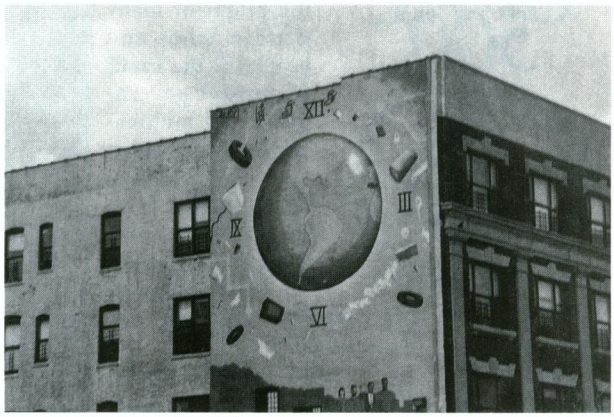
New Asthma Efforts in The Bronx

For more than 14 million Americans, the simple act of breathing can be a struggle because of the effects of asthma. Approximately a third of all asthmatics are children under age 18, and asthma is the most common chronic illness affecting children. In the United States, the proportion of people diagnosed with asthma has increased 45% over the last ten years and this rise continues, although it is not distributed uniformly among the population. According to the National Institutes of Health Guidelines for the Diagnosis and Management of Asthma, African-Americans are more than twice as likely as whites to die from asthma. One community, the Hunt's Point area of The Bronx in New York City, is working with environmental health scientists to determine the cause of these effects and to fashion solutions.



Paule Epstein Rogol/Mount Sinai Medical Center

Message in the mural. The Hunt's Point community in The Bronx is using more than pictures to fight sources of toxic exposures that may be resulting in high rates of childhood asthma.

Daunting Data

A recent study conducted by Vera De Palo and colleagues at the Mount Sinai Medical Center determined that rates of hospital admissions for asthma in New York City have increased by 12.7% in the last three years. The annual hospitalization rates for asthma were 7.5 times higher for minorities than for whites, and the boroughs of The Bronx and Harlem had the highest asthma admission rates in New York.

Other studies have shown similar results. A study by Ellen F. Crain and colleagues from the Albert Einstein College of Medicine, which was published in the September 1994 issue of *Pediatrics*, estimated the prevalence of clinically diagnosed pediatric asthma to be 8.6% in The Bronx, nearly twice the national average. This is likely to be an underestimate since wheezing without diagnosis of asthma totaled 4.2% nationwide, raising the total possible pediatric asthma cases in The Bronx to 12.8%.

Recently, Meyer Kattan, director of the Mount Sinai Pediatric Pulmonary Center and one of the principal investigators working in the National Cooperative Inner City Asthma Study (a multicenter effort supported by the National Institute of Allergy and Infectious Disease), has shown that a large proportion of children with asthma in the inner city have significant environmental and psychosocial risk factors that could have an impact on asthma morbidity. In particular, there has been considerable national attention focused on the recent finding by this study that cockroach antigens may be important contributors to asthma morbidity because 38% of 1,528 children tested were found to be allergic to the insects.

Many investigators now disregard outdoor air pollution as one possible cause of the rising incidence of asthma because overall air quality has improved in the last decade. However, this interpretation does not take into consideration the disproportionately high levels of air pollution that exist in minority communities. An analysis of EPA air quality control regions published in the March/April 1992 issue of the *EPA Journal* found that minorities are more like-

The NIEHS 30th Anniversary

Major Research Accomplishments Over the Years

Metal Toxicity

NIEHS studies have shown that blood levels of lead as low as 100 micrograms per deciliter impair mental development in children under two years of age, and continued lead exposure may result in decreased intelligence and poor academic performance. NIEHS studies have also shown that lead substitutes for calcium in many critical biochemical functions in the brain, impairing neurotransmitter function, energy metabolism, and other enzyme systems. Lead stored in bone may be mobilized and increase blood lead levels and cause changes in circulating levels of vitamin D. Recent NIEHS studies have shown that exposure to lead also contributes to increased blood pressure, particularly in males.

