved in the exchange of information, experimental drugs, and research protocols and in programs for international exchange of scientists. The Liaison Office collects, reviews, and submits European research protocols for inclusion in PDQ, which is distributed worldwide through various channels, including EORTC's EuroCODE. In addition, the Liaison Office participates on committees and in working groups involved in all aspects of cancer research and drug development throughout Europe. The Office also facilitates international exchange of experimental drugs for treating cancer, seeks new agents with therapeutic potential from European sources, and assists in the development of research protocols that ensure comparability between data gathered in Europe and in the United States. This comparability has resulted in recognition by the U.S. Food and Drug Administration of data from European drug trials.

The EORTC-NCI Exchange Program, administered by the Liaison Office, offers support for up to 3 years for scientists from Europe or the United States to conduct research in an overseas facility. The NCI Liaison Office also supports short-term visits to the United States for European investigators involved in drug discovery and development. These exchange programs have fostered closer working relationships between European and U.S. investigators and have

expedited development of several high-priority new compounds under study in Europe and the United States.

### **Cooperative Group Program**

There is a long history of individual overseas institutions participating in the Clinical Trials Cooperative Group Program. Not all participating institutions receive financial assistance from NCI for this research; many investigators participate for the intellectual and emotional satisfaction of doing so, and their institutions subsidize the research. Participants involved in the Cooperative Group Program include the following:

- American College of Surgeons Oncology Trials Group (Canada, Germany, Switzerland, and United Kingdom);
- Cancer and Leukemia Group B (Canada);
- Children's Cancer Group (Australia and Canada);
- Eastern Cooperative Oncology Group (Israel and South Africa);
- Gynecologic Oncology Group (Canada);
- Intergroup Rhabdomyosarcoma Study (Canada);
- National Surgical Adjuvant Breast and Bowel Project (Australia and Canada);
- National Wilms' Tumor Study Group (Canada);
- North Central Cancer Treatment Group (Canada);
- Pediatric Oncology Group (Canada and Switzerland);
- Radiation Therapy Oncology Group (Canada); and
- Southwest Oncology Group (Korea).

### **International Cooperative Biodiversity Group Program**

International Cooperative Biodiversity Groups strive to achieve the interdisciplinary and synergistic goals of promoting biodiversity conservation, drug development, and economic growth. This initiative is cosponsored by the U.S. National Science Foundation; the U.S. Department of Agriculture; the Fogarty International Center; the National Institute of Allergy and Infectious Diseases; the National Heart, Lung, and Blood Institute; and the National Institute of Mental Health.

The International Cooperative Biodiversity Group Program supports broadly based, international, interdisciplinary projects to

meet each sponsoring agency's missions and objectives in four general areas:

1. collaboration in drug discovery and development for diseases of concern to both developing and developed countries;
2. development of inventories of native species and indigenous knowledge;
3. training directed to the needs of an individual country; and
4. improvements in the scientific infrastructure of the host country.

### **Biomedical Imaging Program**

NCI's Biomedical Imaging Program supports two cooperative agreements with international components. One study, involving two institutions in the United Kingdom and six in the United States, is designed to measure clinical tumor response to therapy by using magnetic resonance spectroscopy. The second study focuses on determining the usefulness of magnetic resonance imaging in diagnosing and characterizing breast cancer. This collaborative effort will accrue data on patients from 14 clinical sites, two of which are located in Germany. The Program also funds the American College of Radiology Imaging Network, a cooperative group for clinical imaging studies. This group is just beginning its first multi-institutional trials and has had discussions with radiologists in Belgium, Germany, and Italy about joint European-North American clinical imaging trials.

### **Cancer Therapy Evaluation Program**

Working with the NIH Office for Protection From Research Risks, staff of the NCI Cancer Therapy Evaluation Program (CTEP) developed a model for International Cooperative Project Assurance (ICPA) that can be used by foreign groups to participate in the Cooperative Group research protocols. This model simplifies and speeds the collaborative process. In the past, if a foreign research group wanted to collaborate with a Cooperative Group, each institution in the group had to apply to the Office for Protection From Research Risks for assurance for each project. Under the ICPA procedure, an assurance application from a central body, such as a ministry of health, covers all institutions involved. Since the inception of ICPA, approvals have been given to the Australian Gastro-Intestinal Trials Group; the Australian-New Zealand Breast Cancer Trials

Group; EORTC, Brussels, Belgium; the International Breast Cancer Study Group; the Italian Association of Pediatric Hematology and Oncology; the Peruvian Society of Medical Oncology; and CRC and the CRC Clinical Trials Unit, United Kingdom.

CTEP continues to provide investigational anticancer agents to overseas investigators involved in Cooperative Group activities and selected clinical trials, provided that the study procedures ensure protection of human subjects and compliance with local regulations. In addition to the Cooperative Group clinical trials, CRC is conducting two trials of bryostatin 1 and one trial of 17-allylaminogeldanamycin (17-AAG) in the United Kingdom.

CTEP continues to work with EORTC, the National Cancer Institute of Canada, and the World Health Organization (WHO), using the NCI Common Toxicity Criteria (CTC), Version 2.0. CTC is mapped to the International Medical Terminology from the European Union system, MedDRA (Medical Directory for Drug Regulatory Affairs). CTC provides a standard language for reporting adverse events and has been widely adopted internationally. CTEP staff have developed several Internet support systems for CTC, including an interactive application, a computer-based training program, and Common Toxicity Criteria for Palm Personal Computers.

CTEP has increased international collaborative efforts in the development of cancer treatment with the National Cancer Institute of Canada and the European Drug Development Network, comprising CRC, United Kingdom; EORTC, Belgium; and the Southern Europe New Drug Organization, Italy. CTEP met with these groups at various international meetings to develop procedures for the collaborative efforts and helped to facilitate the development or submission of a Drug Master File to the Food and Drug Administration, or both, for each of these groups.

### **Developmental Therapeutics Program**

The Developmental Therapeutics Program (DTP) searches for drugs for the treatment of cancer and of AIDS. Through the NCI Liaison Office in Brussels, more than 2,000 compounds per year come from European sources to DTP for screening of therapeutic agents. At least four of the agents in pre-

clinical development leading toward clinical trials for cancer or AIDS originally came from Japan. One of these, a benzoylphenylurea from Ishihara Sangyo, involved very active joint research in which the company provided a number of prodrugs. For many years, there also has been formal collaboration in drug development with CRC (United Kingdom) and EORTC. DTP carried out the formulation, development, and production of clomesone, bryostatin, and rhizoxin, which had their initial clinical study in Europe.

DTP is engaged in the collaborative development of a number of potential drugs to treat cancer that have arisen through the discovery efforts of foreign investigators, principally at CRC. In FY 99, through the efforts of its Drug Synthesis and Chemistry Branch, Pharmaceutical Resources Branch, and Toxicology and Pharmacology Branch, DTP was engaged in the synthesis and formulation of benzothiazole and its analogues and RH-1 (2,5-diaziridinyl-3-[hydroxymethyl]-6-methyl-1,4-benzoquinone) and in the evaluation of the pharmacokinetics and toxicity of these compounds. These studies are aimed at determining the suitability of the compounds for testing in phase I clinical trials.

In addition to these project areas, DTP works with investigators in Europe and Japan who have expertise in the selection of candidate agents for screening. Project areas include cyclin-dependent kinase inhibitors (France and Germany); antiangiogenesis compounds (Italy); benzothiazoles (CRC, United Kingdom); and polymer-delivered therapeutic agents (United Kingdom).

