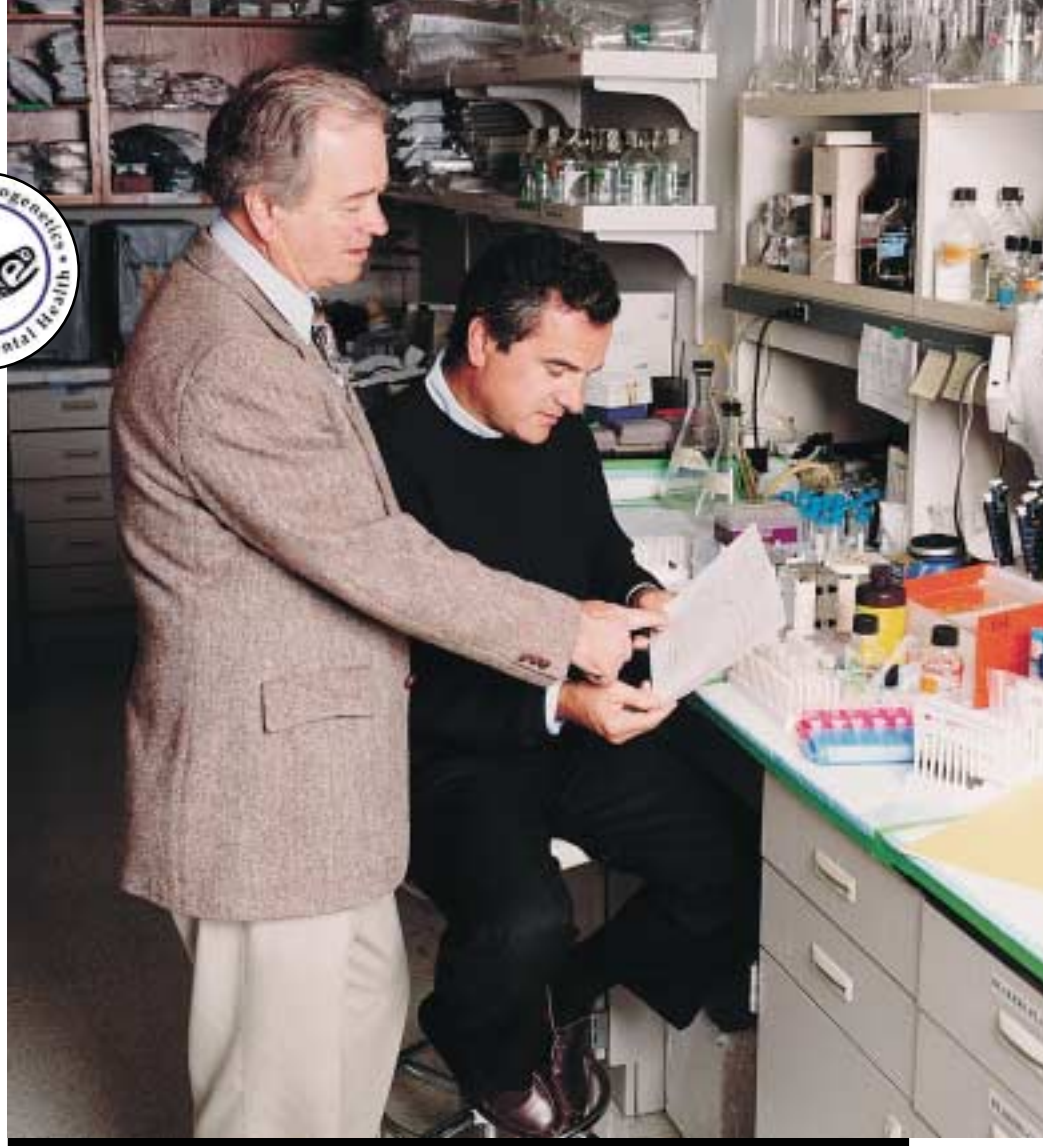
Center Attacks Core Issues in the Land of Apples



A center of widespread appeal. Activities at the CEEH run the gamut of science from research studies such as those of Lucio Costa (above, right) and Clement Furlong (above, left) on pesticides, to laboratory training for all levels of students, to outreach programs such as health fairs.

Photos: (left, center) Kathy Sauber; (right) Joel Levin

Seattle, Washington, is an area perhaps best known for high-tech names like Microsoft, Immunex, and Amazon.com. However, much of Washington is rural. The state is a leading producer of tree fruit, berry, and flower crops, which require extensive hand labor—picking and pruning—for cultivation and harvest. To meet this demand, Washington's population of seasonal and full-time farmworkers now numbers about 90,000, according to a report titled *Agricultural Work Force in Washington State 1999*, published in June 2000 by Washington State Employment Security. Many of these workers and their families are regularly exposed to pesticides, as well as to wood smoke, because woodstoves are a common source of heat in the rural areas where they live.