Cadmium accumulates in the liver and kidneys over a lifetime and may cause renal tube disease and bone disease. NIEHS studies have shown that pregnancy enhances cadmium accumulation in bone and that menopause and ovariectomies increase cadmium-induced bone loss.

NIEHS research is helping to set safe levels of fish consumption to avoid methylmercury.

Methylmercury exposure from consumption of fish during pregnancy may produce irreversible fetal brain damage. NIEHS studies determined the dose of methylmercury that produces fetal brain effects in a population of people with accidental acute methylmercury poisoning. From this information, guidelines have been established for safe levels of fish consumption during pregnancy.

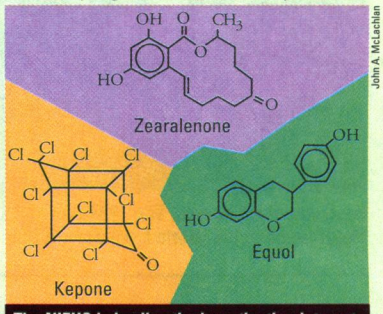
Endocrine Disruptors

The NIEHS has pioneered research on the health effects of endocrine disruptors such as dioxin, and the basic mechanisms through which they act, such as the Ah receptor and the estrogen receptor. In 1979, the NIEHS convened the first Estrogens in the Environment conference to promote scientific discussion of endocrine disruptors.

Potential endocrine disruptors such as pesticides, pharmaceuticals, industrial chemicals and by-products, incineration products, and natural plant components have been evaluated at the NIEHS since the 1970s for cancer-causing ability, reproductive effects, effects on the immune system, neurologic effects, and effects on the fetus and infants. These studies have led to the development and validation of biomarkers for estrogen and dioxin exposure, which provide early evidence of exposure and indicate the potential for adverse effects.

The mechanisms by which endocrine disrupting chemicals affect reproductive health are being investigated using molecular endocrinology approaches and the development and use of transgenic animals. A combination of *in vitro* and *in vivo* assays has been developed and evaluated at the NIEHS with the purpose of providing a rapid, reproducible means to determine the estrogenicity or dioxin-like potency of environmental chemicals.

In 1976, NIEHS scientists developed a mouse model that mimicked human exposure to DES. In 1988, the NIEHS reported that PCB compounds were potentially estrogenic.



John A. McLachlan

The NIEHS is leading the investigation into natural and synthetic chemicals that may disrupt the endocrine system.

ly to live in nonattainment areas for criteria pollutants such as ozone, lead, carbon monoxide, and particulates.

The Bronx is one of the most racially segregated and poorest areas in the United States, with a high concentration of polluting facilities. The Bronx generates approximately 5% of New York City's commercial waste, yet it processes 21% of the municipal total; it generates 29% of city sludge, yet it treats 70% of this waste. The Bronx also houses the largest sludge/pelletization plant in the Northeast and the Bronx-Lebanon medical waste incinerator, which violated federal emission standards 86 times in a period of 6 months during 1994, according to the *New York Times*.

Researchers believe that this high pollution burden concentrated in The Bronx is having a negative impact on the health of residents. Harold Osborn, chairman of the Department of Emergency Medicine at Lincoln Hospital in New York, has documented dramatic increases in asthma-related hospitalizations. Osborn estimates that, of the 15,000 patient visits to the hospital last year due to acute asthma attacks, between 1,500 and 2,000 patients were hospitalized. Lora Lucks, principal of P.S. 48 located in the Hunt's Point area of The Bronx, reported that 293 out of 1,143 students in the school experienced asthma attacks or breathing problems, bolstering the claim of negative health effects. According to an EPA report released last April, odors in The Bronx, possibly from a nearby sludge pelletizing plant, became so severe during the week of 4 February 1996, that 14 of 30 students in one class developed respiratory problems and 11 were hospitalized. P.S. 48 had to hire a nurse to treat asthmatic students, but the nurse now suffers from asthma herself and is often unable to perform these duties.