#### *Biological Testing Branch*

The DTP Biological Testing Branch has collaborated actively with a number of foreign investigators in developing and refining the panel of in vitro human tumor cell lines for screening of anticancer agents. For example, human tumor specimens have been provided by investigators from the University of Freiburg, Germany, and the Mario Negri Institute, Milan, Italy. Investigators at these institutions, in turn, participate with DTP in the evaluation of promising antitumor drugs. The agreement with CRC and EORTC has permitted the free flow of material and information for the assessment of compounds provided through the European

group. This cooperation has resulted in a number of significant joint research activities leading to the identification and further development of classes of compounds through the use of unique in vitro and in vivo assays.

#### *Natural Products Branch*

The DTP Natural Products Branch has a program of plant collections in Africa and Southeast Asia. The work is coordinated through contracts with the Missouri Botanical Garden, St. Louis (Africa), and the University of Illinois at Chicago (Southeast Asia). In Central and South America, there are direct collaborative activities with organizations in Brazil, Costa Rica, Mexico, and Panama. Joint efforts also have been established with groups in Bangladesh, China, Iceland, Korea, Pakistan, South Africa, and Zimbabwe. Collection of marine organisms in the Indo-Pacific region is performed through contract with the Coral Reef Research Foundation. Direct cooperative studies of marine organisms have been established with groups in New Zealand and South Africa.

License agreements have been negotiated with countries that are a source of naturally occurring biological materials found through NCI's drug-discovery program. Three compounds have demonstrated highly significant inhibitory activity in vitro against human immunodeficiency virus (HIV). Two possible anti-HIV agents, concurvone and calanolide, were isolated from plant material obtained under the NCI Natural Products Program, from Western Australia and Malaysia, respectively. In addition, NCI provides screening results to the countries where the material was collected, as well as invitations to scientists from the source countries to join NCI-supported U.S. scientists in the study of plants and marine organisms with potential for therapeutic activity that were collected within their borders. All expenses are paid by NCI. Agreements have been reached with organizations in Bangladesh, Ecuador, Fiji, Gabon, Ghana, Laos, Madagascar, Malaysia, Palau, the Philippines, Tanzania, Vietnam, and Zimbabwe. Additional joint agreements are in place with the South American Office for Anticancer Drug Development, Fundação Oswaldo Cruz, and University Paulista, Brazil; Kunming Institute of Botany and the

Hong Kong University of Science and Technology, China; Instituto Nacional de Biodiversidad, Costa Rica; the University of Iceland; the Korean Institute of Science and Technology; Instituto de Quimica, Mexico; H. E. J. Research Institute of Chemistry, Pakistan; Universidad de Panama; and the South African Council of Scientific and Industrial Research.

### **HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES**

Substantial progress has been made in many areas of basic cancer research. For example, a number of genes involved in specific cancers have been identified, and each new genetic discovery guides the development of specific diagnostic approaches, interventions, and treatments. The improving ability to detect very small tumors and to identify rapidly growing tumors is increasing the potential to treat cancer more effectively and to reduce cancer mortality.

Cancer prevention plays a growing role. There is convincing evidence that about one-third of the cases of cancer in the United States are related to the use of tobacco products and that another one-third may be related to dietary factors. One of the most dramatic advances has been the identification of specific cancer susceptibility genes that can be used to identify individuals at high risk of developing cancer. The discovery of the BRCA1 gene, which is present in patients who have an inherited form of breast cancer, is an example.

During FY 99, NCI supported 58 foreign grants and 29 foreign contracts (Table VIII-3). Also, 103 grants and 7 contracts awarded to U.S. institutions during FY 99 had a foreign component. In addition to awards to extramural institutions, scientists in the NCI intramural laboratories are involved in many joint research projects with foreign investigators, institutions, or both. International cooperation in cancer research has played a key role in virtually all areas of progress in the fight against this disease. The projects cited in subsequent sections of this chapter are examples, not an exhaustive list, of NCI international activities.

#### **Breast Cancer**

At the University of Melbourne, Australia,

**TABLE VIII-3.****NCI Foreign Grants and Contracts,  
Fiscal Year 1999**

Country or Area	Grants	Contracts
Australia	8	—
Belgium	1	—
Canada	27	4
China	8	—
Costa Rica	1	—
Denmark	1	2
Finland	2	—
France	4	—
Germany	1	—
India	1	—
Israel	4	—
Italy	2	4
Jamaica	1	—
Japan	1	1
Mexico	1	—
The Netherlands	1	1
New Zealand	1	—
Poland	1	—
Russia	1	—
South Africa	1	—
Sweden	3	—
Switzerland	1	—
Trinidad and Tobago	1	—
United Kingdom	2	—
<b>Total</b>	<b>58</b>	<b>29</b>

NCI is supporting the establishment of a large registry of Australian multigenerational pedigrees by collection and storage of epidemiologic information on the major recognized and putative risk factors for breast cancer and by performance of follow-up studies. This resource will be made available worldwide for research into the genetic epidemiology, biology, causes, prevention, and treatment of breast cancer. Australia is an excellent country in which to establish a Breast Cancer Family Registry. The size of the population is manageable yet sufficient for a study. Other advantages include ethnic diversity and a highly localized, relatively stable population in which families are usually intact and family members are in contact with one another.

The Study of Tamoxifen and Raloxifene (STAR), one of the largest breast cancer prevention studies ever performed, was recently launched. The trial is now recruiting volunteers at more than 400 centers across Canada and the United States, including Puerto Rico. The trial will include 22,000 postmenopausal women at increased risk of breast cancer. The purpose of the trial is to determine whether the drug raloxifene, for prevention of osteoporosis, is as effective in

reducing the chance of developing breast cancer as tamoxifen has proven to be. Tamoxifen was shown to reduce the chance of developing breast cancer by about one-half in the Breast Cancer Prevention Trial, a study of more than 13,000 premenopausal and postmenopausal women at high risk of breast cancer.

**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.

**Biological Markers**

A critical goal for prevention research is the application of new technologies for the detection of biological markers (biomarkers) to identify human disease and, perhaps more important, to identify individuals at high risk or predisposition to develop a particular disease. NCI supports a project at Laval University, Quebec, which is developing methods for sensitive, noninvasive detection of bladder cancer, for use in early detection and in monitoring patients with superficial disease. This research includes clinical studies to evaluate promising diagnostic and prognostic markers, including development of a rapid and sensitive urine test for bladder cancer; the test is based on capture assays using a panel of monoclonal antibodies.

NCI is funding several laboratories for development of biomarkers, as part of the Early Detection Research Network. A set of cooperative agreements have been signed to establish this Network for the development, evaluation, and validation of biomarkers for earlier cancer detection and risk assessment. Two of the developmental laboratories are in Canada—at the University of British Columbia, Vancouver, and the University of Toronto, Ontario. The third international laboratory is at Oxford Glycobiology Institute, England.

**Dietary Factors**

NCI scientists have been conducting a number of research projects on esophageal cancer in China, where the incidence of this malignant disease is the highest in the

world. Two nutritional intervention trials, in collaboration with the Chinese Academy of Medical Sciences, were conducted in Linxian, where study findings suggest that the population's chronic deficiencies of multiple nutrients may contribute to the high incidence of esophageal cancer. Daily vitamin and mineral supplements were shown to lower cancer rates both for patients with esophageal dysplasia and for the general population. A 5-year postintervention follow-up of these cohorts has been completed, and investigators are preparing the data for analyses of whether these early effects of micronutrient supplementation persist. Serum collected in 1985 is being used to investigate the association of micronutrient levels and some infectious agents, found by serology, with subsequent esophageal cancer, gastric cancer, and stroke in these cohorts.