Researchers at the University of Washington Center for Ecogenetics and Environmental Health (CEEH), located in Seattle, study susceptibility to pesticides, particulate matter in wood smoke, and a wide range of other toxicants from methylmercury to solvents to aflatoxins. The CEEH, one of 21 enviromental health sciences centers funded by the NIEHS, focuses primarily on the interactions among genetics, the environment, and human health. "The development of complex diseases such as many cancers and some chronic degenerative neurological diseases may never be explained by genetics or environmental exposures alone," says CEEH director David L. Eaton, a toxicology professor in the Department of Environmental Health and associate dean for research at the School of Public Health and Community Medicine. "CEEH researchers are taking a multidisciplinary approach to study the biochemical and molecular mechanisms that influence individual responses to environmental risk and exposures."

Approximately 50 CEEH investigators work in many disciplines, including medical genetics, epidemiology, toxicology, and pharmaceutical sciences. They are organized into five research cores focused on human systems. The Biotransformation Core studies the metabolism of drugs and nondrug chemicals, and the Carcinogenesis Core studies interactions between environmental exposures and genetic traits affecting cancer. The Reproductive and Developmental Toxicology Core studies the molecular and biochemical mechanisms of reproductive and developmental toxicity, including birth defects, and the Neurotoxicology Core studies mechanisms of neurotoxic damage, including potential environmental factors that may influence the development of chronic neurologic diseases such as Parkinson and Alzheimer diseases. Finally, the Cardiorespiratory Susceptibility Core studies cardiac and respiratory function and disease, including asthma and sensitivity to air pollution.

The research cores are supported by five facility cores. The Molecular Biomarker Laboratory Core develops gene assays and provides high-throughput genetic analysis. This core is currently developing a new facility that will provide CEEH investigators with access to gene expression array analysis, an addition that will allow investigators to study the effects of a variety of exposures or disease conditions on the expression of over 40,000 genes on the human "gene chip" (a glass chip that can be used to screen a single DNA sample for hundreds or thousands of genetic polymorphisms). Arrays for rat and mouse genomes are also under development. Access to flow cytometry, laser cytometry–confocal microscopy, and digital image analysis is provided by the Analytical Cytology Core. The Transgenic Animal Support Core develops transgenic strains and currently maintains about 70 transgenic lines for investigators, and the Molecular Structure Visualization Core provides three-dimensional images of molecules. The fifth core, the Electron Spin Resonance (ESR) Core, uses magnetic resonance signals to detect and measure the presence of free radicals in tissues.

Core Collaborations

The CEEH's organization and the wide variety of services it provides have fostered

numerous collaborations both within the center and with outside facilities. For example, the nearly unique opportunity to work with both ESR and analytical cytology technology has given a strong boost to CEEH research into the role of the antioxidant glutathione (GSH) in protecting cells from oxidative stress. This basic research may have wide implications for human health, because free-radical injury is thought to promote aging and contribute to rheumatoid arthritis, many types of cancers, neurologic disorders such as Alzheimer and Parkinson diseases, and other chronic health problems.

Environmental health professors James S. Woods, director of the ESR Core, and Terrance Kavanagh, director of the Analytical Cytology Core, are collaborating on GSH research. They are using ESR technology to measure free-radical production in intact cells exposed to prooxidant chemicals such as menadione and potassium dichromate. Initial results suggest that the ability of a cell to increase GSH production quickly may be more important than sustained high GSH production in protecting cells against damage caused by free radicals. In future work, Woods and Kavanagh plan to use ESR along with adherent cell analysis and sorting fluorescent microscopy to determine if transgenic cells and mice that have increased capacities for GSH synthesis are resistant to various chemicals that generate free radicals. This project has also used the services of the Transgenic Animal Support Core to develop mice that have increased ability to produce GSH, and those of the Molecular Biomarker Laboratory Core to test for the expression of the genes associated with GSH production.

Other CEEH researchers have focused on pesticide exposures, specifically variations in the enzyme paraoxonase, which breaks down certain pesticides including diazinon and chlorpyrifos. Lucio Costa, director of the Neurotoxicology Core and a professor of environmental health, and Clement Furlong, a member of the Neurotoxicology Core and a professor of medical genetics, have determined that people can vary in both the amount and type of paraoxonase their bodies produce. As a result, the ability to process common organophosphate insecticides can vary dramatically among individuals—one adult can have 15 times the paraoxonase blood concentration as another, for instance. Low blood concentrations of paraoxonase, which are linked to less efficient processing of organophosphate pesticides, have also been have been correlated to carotid artery disease.