Community residents believe that the breathing problems they suffer are caused by pollutants emitted intermittently from nearby waste management facilities. In a letter, members of the Hunt's Point Awareness Committee stated recently that their main concern is to find "what is in the air that is causing us to suffer respiratory problems and high asthma rates." Community complaints about these health effects have prompted Representative José E. Serrano (D-New York) and Borough President Fernando Ferrer to ask Mount Sinai Medical Center to unite with other agencies to address this issue.

Community Solutions

To this end, the Community Outreach and Education Program of the Mount Sinai Environmental Health Sciences Center, an extramural research center funded by the NIEHS, has proposed a research and intervention program for The Bronx. This program will seek to find if correlations exist between levels of outdoor air pollution and asthma hospitalization rates and to increase the numbers of nurses specially trained in asthma management in the community (this is important in a community where the ratio of 2 doctors per 1,000 residents pales compared to 60 per 1,000 on the Upper East Side of Manhattan). The proposed program is based on a strong partnership between community leaders, Mount Sinai researchers, physicians, nurses, and the Hostos Community College, which is providing a geographical information system for the data analysis and a community-based nurses' training program.

For the program's partners, the creation of a mechanism for bidirectional communication is crucial. Through this approach, the neighborhood residents will not be used solely as study subjects but as collaborators in a project that seeks to address their needs and concerns while finding answers to fundamental scientific questions. The observations and expertise of community residents will be integrated into the research design so that the residents can become "researchers" in their own neighborhood.

Luz Claudio

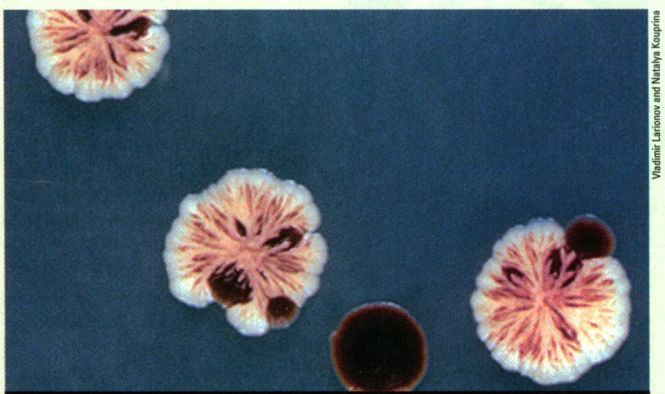
Signal Transduction and DNA Repair

A better understanding of environmental disease requires a basic knowledge of the molecular mechanisms of cell communication called "signal transduction pathways." Signal transduction research was expanded at the NIEHS ten years ago with an initiative in cell signalling. This inititiative was led by Martin Rodbell, who received the Nobel Prize for Physiology or Medicine in 1994 for his discovery of the guanosine triphosphate (GTP)-binding proteins that couple cell surface receptors for many important hormones to the intracellular proteins that regulate cell activity. NIEHS researchers have discovered a new signalling pathway for controlling calcium entry into cells that ultimately produce changes in cell movement and secretion. In addition, researchers have identified new signalling pathways activated by GTP-binding proteins for ion channel regulation by inositol phosphates and protein phosphatases, which are the primary targets of some of the most potent industrial xenobiotics and microbial toxins in the environment. Research has also focused on genetic studies of the signalling proteins controlling cell proliferation and led to the identification of proteins that are essential for preventing cancers of the breast and the prostate.

NIEHS scientists have made several discoveries in the area of DNA repair, including a system called "replication repair" which circumvents DNA damage using some of the components of DNA replication itself, as well as "antimutagenic" DNA polymerases that sharply reduce mutagenesis by DNA damage, such as ultraviolet irradiation.

Between 1994 and 1996, NIEHS studies found that genetically unstable human tumor cells have defects in genes of DNA mismatch repair (MMR), thus establishing the functional significance of five human MMR genes, and demonstrated that these defects can be overcome by chromosome transfer. A human enzymatic activity for correcting DNA containing multiple unpaired nucleotides was also discovered by NIEHS scientists, as well as another gene, *PCNA*, that functions in human MMR.