### **Early Detection**

NCI supports the work of investigators at Tata Memorial Hospital, Bombay, India, in a community-based, randomized-control evaluation of low-cost methods for early detection of common cancers in women. Breast cancer and cervical cancer account for about 50% of cancer deaths in women in India. Among the diagnostic methods being evaluated are clinical breast examination without mammography, self-examination, and visual inspection of the cervix by trained female health workers. The goal is to reduce mortality by detection and diagnosis of breast cancer and cervical cancer at an early stage. This trial is one of the first of its kind to be conducted in a developing country, and findings may be relevant to other countries and populations with limited resources (e.g., underserved populations in developed countries).

### **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 Cancer Consortium (MECC) agreement. 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 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.

## **SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES**

### **Cooperative Research Programs**

Formal cooperative research programs are governed either by agreements between governments or by agreements between institutes. NCI participates in many of the bilateral agreements that the NIH has with some 40 nations, and NCI also has direct agreements or informal ties with institutions in many more countries.

### **Selected Country-to-Country Activities**

#### **Australia**

NCI supports studies at the Walter and Eliza Hall Institute of Medical Research, Melbourne. One project focuses on understanding the external regulation of granulocytes and macrophages at the cellular and molecular levels and on defining the molecular defects in those cells that lead to the formation of myeloid leukemia. In another NCI-supported study at this institute, researchers

are investigating oncogene-induced leukemogenesis in transgenic mice.

NCI also supports a project at the University of Queensland to establish a registry of multigenerational pedigrees in Australia and New Zealand, to be used in research on the cause, pathogenesis, and prevention and treatment of colorectal cancer.

#### **Belgium**

NCI provides partial funding to assist the EORTC Data Center, Brussels, in providing statistical assistance and expertise to the clinical cooperative groups of EORTC, which have 200 multicenter trials in progress. NCI also maintains a Liaison Office in Brussels.

#### **Brazil**

NCI supports an investigator from McGill University, Montreal, Quebec, who is performing an epidemiologic cohort study of the natural history of HPV infection and cervical neoplasia in a population of low-income women in São Paulo, one of the highest-risk areas worldwide for cervical cancer. Although HPV infection is known to be an important cause of cervical cancer, most of the epidemiologic data have come from retrospective studies, which do not provide information on the dynamics of cervical HPV infection in an individual. This study is testing the hypothesis that persistent infections with oncogenic HPV types are likely to be the true precursor events leading to cervical carcinogenesis. Persistence of infections is being documented by study of molecular variants of HPV, which provides a much finer level of detail than simple HPV typing. In addition, this molecular approach may unveil other prognostic markers of progression, across the spectrum of cervical lesions.

NCI scientists are studying risk factors for perinatal HIV transmission by comparing data from Brazil with results from Africa. The similarities and differences shown by these data may reveal specific practices (e.g., duration of breast-feeding) that could be modified to reduce the risk of perinatal HIV transmission.

#### **Canada**

NCI supports research projects at several Canadian universities, cancer centers, and hospitals. Efforts include studies in the following areas:

- cellular thermostability and thermotolerance;
- immunologic and molecular markers for diagnosis and prognosis of bladder cancer;
- genetic epidemiology of epithelial ovarian tumors;
- reduction in fat intake and risk of benign breast disease;
- molecular epidemiology of persistent HPV infection;
- protective effects of dietary supplementation with garlic derivatives in lung cancer;
- quantitation of hypoxic tumor cells;
- plasminogen regulation by annexin II tetramer;
- inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase in treatment of acute myeloblastic leukemia;
- analysis of risk factors for carriers of the BRCA1 or BRCA2 gene; and
- hormone replacement therapy and risk of colon cancer.

At the Ontario Cancer Treatment and Research Foundation, Toronto, NCI is supporting projects on development of population-based registries of familial colon cancer and familial breast cancer. Such registries will serve as resources for future epidemiologic studies, primary prevention trials, genetic studies, and research on surveillance strategies.

NCI is collaborating with the Cancer Division of the Laboratory for Disease Control, Health and Welfare, to evaluate exposure of agricultural workers to pesticides and the impact of protective practices on these exposures. A joint project with investigators at McGill University, Montreal, is examining the association of insulin-like growth factor and the risk of prostate, colorectal, or other cancers. NCI is also working with investigators at the University of Toronto in genetic analyses of melanoma-prone families, in both Italy and the United States, and in performing functional analyses of identified mutations.

Several Canadian institutions also participate in many of the NCI Clinical Trials Cooperative Groups and in other NCI-sponsored clinical trials.

## China

NCI collaborates in many projects in China that involve research on the cause, preven-

tion, and treatment of various types of cancer. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

In Shanghai, a randomized trial of breast self-examination is under way in 435 factories of the Shanghai Textile Industry Bureau. The purpose of the study is to determine whether the regular practice of breast self-examination will reduce mortality from breast cancer. Nearly 300,000 current and retired female workers between the ages of 30 and 64 years are participating in this study.

A study of biochemical and molecular early markers of lung cancer, which is the leading cause of cancer death in the United States, is being performed in a high-risk population in China. The subjects of the research are underground miners from the Yunnan Tin Corporation, who are at extraordinary risk of lung cancer from exposure to radon, arsenic, and tobacco. More than 7,000 miners receive annual screening by chest x ray and sputum cytology to identify new cases; biological specimens, including sputum samples, are stored for evaluation of potential early markers of lung cancer. The study is being conducted jointly with scientists from the Yunnan Tin Corporation; NCI; Johns Hopkins University, Baltimore, Maryland; and the University of South Florida, Tampa.

Primary hepatocellular carcinoma (PHC) is one of the three most common causes of cancer death in the world and accounts for up to 1 million deaths per year. Little is known about the genetic epidemiology of PHC or the specific molecular mechanism responsible for the disease. NCI investigators are conducting studies in a cohort from China in which the carrier rate for the hepatitis B virus (HBV) is 12.6%. HBV is thought to be a causative agent of liver cancer. To investigate genetic outcomes, a nested case-control study is being conducted in collaboration with the Zhong Shan Hospital of the 1st Shanghai Medical School and the Qidong City Liver Cancer Prevention Program. The study will correlate the genetic constitution of healthy tissue and tumor tissue in patients for whom clinical and epidemiologic information is available, to evaluate the clinical significance of genetic differences. Statistical methods will be used to evaluate the role of genetic and environmental factors in PHC, and molecular stud-

ies are being conducted to determine whether genetic changes observed in tumors are consistent with a tumor-suppressor gene model of oncogenesis.

An NCI project in collaboration with the Ministry of Public Health, Beijing, is assessing health risks associated with exposure to indoor radon. Investigators are comparing lung cancer risk due to radon exposure in males and females and are investigating whether exposure to tobacco smoke or other contaminants of indoor air may influence lung cancer risk due to radon exposure.

In other studies, NCI is working with scientists at the Chinese Academy of Preventive Medicine (a) to evaluate cancer risks among workers exposed to benzene and (b) to determine mechanisms of carcinogenicity. In collaboration with the Shanghai Cancer Institute and the University of South Carolina, Columbia, a prospective cohort study is under way to assess the role of occupational and environmental factors in the development of cancer in women. Case-control studies of several cancers of the digestive system are also being conducted with the Shanghai Cancer Institute.

