XIV.
National Institute of Environmental Health Sciences

INTRODUCTION

The National Institute of Environmental Health Sciences (NIEHS) is located in Research Triangle Park, North Carolina. Since its creation in 1966, the Institute has been the primary source of Federal efforts to study how environmental factors affect human health. Because of the broad scope of the NIEHS mission, its research relies on essentially every discipline in the biological, chemical, and physical sciences.

Human health and disease result from three interactive elements: environmental factors, genetic susceptibility, and time or age. From conception to death, we are all exposed to a multitude of environmental agents with the potential to disrupt normal physiological function and cause disease. Critical to establishment and maintenance of a healthy human environment is an understanding of the biological basis of these hazards. Without such understanding, we can only guess about which human exposures should be controlled and at what levels.

The opportunity to make a difference in the environmental health sciences has never been greater. A rapid transition in the discipline, coupled with advances in genetic research, has brought scientists near to a breakthrough in the bottleneck of our lack of knowledge about the identity and mechanisms of environmental hazards that contribute to human illness. We are now poised to make enormous progress in prevention, diagnosis, and treatment of diseases associated with environmental factors. The goal is to learn which environmental or genetic components are the most important contributors to a specific disease and which individuals are most likely to develop that disease.

Environmental health problems are not perceived as local in scope or short term in nature. The most difficult issues stem from a dearth of data and understanding about the health consequences of long-term, low-level exposures to environmental agents. Environmental problems have global effects on human health that may not be easily reversible or amenable to quick technological fixes. Assessing the complex environmental health problems facing today's society requires international cooperation on an unprecedented scale. NIEHS continues to take a leading role in conducting international collaborative research, training, and information exchange in environmental health.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Healthy Babies Delivered by Mothers With Malformations

NIEHS researchers have found that more than 96% of babies delivered by women with malformations are healthy, according to a recent study based on the Norwegian Medical Birth Registry. The Norwegian registry is a unique resource, linking medical and birth records through personal identifiers. Researchers from NIEHS and the registry collaborated in an analysis that showed mothers with defects had only a slightly higher chance than healthy women of having a baby with malformation. The risk in offspring was higher for the same defect carried by the mother but no higher for any other defects.

Biokinetics of Lead in Human Pregnancy

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

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

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

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Canada

Researchers in the NIEHS Laboratory of Molecular Carcinogenesis are collaborating with scientists at Queen's University, Kingston, Ontario, to analyze mutations of the p53 gene in lung tumors induced by aflatoxin

B1. They study high-frequency and heterogeneous distribution of p53 mutations in the lung tumors.

France

A joint study in cancer prevention with epidemiologists at the International Agency for Research on Cancer in France is investigating unexplained increases in cancer incidence in the United States in 1975–1994. The analysis focused on long-term time trends in incidence and on deviations from those trends that are attributable to year of birth or to calendar periods. On average, cancer incidence rose 0.8% annually in white women and 1.8% in white men. When smoking and increased screening were taken into account, average annual increases fell to 0.1% in white women but persisted at 1.7% in white men. In particular, yearly increases in non-Hodgkin's lymphoma averaged 2.4% in white women and 4.7% in white men. Among men, incidence changes attributable to year of birth grew progressively greater from one birth cohort to the next. Cancer incidence patterns among black men and women were similar to those among whites, despite smaller population sizes. Unexplained patterns of cancer incidence may signal changes in underlying risk factors, and they highlight the continuing need for research on cancer etiology and prevention.

Italy

A scientist from the NIEHS Laboratory of Molecular Genetics has a collaboration with the University of Rome, to characterize a mutation in *Drosophila melanogaster* that causes telomeric repeat arrays to grow to great lengths. This mutation increases the activity of a reverse transcriptase, apparently stimulating transposition of a telomere-specific retrotransposon. The long telomeres, which have been characterized cytologically and by in situ hybridization, show increased frequencies of telomeric interactions at metaphase.