NIEHS scientists showed that DNA double-strand breaks are repaired via recombination in yeast and that such repair is sensitive to DNA divergence, sometimes causing chromosome loss. NIEHS research also identified the process of repairing double-strand breaks that can be used to clone human DNA in yeast, including cloning specific disease genes. Studies have shown that a single unrepaired double-strand break, even in dispensable DNA, can arrest cell division and cause lethality. NIEHS studies also showed that recombinational DNA repair systems can also be deleterious, playing a role in deletion mutagenesis. NIEHS studies showed that MMR has a limited capacity and can be saturated, leading to hugely increased mutation rates and, under certain conditions, cell death.



Vladimir Larionov and Natalya Kouprina

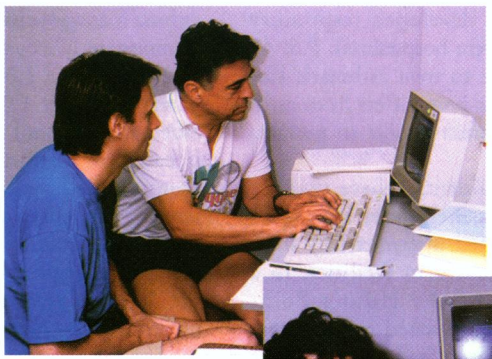
NIEHS scientists are working to clone human DNA, including specific disease genes, in yeast.

International Cooperation and Technology Transfer

The National Toxicology Program (NTP) has been looking for ways to increase the number of chemicals tested for toxicity and carcinogenicity without increasing spending as study costs rise, financial resources dwindle, and the list of chemicals to be tested grows. An innovative program may provide the means to test more chemicals through cooperation with other countries.

Because stringent guidelines regulate chemical testing in the United States, research conducted in other countries does not always meet U.S. standards. For example, many laboratories in Central European countries do not have the experience or the resources to conduct hazard identification studies that meet U.S. standards. Scientists at the NIEHS realized that if U.S. federal agencies assisted laboratories in Central European countries in improving the quality and acceptability of their studies, this information could be used by the NTP to increase the number of chemicals evaluated.

Through a unique collaboration, the NIEHS and the International Agency for Research on Cancer (IARC) are working with the National Institute of Hygiene (HNIH) in Budapest, Hungary, and the Institute of Preventive and Clinical Medicine (IPCM) in Bratislava, Czechoslovakia, to share technology and conduct a hazard identification study. "The idea was that, if we could collaborate, we could learn from them and they could learn from us," said Gary Boorman, NIEHS project officer for the collaboration, "and we thought it would be exciting to do a study together."



Steve Edgerton, Image Associates

Scientific souvenirs. (l to r) Researchers Zsolt Kelecsenyi, Andras Surjan, Dagmar Zeljenkova, and Jaroslav Cerny learn the TDMS.

The International Cooperation and Technology Transfer will involve training scientists from the foreign institutes to conduct a mouse study on the chemical Simazine, an herbicide of interest to both the United States and Central Europe. The mouse studies will be conducted at IPCM because the institute has an established animal care program, good facilities, and strong toxicology/pharmacology expertise, Boorman said. The poststudy pathology support will be conducted at HNIH because it has an excellent pathology department, he said.

The NIEHS and IARC will review the study design, as well as provide advice and support in developing standard operating procedures and administering good laboratory practices. The IARC will also provide advice on pathology and assist in assuring that the study and its results meet the standards for IARC monographs.

The NIEHS will provide a total of $194,000 for the study and is responsible for training the scientists on how to use the Toxicology Data Management System (TDMS), software used for NTP toxicology studies. Dagmar Zeljenkova and Jaroslav Cerny from IPCM, and Zsolt Kelecsenyi and Andras Surjan from HNIH spent the week of July

Integrating Fundamental Research, Toxicology, and Risk Assessment

The NIEHS is leading research in the fundamental link between basic research, toxicology, and risk assessment in the analysis and design of experimental research. The NIEHS has developed the world's largest and most systematic database of toxicology data on about 2,000 environmental and occcupational chemicals. The database, which contains information on carcinogenesis, as well as noncancer endpoints including reproductive, developmental, immunotoxicological, and neurotoxicological effects, is helping to reduce uncertainty in human risk.