In addition, NCI is working with researchers at the Shanghai Cancer Institute in a case-control study of the cause of cancers of the biliary tract in Shanghai, where the incidence of these cancers has been increasing. Risk factors being investigated include gallstones, bacterial infections, obesity, reproductive factors, and family history. In addition to structured in-person interviews, biological specimens (blood, urine, bile, and gallbladder tissue) are being collected for assessment of nutrients, hormones, microbes, genes, and other factors.

Several descriptive studies are planned to investigate trends in cancer rates in China and elsewhere. A joint project is planned with the Cancer Institute, Chinese Academy of Medical Sciences, Beijing, to compare cancer mortality rates for various types of cancer in 1990–1992 with rates from an earlier exhaustive survey in 1973–1975. NCI researchers are collaborating with researchers at the Shanghai Cancer Institute to analyze cancer incidence trends in 1972–1994 in the Shanghai region and to correlate them with changes in lifestyle factors and environmental exposures.

Data from a population-based, case-control study conducted in Shanghai to



investigate the reasons for the extremely low, but increasing, risk of prostate cancer in this population are being analyzed. The scientists are addressing a variety of hypotheses related to hormone levels, dietary intake, anthropometry, and medical practice. They are using both interviews and biological information. In addition, the scientists are exploring whether genetic factors are related to the very low risk of prostate cancer in China.

A laboratory study on mutagenicity of heated cooking oils was conducted to support a substudy investigating cooking practices and risk of lung cancer in residents of Gansu Province. The study is also evaluating the possible role of indoor air pollution from environmental tobacco smoke and coal combustion, as well as diet and other factors, in the risk of lung cancer.

NCI funds the Transdisciplinary Tobacco Use Research Center at the University of Southern California, Los Angeles. The focus of this center is preventing tobacco use among youth of diverse cultures. The investigators will conduct smoking-prevention programs with middle school and high school students in California, Hawaii, and Wuhan, China, and will examine the relationship of ethnicity and acculturation to adolescent smoking.

### **Costa Rica**

Guanacaste Province is the site of a large NCI research project on the etiology, detection, and treatment of cervical cancer. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.") In addition, NCI is collaborating with the Universidad Nacional, Heredia, to determine the relationship between exposure to pesticides and occurrence of cancer in a cohort of workers exposed to pesticides.

### **Czech Republic**

NCI intramural scientists are collaborating with colleagues at the Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague, on the following projects: (a) research on the role of methylation in downregulation of oncogene expression; (b) studies on expression of avian retroviral vectors; (c) investigation of tumor immunology and tumor rejection, particularly in relation to the antigenicity of products of the v-src oncoprotein and to the genes coding for cy-

tokines such as interleukin 2; and (d) studies of avian leukosis virus in the duck embryo, especially the relationship of the virus to wasting disease and atrophy of the thymus gland.

### **Denmark**

NCI supports the work of investigators at the Danish Cancer Society in research using record linkage to identify and quantify the risk of cancer associated with particular occupations and with diagnosis of selected medical conditions or treatment with certain surgical procedures. Unique opportunities to conduct cost-efficient, record-linkage studies of causes of cancer are provided by the availability of (a) population-based rosters of patients with diagnosis of various medical conditions and treatment with specific procedures and (b) cancer registry data from the same population.

A population-based, record-linkage study of cancer risk in patients with ataxia-telangiectasia and their relatives is being conducted in Denmark, Finland, Norway, and Sweden. The researchers will sequence the gene for ataxia-telangiectasia to identify and characterize mutations in patients with the condition, and they will perform screening for family-specific mutations in relatives.

NCI is working with the Danish Cancer Society in a record-linkage study on risk of prostate cancer after benign prostatic hyperplasia. An additional investigation is following up the health status of children born after use of drugs that stimulate ovulation.

NCI has had a long-standing scientific collaboration with the Epidemiology Research Unit, Copenhagen. The investigators are using U.S. data on AIDS and cancer to determine whether the mechanism by which mothers pass HIV to their infants at delivery is microtransfusion through the placenta. Follow-up studies of a cohort of homosexual men in Denmark showed that human herpesvirus type 8 (HHV-8) may have been introduced into that country only in the late 1970s and that the incidence of infections in later years was lower. The findings indicate that the virus may have been transmitted sexually and was associated with the later development of Kaposi's sarcoma (KS).

### **Finland**

Follow-up continues in the lung cancer prevention project started in Finland in 1984 as

a joint effort of NCI and the National Public Health Institute of Finland. The main activity has been a study of the effects of dietary supplements of  $\alpha$ -tocopherol and  $\beta$ -carotene on lung cancer incidence and mortality.

Another NCI project, with the Finnish Cancer Registry, is examination of cancer risks by using data from nationwide, linked registries of disease.

### **France**

At IARC in Lyon, NCI provides support for the IARC Program on the Evaluation of Carcinogenic Risks to Humans. In this project, investigators use published epidemiologic and experimental data to identify chemicals or complex mixtures of chemicals that may pose a carcinogenic risk to humans. The results of data analyses are published in *IARC Monographs*.

Also at IARC, NCI supports (a) a project on the role of intercellular communication at the gap junction and mechanisms for its control in multistage carcinogenesis and on the control of cell growth by connexin genes and (b) investigation of the role of insulin and insulin-like growth factor I in breast, endometrial, and ovarian cancer.

NCI is collaborating (a) with Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France, on a study of brain cancer to evaluate risks from occupational exposures and (b) with scientists at IARC on a study of kidney cancer in several Eastern European countries. In another project, NCI is working with investigators from INSERM to develop new techniques for statistical genetic analysis. These techniques will be used to analyze data from melanoma-prone families in an NCI study and in a study of the International Melanoma Genetics Consortium.

### **Germany**

In Germany, NCI cooperates mainly with the German Cancer Research Center (Deutsches Krebsforschungszentrum), Heidelberg, and Westdeutsches Tumorzentrum, Essen. Scientists at the research center are working with NCI-supported scientists at Georgetown University, Washington, D.C., on the development of mucosotropic vaccines against HPV and with scientists at the University of Arizona, Tucson, on the overexpression of the gene for TGF- $\beta$  in cells of

squamous cell carcinoma. For their work in developing and further refining the panel of *in vitro* human tumor cell lines that is used for screening agents for cancer treatment, the Biological Testing Branch, DTP, has received human tumor specimens from investigators at the University of Freiburg.

In collaboration with the National Institute for Occupational Safety and Health, NCI is examining the occurrence of epithelial proliferative lesions and lung cancers, by histologic type, in a large population of uranium miners from the Saxony region in Germany who had heavy exposure to silica, radiation, or both in the 1950s and 1960s.

### **India**

NCI investigators work with the Indian Council on Medical Research, New Delhi, and with the following cancer centers on treatment protocols for lymphoblastic leukemia and nonlymphoblastic lymphomas: Kidway Memorial Institute of Oncology, Bangalore; Tata Memorial Center, Bombay; the Cancer Institute, Madras; and the Rotary Cancer Center, All India Institute of Medical Sciences, New Delhi. NCI also cooperates with cancer centers in Chandigarh, Trivandrum, and Vellore.

NCI researchers are collaborating with investigators at the Trivandrum Cancer Centre on an epidemiologic study to evaluate the relationship between pesticide exposure and the risk of progression of breast cancer. In addition, a project to study the mechanisms of action of benzidine is being conducted with scientists at the National Institute of Occupational Health.