For a decade, scientists from the NIEHS Laboratory of Computational Biology and Risk Analysis have been involved in joint research with scientists at the University of Ferrara to design and develop new opioid compounds as nonaddictive agonists for the cessation of pain associated with cancer and new antagonists for application in stemming alcohol dependency and for immunosuppression in organ transplantation.

Japan

A researcher from the Laboratory of Computational Biology and Risk Analysis is a coinvestigator on a 3-year grant by the Japan Society for the Promotion of Science for the development and design of opioids to combat cancer pain and is collaborating with Kobe Gakuin University on development of a new class of opioid peptides.

Scientists from the Laboratory of Reproductive and Developmental Toxicology are working with the School of Medicine, Kyoto, to investigate the role and function of the HSP70-2 heat shock protein expressed specifically in spermatogenic cells during the G2 phase of meiosis.

Collaborations between the NIEHS Laboratory of Reproductive and Developmental Toxicology and the National Institute of Animal Health, Tsukuba, are focusing on the identification of protein in complexes that bind to consensus sequences within gene recombination hot-spot regions and are involved in meiotic recombination.

A member of the Laboratory of Molecular Carcinogenesis and researchers in Japan are working to identify and characterize novel cytoplasmic signaling proteins.

Mexico

NIEHS epidemiologists are collaborating with investigators at the Instituto Mexicano de Seguredad Social, Mexico City, on protocols for collection of samples for a study of asthma in parents and children in Mexico City. Similarly, NIEHS pathobiologists are collaborating with the scientists from Mexico City to investigate the in vitro effects of air pollution particulate matter. The research is an effort to understand which components of air pollution particles in Mexico City are responsible for mediating cellular injury.

Norway

An NIEHS epidemiologist met with researchers at the National Institute of Public Health, Oslo, and the University of Bergen, in October 1999, to plan collection of samples of urine and blood for the Norway birth cohort study. The goal of the study is to enroll and perform follow-up on 100,000 women and their children, to determine subsequent effects of polychlorinated biphenyls (PCBs), phthalates, and arsenic on health. The NIEHS researcher and the Norwegian coordinators of this study also discussed the collection of additional samples of blood and urine for joint use in future chemical analyses to evaluate environmental exposures that may influence mothers' health and children's health and development. A pilot study is being conducted, and the nationwide study is scheduled to start in late 2000.

The NIEHS Epidemiology Branch is cooperating with colleagues at the University of Bergen for a study of facial clefts and associations with exposures to environmental chemicals. A parallel project with Norwegian scientists at the Medical Birth Registry of Norway will examine seasonal effects on premature delivery and genetic effects on gestational survival and on preeclampsia.

Russia

A scientist in the Laboratory of Molecular Genetics is working with the Russian Academy of Sciences, St. Petersburg, to characterize the formation of telomeric heterochromatin in *D. melanogaster.* The scientists have shown that disruptions of homologous or even nonhomologous telomeres cause derepression of transgenes that were repressed because they inserted into a telomere. Thus, the telomere associations that have been observed cytologically in many species may affect telomere structure and expression of neighboring genes.

Slovakia

An NIEHS pathologist is collaborating with the Hungarian National Institute of Hygiene, Budapest, and the Slovak Academy of Sciences, Bratislava, in a 2-year study of mice that are being fed with simazine, a pesticide. The Hungarian National Institute of Hygiene is conducting the pathology evaluation.

Spain

The Chief, Laboratory of Signal Transduction, is working with scientists at the University of Barcelona to investigate the expression of the alpha and beta isoforms of the human glucocorticoid receptor in a human bronchial epithelial cell line and their regulation by dexamethasone.