The NIEHS and NTP are partners in research and risk assessment.

In 1987, NIEHS scientists had a profound influence on the field of genetic toxicity through the publication of a paper, entitled *Prediction of Chemical Carcinogenicity in Rodents from In Vitro Genetic Toxicity Assays*, that led to the utilization of data to predict the outcome of two year rodent bioassays.

Many of the studies carried out by the National Toxicology Program to identify toxic or carcinogenic hazards associated with occupational or environmental chemical exposures have resulted in federal regulations affecting the permissible exposure limits and means of handling chemicals. These include exposures to chemicals such as lead, benzene, butadiene, methylene chloride, various phthalates, and dioxin, as well as dyes, drugs, food additives, and byproducts of molds and other natural food contaminants.

Development of Alternative Methods in Toxicology

The NIEHS has been working to develop alternative methods and approaches to the use of animals in research and testing. In 1994, the NIEHS established an *ad hoc* Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which includes representatives from 15 federal agencies.

Several alternative models have been developed by NIEHS scientists, including transgenic models, such as the TSG p53 transgenic mouse, which contains a single wild-type *p53* tumor suppressor gene, and an inactivated *p53* gene, which was inserted in the original founder mouse by homologous recombination, or the "gene knockout" technique. NIEHS scientists also developed FETAX, the Frog Embryo Teratogenesis Assay, which utilizes the embryos of the South African clawed frog, *Xenopus laevis*. FETAX endpoints can potentially detect all four manifestations of mammalian developmental toxicity. Genetically engineered cell systems and a functional toxicology program to assess the biological activity of chemicals using transgenic cell lines, were also developed by NIEHS scientists.

Mitch Eddy

The development of transgenic mice at the NIEHS has opened new doors to genetic research.

7–12 at the NIEHS learning how to use TDMS and the Laboratory Data Acquisition System (LDAS). LDAS is the microprocessing system used by scientists to collect and organize animal data. The NIEHS is providing two computer workstations loaded with LDAS for each institute's laboratory.

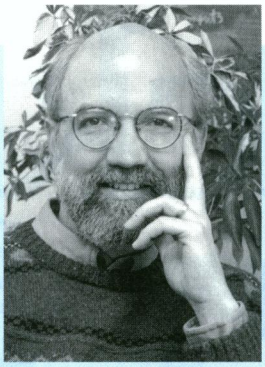
Occasionally, the Czechoslovakian and Hungarian scientists will dial into the TDMS mainframe at the NIEHS and transmit their data. This will enable NTP scientists to monitor the data and the quality of the study as it proceeds. According to Mike Rowley, project officer for the NTP computer support contract, the July training session went smoothly. "It was great; we talked to them for months over the phone, but nothing can compare to them actually being here," he said. "They picked right up on both TDMS and LDAS."

The visiting scientists said the information they have gained will enable them to study other chemicals in the future. According to Boorman, the ultimate goal is for the Central European scientists to have the technology to do more studies on their own.

The collaboration offers not only an opportunity for the Hungarians and Czechoslovakians to learn from the Americans, but for NTP scientists to learn from their foreign colleagues. Because many Central European laboratories face economic limitations, they are more active in searching for ways to reduce costs, which the NTP is also aiming to do. In addition, having outsiders learn and review NTP study methods will provide a chance for them to offer suggestions about the methods, Boorman said.

Upon completion of the study in 1998, NIEHS scientists will review the data and pathology specimens, as well as carry out a pathology peer review with HNIH pathologists. The NIEHS will help in the publication and dissemination of the study report. The study materials will then be stored in the NTP archives.

Wilcox Elected President of Society for Epidemiologic Research


Steve McCaw, Image Associates

Allen Wilcox, chief of the NIEHS Epidemiology Branch, has been elected president of the Society for Epidemiologic Research. The society is an international professional organization for epidemiologists and has over 3,000 members.