### **Israel**

Studies at the Weizmann Institute of Science, Rehovot, are aimed at understanding the mechanism of action of the p53 tumor-suppressor gene in its normal (wild type) and mutated forms. Inactivation of the endogenous wild-type p53 gene is associated with more than one-half of all cases of human cancer. Studies are focusing on the identification and characterization of genes involved in p53 regulation. Other NCI-supported projects at the Weizmann Institute of Science include (a) use of magnetic resonance imaging and spectroscopy as noninvasive procedures for early evaluation of breast cancer response to hormonal therapy and (b) investigation of molecular mecha-

nisms through which the ErbB-2/HER2 oncoprotein contributes to tumorigenesis in various adenocarcinomas.

At Tel Aviv University, NCI supports research on the neuroendocrine and immunologic mechanisms underlying the modulatory effects of the estrous cycle, gonadal hormones, and gender on immune competence and tumor development.

NCI is supporting an epidemiologic study of ovarian cancer at the Chaim Sheba Medical Center, Tel Hashomer, to evaluate a broad range of potential risk factors (e.g., reproductive, hormonal, nutritional, genetic, and occupational factors). In addition, a feasibility project is being conducted to ascertain whether ataxia-telangiectasia is hereditary in approximately 24 candidate families and to determine procedures for a population-based study of cancer risk in these families.

NCI is collaborating with researchers at Bar-Ilan University, Ramat Gan, and the International Fertility Institute, Ra'anana, to conduct a review of tumor pathology in men with incident prostate cancer. The purposes of this study are to obtain better population-based estimates of the prostate cancer risk associated with mutations of the BRCA1 and BRCA2 genes and to review the pathologic characteristics of tumors containing these genes.

### **Italy**

A new joint study by scientists from NCI and the University of Milan has collected 25 pedigrees and biological specimens on kindreds with cutaneous malignant melanoma. This material, in conjunction with a case-control study of melanoma, will provide a means to investigate a genetic component to melanoma in this Mediterranean population. Genotyping of these families is under way. The study will also investigate whether deficits in DNA repair may contribute to development of melanoma. In addition, NCI and the University of Cagliari, Sardinia, are engaged in a study to evaluate cancer risks among workers who applied pesticide in a campaign to eradicate malaria.

At the European Institute of Oncology, Milan, NCI is supporting a study using insulin-like growth factor I in blood plasma as a potential surrogate marker of contralateral breast cancer in women younger than 50 years of age who are being treated with the

synthetic retinoid *N*-(4-hydroxyphenyl)-retinamide (fenretinide). In a related NCI-supported project at the same institute, investigators are examining interactions between low-dose tamoxifen and fenretinide on a set of biomarkers in premenopausal women with minimally invasive (*in situ*) breast cancer.

NCI is working with investigators at the University of Milan, the Centers for Disease Control and Prevention, and the National Institute of Environmental Health Sciences, NIH, in a study of the effects of dioxin on subjects from Seveso, who were exposed to this environmental toxin after an industrial accident in 1976. A population-based study of healthy subjects from the town indicates that blood levels of dioxin remain elevated 20 years after exposure. The investigators plan to conduct a case-control study of persons with cancers that have been linked to exposure to dioxin (i.e., non-Hodgkin's lymphoma and soft tissue sarcoma).

The Division of Cancer Control and Population Sciences collaborates with Istituto Superiore di Sanità, Rome, and Istituto Nazionale Tumori, Milan, to accomplish three purposes: (1) to apply demographic, back-calculation models developed by these groups to estimate U.S. cancer incidence and prevalence from mortality and survival data; (2) to reach European-U.S. consensus on methods to estimate cancer prevalence on the basis of tumor registry data; and (3) to use models developed by these groups to estimate complete prevalence for years before establishment of a given cancer registry.

### **Jamaica**

Since the early 1980s, NCI has been involved in studies of the natural history of infection with human T-cell leukemia/lymphoma virus type I (HTLV-I) and its relationship to adult T-cell leukemia/lymphoma. NCI investigators have established several prospective cohorts, particularly in Jamaica. These cohorts have matured and currently serve as a source of biological specimens for exploration of important questions in disease pathogenesis. The major emphasis is on studies to evaluate familial and genetic aspects of HTLV-I infection and associated diseases. The families in the cohort are a high-risk population suitable for continued follow-up to evaluate both environmental and genetic aspects of disease pathogenesis.

NCI investigators plan to extend the family studies by developing a population-based cohort of 500 HTLV-positive and 1,000 HTLV-negative participants for comparative analyses to evaluate genetic and environmental risk factors identified in the family studies.

In a study of nearly 2,000 Jamaican women, NCI is examining potential risk factors for progression of low-grade cervical lesions that are a precursor to cervical cancer. Jamaica was chosen for this investigation because of the high incidence of cervical cancer and the high prevalence of sexually transmitted infections, particularly HTLV-I, in the general population. An earlier study in Jamaica showed that HTLV-I infection was strongly associated with development of more severe cervical neoplasia. Findings show that HTLV-I proviral DNA is detectable in cervical specimens from more than one-half of infected women. This observation suggests that direct interaction between HTLV-I and HPV, the principal cause of cervical neoplasia, could contribute to cervical tumorigenesis in women infected with both viruses. To further examine this possibility, researchers are using *in situ* hybridization and immunohistochemistry to evaluate tissue samples from women with both viruses.

### **Japan**

There is extensive collaboration between the United States and Japan in therapy using boron neutron capture, particularly in treatment of malignant brain tumors and melanomas. Another area of joint research is the study of modulation of neoplasia associated with liver fluke parasites, in Nagoya.

Hepatitis C virus (HCV) is highly prevalent in Japan, which provides a situation conducive to its study. In a cohort study, NCI scientists examined the interactions of HCV and HTLV-I in an area of Japan where both viruses were endemic. Death from liver cancer was strongly associated with antibody to HCV. Antibody to HTLV-I was somewhat correlated with HCV infection but provided no added risk for liver cancer.

In collaboration with the Radiation Effects Research Foundation, Hiroshima and Nagasaki, NCI is conducting epidemiologic and multidisciplinary studies of cancer risk in relation to radiation dose among a cohort of atomic bomb survivors. Studies under way include site-specific surveys for

incidence of (a) benign and malignant tumors of the thyroid gland, central nervous system, and ovary and (b) cancers of the breast, liver, colon and rectum, lung, and lymphoid tissue. In addition, the researchers are conducting case-control interview studies of patients with thyroid or colon cancer. NCI investigators are also collaborating with the National Cancer Research Center, Tokyo, to identify mutagens and carcinogens in cooked meats. In another study, NCI is working with Japanese scientists who have studied families with Werner's syndrome, to evaluate the unusual melanomas that occur in excess in persons with this condition.

### **Malawi**

NCI supports research in Malawi by investigators at the University of North Carolina, Chapel Hill, who are studying HHV-8 associated with AIDS-related KS. HHV-8 has now been identified in all forms of KS. The mode of transmission of HHV-8 infection in Africa, where HIV is transmitted heterosexually and KS is endemic, is unknown. Molecular studies are being performed to determine the likely mode of transmission of HHV-8 in this population. A sexual route of HHV-8 transmission has been suggested by several studies in the United States, where homosexual and perinatal exposure are the predominant routes of HIV transmission.