Ukraine

NIEHS epidemiologists are cooperating with the Ukraine Research Institute, Kiev, to study the toxicants in human placenta and reproductive outcomes in Ukraine. They have collected data on 3,000 pregnant women in two urban areas where pollution is high. Breast milk and placentas from 2,000 women have been analyzed for organochlorines and dioxin, and the results show low levels of these compounds, despite the high levels of pollution in the immediate environment, air, and water. Articles on the findings were published recently.

Taiwan

NIEHS epidemiologists are collaborating with the National Cheng Kung University, Tainan, to review and analyze 14-year follow-up data on children poisoned with PCBs. They are also performing follow-up on a cohort from a mass poisoning of 2,000 people by ingestion of cooking oil contaminated with PCBs and PCDFs (polychlorinated dibenzofurans), in central Taiwan.

Activities With International and Multinational Organizations

In efforts to focus on environmental epidemiology research in the sub-Saharan region, NIEHS is working with the International Society of Environmental Epidemiology to establish a branch in southern Africa. A workshop and training course organized by the leadership of the Society was held in February 1999, in conjunction with the meeting of the Epidemiological Society of Southern Africa, in South Africa's Eastern Cape Province. NIEHS provided major support for the workshop. Staff from the South African Medical Research Council (MRC) were the local leaders for this meeting.

A workshop on Children's Health and the Environment is planned for February 2001, at MRC in Cape Town, South Africa. Staff from NIEHS and MRC will focus on key environmental factors affecting the health of children, including ambient and indoor air quality and childhood exposure to lead, environmental tobacco smoke, pesticides, and contaminated water.

The Director, Office of International Programs, represented the NIEHS Director at the Program Advisory Committee (PAC) meeting for the World Health Organization (WHO) International Program on Chemical Safety (IPCS). PAC recommended further integration of the programs on food, water, occupation, environment, and chemical safety, because there are no real boundaries among the sciences underpinning these efforts. In addition, PAC emphasized the importance of the role of WHO in moving forward the integration of new science into public policy.

Extramural Programs

A large portion of the NIEHS financial resources supports extramural programs, including grants, cooperative agreements, and contracts that are awarded competitively to academic and research institutions. The Extramural Division offers a broad range of research opportunities for foreign scientists.

Research Grants

In FY 99, 30 research projects were undertaken, in Argentina, Australia, Canada, Chile, China, Denmark, the Faroe Islands, France, the Gambia, Italy, Japan, Mexico, Norway, Seychelles, Singapore, South Korea, Sweden, Yugoslavia, and Taiwan. The following are projects that include a foreign component:

- an epidemiologic study with Argentinean investigators, to examine the relationship between bladder cancer and arsenic exposure in Argentinean populations;
- a study in Australia to investigate the relative exposure of the infant in utero due to the mother's current environmental exposure to lead, compared with exposure due to mobilization of lead from maternal stores, especially from bones;
- work with a Canadian researcher on the mechanism of function of the *Schizosaccharomyces pombe* rad12$^+$ gene (a structural ortholog of the human BLM gene, with mutations that lead to Bloom syndrome), by studying the hypothesis that rad12$^+$ and BLM gene products negatively regulate the pathway for checkpoint control of DNA replication;
- a project that includes a Canadian researcher, to investigate lung disease in children in rural areas, many of whom are exposed to endotoxin and grain dust;
- a continuing study of the relationship between exposure to PCBs and thyroid function and development of the central nervous system in infants of the native Inuit population in Canada and extension of this study to a cohort of Greenland Inuit, by Danish investigators;
- an investigation of the relationship between airborne acidic air pollutants and the respiratory health of approximately 3,300 older adolescents living in 15 communities in Canada and the United States;
- research to validate a challenge test for arsenic in persons exposed to DMPS (2,3-dimercapto-1-propanesulfonic acid) in populations in Northern Chile and Mexico;
- a molecular biology–epidemiologic study that uses a significantly more sensitive and rapid method to detect benzene exposure by identifying specific chromosome alterations in blood samples from workers exposed to benzene in China;
- an investigation in China to determine whether biomarkers of aflatoxicosis caused by consumption of aflatoxin-contaminated foods can be modulated by ingestion of oltipraz or chlorophyllin;
- a project to evaluate a common polymorphism at the gene locus for aminolevulinate dehydrase, which is associated with elevated lead levels in blood of children and adults, to determine whether the polymorphism is a useful biomarker for effectiveness of a chelation therapy used in the treatment of lead poisoning in a population in Anhui Province, China;
- an epidemiologic study of persons in China who have been exposed to dithiocarbamates (known neurotoxicants), to delineate potential interactions of these compounds and their decomposition products within biological systems and to determine both the relevance of these interactions as mechanisms of toxicity and their utility as biomarkers of exposure;
- a comparison of reproductive function in two populations in China—one in a highly industrial area with multiple sources of exposure to industrial lead and one in a rural area with few opportunities for exposure to lead;
- studies (a) for follow-up of a prospective cohort in rural China to examine the relationship and interaction between levels of aflatoxin biomarkers and intrinsic risk factors and disease outcome; (b) to develop and validate molecular biomarkers of aflatoxin exposure in carriers and noncarriers of hepatitis B virus in Qidong Province, China, and the Gambia; and (c) to determine the effect of primary prevention methods in