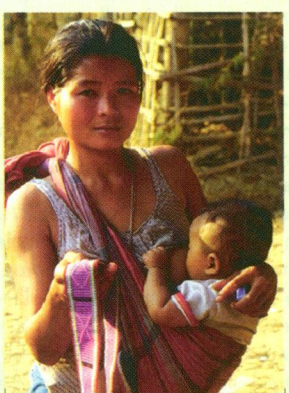
Wilcox will serve on the society's executive committee for three years—one each as president-elect, president, and past president. During this time, Wilcox says he plans to achieve several goals. "One is to enhance the scientific content of the [society's] annual meeting to promote more interaction between senior and junior epidemiologists," he said.

Also, "I'd like to help our profession focus on issues most crucial to our future. One issue that seems especially important is the use of molecular genetics," Wilcox said. "Epidemiology, like all biologically related disciplines, is being transformed by access to the genome. There are new scientific opportunities, and also sensitive issues of confidentiality and the protection of privacy that we need to address as a profession."

Wilcox led a fertility research project that found in 1995 that intercourse during the six days prior to ovulation would most likely result in conception, contrary to the conventional belief that fertility peaks during ovulation. Wilcox has received many honors, including a U.S. Public Health Service Commendation and Outstanding Service medal. He was also elected a fellow of the American College of Epidemiology and served as president of the Society of Pediatric Epidemiologic Research.

Sensitive Subpopulations

The NIEHS has worked to identify certain populations that are predisposed to environmental diseases based on factors such as age, gender, and genetic makeup. NIEHS studies have shown that the pesticide metabolite DDE in breast milk reduces the lactation period of women, a finding which affects developing countries in particular, where breast-feeding is the healthiest and cheapest way to nourish infants. DDE has also been shown to affect neurological function in infants. A 1996 NIEHS study showed that *in utero* exposure to PCBs in concentrations slightly higher than those experienced by the general population can have long-term effects on intellectual function of infants.

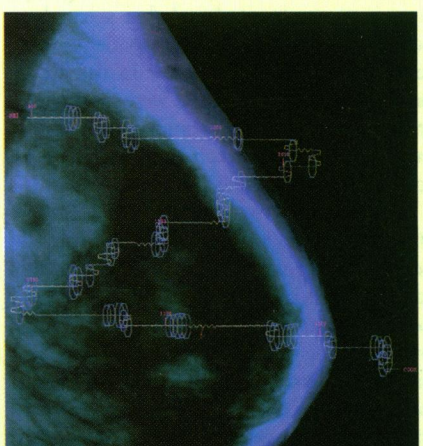

NIEHS research is uncovering the particular effects of environmental chemicals on sensitive subpopulations such as women and children.

NIEHS scientists have also found that certain occupations and occupational exposures are highly associated with *ras*-mutation positive acute myeloid leukemia. In studying lung cancer, NIEHS scientists have found one of four known examples of an exposure-specific pattern of critical target gene mutation in human tumors in the lungs of uranium miners.

NIEHS scientists were the first to observe that individuals with inherited defects in the carcinogen metabolism enzymes glutathione *S*-transferase M1 (GSTM1) and glutathione *S*-transferase T1 (GSTT1) have increased risk for bladder cancer and myelodysplastic syndrome, respectively.

Women's Health

NIEHS research supports the probable role of environmental factors and chemical carcinogens in the etiology of breast cancer, a major health problem for women. In 1995, NIEHS scientists, along with the University of Utah Medical Center, isolated the tumor-suppressor gene *BRCA1*, which is thought to play a role in the hereditary breast and ovarian cancer.


NIEHS advances in women's health include isolating the gene for inherited breast cancer and pinpointing the timing of a woman's fertility.

NIEHS studies have shown that a woman's fertility can be impaired by smoking, occupational exposure to nitrous oxide, vaginal douching, and consumption of caffeinated beverages. In 1996, NIEHS scientists found that a woman is most fertile during the six days in her menstrual cycle that end on the day of her ovulation, contrary to the traditional belief that women are most fertile during ovulation. NIEHS studies have also shown that at least 25% of pregnancies are lost very early, before women even realize they are pregnant.