In 1994, NCI established a large clinical trial in Malawi, which showed that vaginal cleaning with an antiseptic had no effect on the risk of HIV transmission but did lower the risk of infections and early neonatal deaths. This study enrolled a cohort of more than 2,000 HIV-infected women who delivered infants, to determine how frequently breast-feeding transmits HIV in this setting. The infants who were not HIV positive at birth and were breast-fed by HIV-positive mothers were shown to have about 1% risk of infection per month of breast-feeding after the 1st month of life. These results are being used to help WHO to formulate policy recommendations on the advisability of breast-feeding in Africa.

New studies are also under way to examine HIV infection in twins born to infected mothers in Malawi. More than 600 twin pairs have been enrolled; about 30% were born to HIV-positive mothers. These infants will have follow-up for 1 year, to determine the risk of infection in first- and second-

born twins and to determine whether genetic factors influence the response to infection.

### **Mexico**

NCI is collaborating with the National Institute of Public Health in Mexico on studies of breast cancer and stomach cancer. The breast cancer project is evaluating the relationship between cancer risk and serum levels of organochlorine chemicals, such as dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyls (PCBs). The stomach cancer study focuses on dietary factors.

NCI is sponsoring studies by an investigator from Stanford University, California, on the role of infection with *Helicobacter pylori* as a cause of adenocarcinoma of the distal stomach, a cancer with highest incidence in developing countries. Studies are being conducted in Chiapas, a region with high rates of gastric cancer and preneoplasia. Evidence that therapy for *H. pylori* reverses preneoplastic lesions could provide a foundation for gastric cancer screening and prevention trials and could enhance understanding of preneoplasia and inflammation-related carcinogenesis.

### **The Netherlands**

The Division of Cancer Prevention is working with the Department of Public Health, Erasmus University, Rotterdam, to develop a microstimulation model designed to analyze the cost and effectiveness of various screening strategies and methods for the early detection of colorectal cancer.

Cancer risk associated with nasopharyngeal implantation of radium (Crowe method) for treatment of eustachian tube dysfunction is being evaluated retrospectively in a cohort of patients treated at a number of clinics in the Netherlands during the 1940s and 1950s.

### **Norway**

NCI and the Centers for Disease Control and Prevention are collaborating with the Cancer Registry of Norway to investigate the risks of several cancers associated with serum levels of persistent organohalide chemicals, including DDT and PCBs.

### **Panama**

Serological studies have found the human T-cell leukemia/lymphoma virus type II

(HTLV-II) to be endemic in some isolated Indian tribes of the Amazon and other regions in the Americas. This finding suggests that HTLV-II is an ancient virus that entered the Western Hemisphere with human migration. NCI has conducted studies on the transmission of HTLV-II and its effects on health among the Guaymi Indians residing in Changuinola, the capital of the Bocas del Toro province in Western Panama. Transmission appears to resemble transmission for HTLV-I, which is primarily a consequence of breast-feeding and, for women, a result of sexual intercourse. No health consequences of infection with the virus have been clearly identified.

#### **Peru**

NCI researchers are working with the Universidad Peruana Cayetano Heredia, Lima, on a descriptive study of recent changes in the incidence and pathology of esophageal cancer and stomach cancer in Peru.

#### **Poland**

NCI is collaborating with investigators at the Institute of Oncology, Warsaw, to explore the role of diet as a cause of gastric cancer, which occurs at unusually high rates in Poland. Another study is examining smoking and infection with HPV as cofactors associated with the risk of cervical cancer.

NCI researchers are working with researchers at Marie Curie-Sklodowska University, Lublin, in a large, population-based study to assess both environmental and genetic risk factors for breast cancer among women living in two major cities in Poland: Lodz and Warsaw. Primary areas of interest will be the relationship of risk to physical activity, active and passive smoking, occupational exposures, and dietary patterns, as well as the influence of genetic factors on these relationships. The study will also evaluate the influence of genetic susceptibility on the effects of more established risk factors for breast cancer, such as reproductive and hormone-related factors. In addition, NCI is conducting a joint study to identify etiologic factors associated with the high prevalence of stomach cancer in Poland. Other cooperative efforts include molecular studies of lung and laryngeal cancer in regions of Poland with severe industrial pollution.

#### **Russia and Other Countries of the Former Soviet Union**

NCI researchers and colleagues from the Jonsson Cancer Center, Los Angeles, California; Dana Farber Cancer Center, Boston, Massachusetts; and Roswell Park Cancer Center, Buffalo, New York, are participating in clinical trials based in Moscow, Russia. Two of the trials use 5-fluorouracil plus leucovorin in the treatment of colorectal carcinoma, and a third uses granulocyte colony-stimulating factor in adjuvant therapy for breast cancer.

NCI investigators are evaluating the relationship between thyroid disease, especially thyroid cancer, and doses of radiation to the thyroid from exposure to radioactive iodine and other radionuclides that were released in the 1986 nuclear power plant accident at Chernobyl. The study subjects are residents of Belarus and Ukraine who were children and adolescents at the time of the accident. The incidence of leukemia and lymphoma among Chernobyl cleanup workers in Ukraine also is being studied. In addition, NCI is cooperating with WHO, the European Commission, and the Sasakawa Memorial Health Foundation of Japan, to establish thyroid tissue repositories in Belarus, Russia, and Ukraine.

NCI is working with Japanese and Russian scientists in epidemiologic studies of cancer risk among plutonium workers at the Mayak weapons fabrication plant near Chelyabinsk, Russia, and among residents of the Techa River area, in relation to exposure to radionuclides that entered the river from the plant. Also, NCI is performing a joint study with the St. Petersburg Medical Academy for Postgraduate Training, to evaluate occupational factors as a cause of lung cancer and their interaction with genetic susceptibility markers.

A survey of the prevalence of thyroid nodules and cancer has been initiated in relation to radiation dose in a cohort of 2,500 residents of Semipalatinsk, Kazakhstan, who were present as children during a period of substantial radioactive fallout from atomic bomb tests in 1949–1956. Blood samples will be collected to verify estimates of radiation dose, and subjects will be clinically examined to verify the presence of thyroid nodules.

#### **Senegal**

NCI supports research by an investigator from the University of Washington, Seattle, on cervical neoplasia and HIV infection in Senegal. This research focuses on the role of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) as risk factors for cervical cancer and its precursor lesions, in this region of the world where people are at very high risk of contracting HIV. Related studies are concerned with the contribution of HPV to the development of cervical cancer. Recent cross-sectional studies have shown HIV infection to be associated with an increased risk of HPV-related lesions. Invasive cervical cancer is now considered an indicator of AIDS in HIV-infected women.

An NCI-supported study in Senegal, where the incidence of PHC is high, is using molecular and biochemical methods to identify viral, genetic, and environmental factors associated with increased risk of developing PHC. This research is being conducted by investigators from Fox Chase Cancer Center, Philadelphia, Pennsylvania. Even though chronic HBV infection is associated with 80% of the cases of PHC in the world, 75% of chronic carriers of HBV do not develop PHC and at least one-half do not develop liver disease. Little is known about the specific environmental, viral, or genetic factors that affect risk of these diseases and how these factors interact.