Guinea, West Africa, by using a targeted strategy to reduce contamination in community settings, as evidenced by lower levels of aflatoxin biomarkers;

■ research to refine and validate molecular biomarkers of human exposures to aromatic and heterocyclic amines and to use the markers to determine the role of heterocyclic amines in the risk of colon cancer and the role of aromatic amines in the risk of bladder cancer in smokers and nonsmokers, in defined cohorts in China, Japan, and Singapore;

■ a study to determine whether patients with breast cancer in Denmark had an increased body burden of organochlorine compounds, as reflected in the serum concentration before the disease developed;

■ studies to assess the neurobehavioral effects of prenatal exposure to PCBs on the developmental outcomes for the offspring on the Faroe Islands;

■ an epidemiologic study of workers in France who have been exposed to vinyl chloride in the manufacture of polyvinyl chloride, to investigate the possibility of differential genetic susceptibility, by using mutation frequencies in biomarkers in blood lymphocytes; to examine DNA repair capability; and to evaluate whether the presence of a mutant protein is (a) a predictor of high frequencies of mutation, (b) a predictor of high risk for developing liver angiosarcoma, and (c) an early marker of the onset of liver angiosarcoma;

■ research with a French scientist to investigate the role of dietary carcinogens in colon carcinogenesis;

■ an epidemiologic study of the risk of endometriosis in women exposed to high levels of dioxins after a chemical company explosion in Seveso, Italy;

■ a prospective study of (a) the importance of lead levels in bone matrix and of DMSA-chelatable lead in soft tissue and (b) the effect of modification by the aminolevulinate dehydrase genotype, in the prediction of important health outcomes in a population of battery makers exposed to lead, in South Korea;

■ outreach to jointly sponsor conferences with Mexican colleagues that address problems related to hazardous wastes and their dump sites;

■ a study with Mexico to explore biosurfactants as a means to enhance removal of heavy metals from contaminated soil;

■ a project in Mexico City, Mexico, to examine the effect that maternal bone stores of lead accumulated from environmental exposures have on fetuses and infants during pregnancy and lactation;

■ a longitudinal study of lead exposure and reproduction in married men and women in Mexico, using potassium fluorescence and x-ray fluorescence to measure lead levels in bone;

■ a population-based, case–control study on the roles of heredity and environment in the occurrence of cleft lip and palate, in Norway;

■ studies to examine the neurodevelopmental effects of long-term exposure to low levels of methyl mercury (MeHg) in cohorts of children living in Seychelles, who are exposed to the compound by eating fish;

■ epidemiologic research in a smelter town and in an unexposed town in Yugoslavia (a) to determine whether the adverse effects of lead exposure persist beyond early childhood and (b) to test the hypothesis that there may be a strong association between cognitive function and concentration of lead in bones—the best marker of cumulative lead exposure;

■ a population-based, case–control study of squamous cell carcinoma of the skin and of bladder cancer in an area of Taiwan where exposure to arsenic through drinking water is still substantial;

■ research in a population of petrochemical workers in Taiwan, to quantify exposure–dose relationships for three types of biomarkers that show promise for estimating the internal dose of metabolic products of 1,3-butadiene, a human carcinogen; and

■ a molecular biology–epidemiologic study in Taiwan, to assess the relationship between exposure to aflatoxin and liver cancer, as quantified by aflatoxin B1–DNA adducts and hepatitis B status.

International Training and Research in Environmental and Occupational Health Program

NIEHS continues to participate with the Fogarty International Center, the National Institute for Occupational Safety and Health, and the Centers for Disease Control and Prevention in supporting the International Training and Research in Environmental and Occupational Health Program, a grant program for foreign scientists that is aimed at developing international training and research programs related to environmental health. A major goal of the program is to train scientists of other countries to deal effectively with environmental and occupational health problems through epidemiologic research, environmental monitoring, engineering control, and communication.

Through this program, awards are made to U.S. investigators to support the training of foreign nationals. The program provides for training at U.S. universities and institutions and for in-country training and is followed with financial assistance for conducting research in the trainee's home country. Participants in this program are foreign nationals who are involved in environmental or occupational health research and prevention activities in their home countries.

The training program extends to scientists and institutions in Central and South America, Eastern Europe, Thailand, Ukraine, and Vietnam.

International Meetings

During FY 99, NIEHS scientists were involved in various capacities in international meetings as follows:

■ invited participant at the 4th Meeting of the Global Information Network on Chemicals Project: Building and Promotion of Network for Information Exchange on Chemical Safety, in Tokyo, Japan, on November 25–28, 1998;

■ attended the Electron Spin Resonance Group Meeting on ESR Spectroscopy: Recent Advances and Applications, at the University of York, England, on April 10–16, 1999;

■ presented a seminar at the Institute of Cancer Studies, University of Sheffield, England, on April 14–15, 1999;

■ presented a report at the British Physiological Society Meeting, University College, London, England, on April 21–24, 1999;

■ invited speaker and made a presentation at the University of Western Ontario, London, and participated in the Annual Awards Day, on May 5, 1999;

■ attended the 10th Global Warming International Conference at the Yamanaski Institute of Environmental Sciences, Tokyo, Japan, on May 6–10, 1999;

■ participated in the Final Review Board

Meeting for Concise International Chemical Assessment Documents, in Stockholm, Sweden, on May 25–28, 1999;

■ made a presentation at the VIIth CEPH Annual Conference on Human Genetics, in Paris, France, on May 27–28, 1999;

■ made a presentation at the 19th International Conference on Yeast Genetics and Molecular Biology, in Rimini, Italy, on May 30, 1999;

■ chaired a session at the International Conference on Lead Exposure, Reproductive Toxicity, and Carcinogenicity, in Gargnano, Italy, on June 7–9, 1999;

■ served as keynote speaker at the World Congress of Mucus Cilia and Mucociliary Interactions, held in conjunction with the 12th Biennial Meeting of the International Society of Aerosols in Medicine, in Vienna, Austria, on June 11–16, 1999;

■ gave a presentation at the conference on Canadian Breast Cancer Research: Reasons for Hope, in Toronto, Ontario, on June 17–19, 1999;

■ presented a series of lectures on Mathematical Problems Arising From Biology, in Toronto, under a program sponsored by Cornell University, Ithaca, New York, on June 21–23, 1999;

■ made a presentation at the Toronto University conference on Hormonal Disruptors in the Environment and Child Health and Development, on June 25, 1999;