#### **Singapore**

NCI supports an investigator from the University of Southern California, Los Angeles, who is conducting a cohort study of 60,000 Chinese residents of Singapore, aged 45–64 years. The primary aim of the study is to definitively establish the causal relationship between ingestion of Chinese salted fish and similar foods and development of nasopharyngeal carcinoma, as suggested by previous case-control studies. A broader aim is to establish a stable cohort for the long-term study of the relationship of dietary and other environmental determinants to cancer and other chronic diseases. Related projects by the same investigator include a case-control study in Shanghai, China, a region of intermediate risk of nasopharyngeal carcinoma, and a case-control study in Taiwan, a region of moderately high risk. These two studies are a part of the investigator's continuing attempt to define the cause of

nasopharyngeal carcinoma in Chinese populations. Incidence rates vary by 20-fold in these populations.

### **Slovenia**

Considerable controversy surrounds the question of whether the two types of asbestos (amphiboles and chrysotile) have different carcinogenic potencies. This issue has been difficult to address because of a lack of quantitative data to estimate separate dose–response curves for the two fiber types. An NCI-supported study by an investigator from the University of Massachusetts, Lowell, is examining risk for lung cancer and for mesothelioma in former employees of a Slovenian asbestos plant. In this study, excellent data on historical exposure to each of the two broad classes of asbestos fibers are available.

### **South Africa**

The injectable contraceptive progestogen (depot medroxyprogesterone acetate [DMPA]) has been used worldwide by more than 11 million women. Concerns exist about breast cancer risk due to use of DMPA, particularly after long-term use. NCI is sponsoring research by an investigator from Boston University, Massachusetts, who is performing a hospital-based, case–control study of DMPA-related breast cancer in the western Cape of South Africa, where more than 30% of the nonwhite women have used DMPA—the highest documented exposure in the world.

A related study by the same investigator is being conducted in Cape Town. Carcinoma of the cervix is causally linked to infection with specific oncogenic types of HPV, but not all infected women develop cancer. It has been suggested that injectable progestogen-only contraceptives (IPCs), combined estrogen–progestogen oral contraceptives (COCs), or both may act as cofactors with HPV as a cause of cervical cancer. Evidence also suggests that IPCs may reduce the risk of cervical cancer. South Africa is an ideal country to test these hypotheses, because exposure to IPCs and COCs is common, as is invasive cervical cancer.

NCI and the National Institute of Occupational Safety and Health are conducting a pilot study with the National Center for Occupational Health, Johannesburg, to identify biomarkers and susceptibility factors in

the development of lung cancer among miners.

The University of Pretoria is one of the institutions participating in NCI clinical trials as part of the Eastern Cooperative Oncology Group.

### **Spain**

Informal cooperation between NCI and scientists in Spain focuses (a) on signal transduction pathways activated by growth factors and their modification in human cancer; (b) on the evaluation of high-dose chemotherapy regimens followed by autologous bone marrow transplantation as therapy for patients with acute lymphoblastic leukemia or malignant lymphomas; and (c) on the elucidation of the cell biology of Ewing's sarcoma and related primary tumors.

NCI and the Institut Municipal d'Investigació Medica, Barcelona, are jointly evaluating the role of occupational exposures and gene–environment interactions in the development of bladder cancer.

### **Sweden**

Investigators in an NCI-supported project at Karolinska Institute, Stockholm, are studying the role of genital HPV as a cause of carcinoma in situ of the cervix. Although a causal role of HPV is likely, no large, population-based, prospective study has examined (a) the contribution of HPV in the natural history from normal epithelium to carcinoma in situ; (b) the role of cell-mediated immunity, as determined by human leukocyte antigen haplotype, microheterogeneity, or mutations in the HPV genome; or (c) the involvement of other factors that may determine transience or persistence of HPV infection. Nor has the purported orderly progression or monoclonal origin of cervical neoplasia been established. The Swedish investigators are conducting an interdisciplinary case–control study, nested in a population-based cohort.

Other NCI-supported research at Karolinska Institute is directed toward understanding how polymorphisms in the estrogen receptor gene may affect the risk of breast cancer and endometrial cancer. NCI investigators are collaborating with colleagues from this institute in studies of the risk of prostate cancer after benign prostatic hyperplasia and studies examining the reasons for apparent

low rates of breast cancer after breast reduction surgery. Another NCI-supported project at Karolinska Institute, is addressing genetic susceptibility to hormonal carcinogenesis.

Data from two Swedish censuses (1960 and 1970) have been linked together and to the nationwide cancer and population registries, for study of occupational risk factors for specific cancers. In addition to analysis of risk from specific occupations and industries, matrices of job exposure have been developed to analyze risk from exposure to pesticides, solvents, sunlight, and electromagnetic fields and from lack of physical activity. Data from a case–control study of rare childhood cancers are being analyzed. The medical data come from linkage of records in the Swedish birth registry, cancer registry, and hospital registry to all cases, matched controls, and the mothers and siblings of all case patients and control subjects. A familial aggregation study is now being planned that will similarly link data on cases and controls and all family members to data from the Swedish cancer and hospital registries, for study of the possible connection between malignant lymphoproliferative diseases and autoimmune diseases in family members.

### **Trinidad and Tobago**

NCI investigators working with the Caribbean Epidemiology Center, Trinidad and Tobago, are continuing studies on the prevalence of HTLV-I and HIV infection in the healthy population in Trinidad and Tobago. The purposes of the research are (a) to systematically obtain samples and data on lymphoreticular malignant disease, (b) to develop and follow cohorts at high risk for HIV (e.g., homosexual men and male and female prostitutes), and (c) to evaluate risk factors related to viral infection and disease outcome, with particular emphasis on interaction of HTLV-I and HIV.

A joint research project of NCI and the University of the West Indies, St. Augustine, involves a series of epidemiologic, clinical, and experimental studies to define the distribution and determinants of HTLV infection and the possible role of HTLV as a cause of cancer. An important future direction is to perform follow-up studies on infection in patients with HTLV and HIV and to use these high-risk populations to define the

natural history and pathogenesis of these viruses in terms of disease outcome.

### **Turkey**

A hospital-based, case-control study of several cancers is being conducted in collaboration with the Social Security Agency Hospital, Istanbul, to identify occupational causes of cancer in Turkey.

### **United Kingdom**

Cooperation continues between NCI and British scientists, particularly in the field of radiotherapy. Clinical trials of fast-neutron therapy have long been supported at Clatterbridge Hospital, Merseyside, England; the University of California, Los Angeles; M. D. Anderson Cancer Center, Houston, Texas; and the University of Washington, Seattle. These NCI-supported trials are the only ongoing phase III studies in the world that are designed to evaluate the use of neutrons in the treatment of cancers of the prostate, lung, and head and neck.

At the University of London, England, NCI supports studies on prediction of human tumor response by using magnetic resonance spectroscopy with <sup>31</sup>P.

NCI is collaborating with researchers at British Nuclear Fuels and Westlake Scientific Consulting (United Kingdom) to evaluate cytogenetic end points as biomarkers of occupational exposure to ionizing radiation in workers at the Sellafield nuclear reprocessing plant, Cumbria, England.

### **Vietnam**

NCI supports studies investigating the efficacy of oophorectomy plus adjuvant therapy with tamoxifen in prevention of breast cancer recurrence in patients in Vietnam. The purpose of adjuvant tamoxifen therapy is to counteract the undesirable effects of oophorectomy on bone and the cardiovascular system.