■ presented a lecture and presented data from dermal toxicity studies of diazoaminobenzene in mice and rats, at the Eurotox '99 meeting, in Oslo, Norway, on June 28–30, 1999;

■ presented a lecture at the Nobel Symposium on Estrogens and Women's Health—Benefit or Threat? in Karlskoga, Sweden, on June 28–July 2,1999;

■ presented a seminar at the Stowe School VIIth Symposium, in Lincolnshire, England, on July 7–11, 1999;

■ presented a report at the meeting on Frontiers in Crustacean Neurobiology, at the University of Hamburg, Germany, on July 10, 1999;

■ presented a lecture at the British Cancer Society Meeting, in Edinburgh, Scotland, on July 11–14, 1999;

■ presented an invited lecture at the Annual Meeting of the Japanese Society of Toxicology, at Hokkaido University, on July 21–28, 1999;

■ presented an invited lecture at the 17th Meeting of the Japanese Society for Bone and Mineral Research, in Osaka, on July 25, 1999;

■ presented lectures and made poster presentations at the Genetic Toxicology Gordon Research Conference, at Queens College, Oxford, England, on July 29–August 9, 1999;

■ invited attendee at the XVth International Symposium on Glycoconjugates, in Tokyo, Japan, on August 22–27, 1999;

■ made a presentation on Transgenic Animals, at the 3rd World Congress on Toxicology, in Bologna, Italy, on August 25–28, 1999;

■ invited attendee at the International Conference on Molecular Interactions of Proteoglycans, in Tokyo, Japan, on August 27–29, 1999;

■ invited contributor to the Humane Endpoints session at the 3rd World Congress on Alternatives and Animal Use in the Life Sciences, in Bologna, Italy, on August 29–September 2, 1999;

■ gave an invited presentation and invited poster presentations at the 11th International Conference on Cytochrome P-450, in Sendai, Japan, on August 30–September 2, 1999;

■ gave a presentation at the meeting of the International Epidemiology Association, in Florence, Italy, on August 30–September 4, 1999;

■ made an invited presentation at a Symposium on Progesterone and Antiprogesterins in the Next Millennium, in Jerusalem, Israel, on August 30–September 7, 1999;

■ served as speaker and session chairman at the Meeting of the German Society for Biochemistry and Molecular Biology, in Hamburg, in September 1999;

■ made presentations at the 11th Conference of the International Society for Environmental Epidemiology, in Athens, Greece, on September 4–8, 1999;

■ attended the 2nd International Workshop on the Function of BRCA1 and BRCA2, at Churchill College, Cambridge, England, on September 9–10, 1999;

■ presented lectures and made poster presentations at Dioxin '99, 19th International Symposium, in Venice, Italy, on September 12–17, 1999;

■ served as a member of the Expert Panel of the Health Effects Institute's Particle Epidemiology Re-analysis Project, which met in Ottawa, Ontario, on September 13, 1999;

■ gave a presentation at the Meeting of the London Chromatin Club, at the GKT Medical School, Kings College, England, on September 13–14, 1999;

■ made a presentation at the COST Mammary Gland Conference, in Tours, France, on September 16–18, 1999;

■ presented a lecture at the Conference on the Importance of Estrogen Hormone Action in the Male, in Caporizzuto, Italy, on September 23–24, 1999;

■ gave a presentation at the 6th European Meeting of Hepatocarcinogenesis, in Vienna, Austria, on September 23–26, 1999;

■ made a presentation at the 5th International Conference of Estrogen Receptor Knockouts, in Liège, Belgium, on September 26–28, 1999;

■ gave a presentation at the Conference of Retinoids and Nuclear Receptors, in Strasbourg, France, on September 26–30, 1999; and

■ made a presentation at the 58th Annual Meeting of the Japanese Cancer Association, in Hiroshima, Japan, on September 29–October 1, 1999.