### **Zambia**

Recent studies have identified HHV-8 in almost all KS tissues and in lymphomas in the body cavity. This virus may play an important role in the transformation and development of KS. One of the many pertinent questions regarding this virus is its route of transmission. NCI supports research by investigators at the University of Nebraska,

Lincoln, in collaboration with the University of Zambia Medical School, Lusaka, to study the causes of KS. Zambia has a very high incidence of HIV infection in women and children; moreover, KS constitutes about 20%–25% of the malignant conditions seen in Zambian infants and children. These rates provide a unique opportunity to explore the possible vertical transmission route of HHV-8 and whether HHV-8 infection leads to development of KS in children. The researchers have already found that Zambian children and infants with KS carry HHV-8 DNA sequences and that many pregnant Zambian women who are healthy or who are infected with HIV-1 are also infected with HHV-8.

### **Taiwan**

Information exchange continues between scientists in the United States and Taiwan on diseases endemic to that part of the world: hepatitis due to HBV, nasopharyngeal carcinoma, and T-cell leukemia.

Since 1989, NCI has collaborated with the National Taiwan University, Taipei, and the National Institute of Dental and Craniofacial Research, NIH, on studies of genetic, viral, and environmental factors as causes of nasopharyngeal carcinoma. This work includes a completed case-control study of nasopharyngeal carcinoma in Taipei and a new country-wide effort to enroll high-risk families in a study to investigate the role of inherited predisposition and genetic and environmental factors in this disease.

### **Multinational Studies**

Second malignant neoplasms are being studied among 1-year survivors of testicular or ovarian cancer reported to population-based cancer registries in Canada, Denmark, Finland, the Netherlands, Sweden, and the United States. A cohort survey will characterize risk of a second cancer, by age and time since treatment, and a nested case-control study is expected to evaluate and quantify leukemia risk associated with specific therapies. In a separate study, population-based cancer registries in these countries are being used to study second cancers in patients with Hodgkin's disease treated by radiation or other therapeutic regimens.

Cancer risk is being evaluated in a cohort of 20,000 patients who have received bone

marrow transplantation for leukemia, aplastic anemia, or other diseases, from 1964 through 1992. Data are being obtained from the United States and from 234 transplant teams in more than 50 countries that report data to the International Bone Marrow Transplant Registry in Wisconsin. A cohort study has been conducted, and analyses are ongoing. A nested case-control study in this cohort is being performed to obtain information on treatment and cancer risk factors that is not available from the computerized files on the cohort.

Thyroid cancer data from 14 case-control studies conducted in Italy, Japan, Norway, Sweden, Switzerland, and the United States are being analyzed together, to clarify associations between hormonal, medical, and environmental risk factors and thyroid cancer.

To facilitate the understanding of mammalian development, infectious disease, and neoplasia and to provide a balance to biological exceptions that may occur in rodent modeling of human genetics, scientists in the NCI Laboratory of Genomic Diversity are developing a comparative genetic map of the domestic cat, in the Feline Genome Project. The cat is an attractive candidate for laboratory genetics for several reasons, including abundant polymorphic morphological loci, heritable defects homologous to those that cause human genetic diseases, and epidemics of two viruses that cause neoplasias and immunodeficiencies—feline leukemia virus and feline immunodeficiency virus, respectively. Insight gained from these studies have helped in exploration of new mechanisms for immune and natural defenses against fatal infections and neoplastic diseases. These studies have involved collection and analysis of samples from Africa, Asia, and South America.

NCI is funding efforts to establish a multicenter clinical trials group, the Proton Radiation Oncology Group (PROG). PROG will initially include three U.S. facilities and will develop protocols to determine whether the clinical application of proton beams is superior to the best current methods of radiotherapy with photons or electrons, for patients with tumors at select anatomic sites. Foreign investigators from proton facilities in France, Japan, Russia, South Africa, Sweden, Switzerland, and the United Kingdom

will be encouraged to participate in the PROG research efforts, and this collaboration will enhance the level of research on proton therapy, through improved communications and increased accrual of participants in clinical trials over shortened periods.

The NCI Applied Research Program administers the International Breast Cancer Screening Network, a voluntary consortium of 25 countries that have active programs for population-based screening by mammography, to detect breast cancer. This network is dedicated to joint research aimed at identifying and fostering efficient and effective approaches to worldwide control of breast cancer through population-based screening mammography.

### **Activities With International and Multinational Organizations**

OIA is NCI's liaison with international agencies involved in cancer research and prevention. OIA also maintains connections with premier cancer centers worldwide and with organizations that have international components.

### **European Organization for Research and Treatment of Cancer**

NCI's collaborative program with EORTC and with CRC in the United Kingdom remains highly successful in providing a regular flow of new compounds for NCI's automated assay for screening potential anticancer and anti-AIDS agents. The therapeutic potential of these agents is tested in a panel of in vitro human tumor cell lines. The collaborative program also provides new drugs for phase I and II clinical evaluations. Participating cancer centers include the following:

- the Jules Bordet Institute, Brussels, Belgium;
- the Finsen Institute, Copenhagen, Denmark;

- the Institute for Cancer Research, Sutton, Charing Cross Hospital, London, and Paterson Institute for Cancer Research, Manchester, England;

- Institut Gustave Roussy, Paris, France;
- the Immunology Research Group, Freiburg, the German Cancer Research Center, Heidelberg, and the Max-Delbrück Center for Molecular Medicine, Berlin, Germany;
- the National Institute of Oncology, Budapest, Hungary;
- the Mario Negri Institute for Pharmacological Research, Milan, Italy;
- the Daniel den Hood Cancer Center, Rotterdam, and Free University and A. van Leeuwenhoek Tumor Center, Amsterdam, the Netherlands;
- the Radium Hospital and Norsk Hydro's Institute for Cancer Research, Oslo, Norway;
- the University of Edinburgh and the University of Glasgow, Scotland; and
- the Swiss Cancer Center, Bellinzona.

EORTC joins some 2,000 European cancer specialists in 250 institutions into a single working team. The EORTC Data Center, Brussels, provides the statistical and data-processing services required for state-of-the-art clinical trials. EORTC provides NCI with early access to results from cancer research supported by the European Community.

### **International Agency for Research on Cancer**

IARC, an organization in Lyon, France, that is affiliated with WHO, has 18 member states: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Norway, Russia, Sweden, Switzerland, the United Kingdom, and the United States. Among NCI-supported projects at IARC is the publication of a monograph series evaluating the carcinogenic risks of chemicals to humans. These *IARC Monographs* are used as authoritative sources of information by gov-

ernments and regulatory bodies worldwide. NCI represents the United States on the Governing Council of IARC. The U.S. portion of IARC's regular budget is provided by the U.S. Department of State.

### **International Union Against Cancer**

UICC, which is based in Geneva, Switzerland, is a worldwide organization with more than 250 members in 84 countries. NCI provides partial support to the UICC Committee for International Collaborative Activities, the UICC Detection and Diagnosis Program, and the UICC Fellowship and Personnel Exchange Program, which receives funding for International Cancer Technology Transfer fellowships. More than 100 short-term fellowship awards were made during FY 99.

### **Organization of European Cancer Institutes**

The Organization of European Cancer Institutes was founded in 1978 to foster cooperation among cancer centers of the Economic Community and the Warsaw Pact countries. With the disintegration of the Warsaw Pact, interaction among cancer centers in the United States, Central and Eastern Europe, and Western Europe has improved greatly. OIA represents NCI at the annual general assembly meetings of the Organization of European Cancer Institutes.

### **Pan American Health Organization**

PAHO has been the recipient of an OIA contract that contributes to the support of the Latin American Cancer Research Information Project. PAHO has also been involved in translation of an oncology textbook and an elementary school health curriculum. (See also the section on "Cancer Information Dissemination.")