During the first step in chemical oxidation of an organophosphate, an intermediate oxygenated form of the pesticide, called the oxon form, is created. "We've found that the genetic differences in susceptibility bear more on the oxons than on the parent compounds, and that the oxon form is dramatically more toxic than the parent compound," says Furlong. Although the oxon form of a pesticide is generally produced by the body following exposure to the less toxic thioate form of the pesticide, some commercial formulations may contain small but significant amounts of the oxon form, and more may be formed following application, according to Furlong. Furthermore, says

Furlong, "Safety studies have looked at the parent sulfur compounds almost exclusively, not at the oxons."

Furlong and Costa's research is using the services of the Transgenic Animal Support Core, which is generating PON1 knockout mice that express isoforms of human *PON1*, the gene that codes for creation of human paraoxonase. In addition, Elinor Adman and coworkers of the Molecular Structure Visualization Core are in the process of crystallizing paraoxonase to determine its structure. Better information on the molecule's structure may allow paraoxonase to be engineered or modified to serve as a therapeutic agent for pesticide poisoning.

Furlong has developed a high-throughput assay for determining the type and amount of paraoxonase in blood, which reflects an individual's susceptibility to the oxon form of specific organophosphate pesticides. Currently, Costa and Furlong are working with other investigators in the university's NIEHS-supported Children's Environmental Health Research Center to study pesticide exposures in children, especially children of farmworkers. This project was based in part on the work of investigators in the Reproductive and Developmental Toxicology Core, which examines critical issues of age- and sex-related susceptibility that are often overlooked, says core director and environmental health professor Elaine Faustman, who also heads the children's health center.

The CEEH has also nurtured the development of another major research center, the U.S. Environmental Protection Agency (EPA) Northwest Center for Particulate Air Pollution and Health, which is devoted to detailing exposures, health effects, dosimetry, biomarkers, and mechanisms of particulate matter, especially that found in wood smoke. This center grew out of the work of the Cardiorespiratory Susceptibility Core and is headed by core director Jane Koenig, an environmental health professor. Koenig and colleagues recently found significant associations between amounts of fine particulate matter in the air and emergency room visits for asthma by Seattle children eattle [see *EHP* 107:489–493 (1999)]. They also found that some types of gaseous pollutants, such as carbon monoxide, and particulate matter of various diameters correlated with increased cardiovascular mortality in Phoenix, Arizona [see *EHP* 108:347–353 (2000)].

The CEEH is also seeding future work through its successful Pilot Project Program. A total of 24 pilot projects were funded during 1995–2000, the period of the first five-year CEEH grant. Results from 10 of the first 20 of these projects provided the basis for major grants totaling over $5.5 million. In addition, 11 journal articles and 12 abstracts have been published based on results from these pilot projects.

Addressing Ethical, Legal, and Social Issues

The CEEH is not only fostering basic research into gene–environment interactions but is also looking ahead to understand the potential ramifications of this research. This year the CEEH added a new Ethical, Legal, and Social Issues (ELSI) Core. The ELSI Core, which includes investigators from the Schools of Law, Medicine, and Public Health and Community Medicine, identifies and studies ethical, legal, and social implications of scientific advances in the study of gene–environment interactions ("ecogenetics") and environmental genomics, or the study of how environmental factors affect the overall expression of genes in human tissues. The ELSI Core is especially interested in how these issues affect genetic variations that are common and have a low probability of causing disease alone, but that may increase disease risk when combined with certain environmental exposures.

The focus of the core's initial case study is on pesticide poisoning susceptibility. "We want these case studies to be science-based, which is why we're starting with a gene–environment interaction, where much of the science has already been done and where there is significant potential for ethical and legal ramifications," says Wylie Burke, ELSI Core deputy director and chairman of the Department of Medical History and Ethics. For example, once tests are commercially available to determine paraoxonase status and susceptibility to the effects of certain pesticides, extermination companies might consider the use of such tests in their hiring. "Even though that makes logical sense and seems like a way to protect people who are susceptible to certain chemicals, testing is also a way to label people and to deny them vocational opportunities," says Burke. Susceptibility research may also have implications for product testing and development. "Should persons with sensitive genotypes be used to set safe or minimum standards for exposure?" asks Burke.

The ELSI Core also works closely with a public health genetics academic program sponsored by the Department of Epidemiology in the School of Public Health and Community Medicine. This program, developed by ELSI Core director Melissa Austin, trains university graduate students in the study of human genetics in the context of public health.

Community Outreach and Education Program

In addition to studying the future ramifications of its research, the CEEH is also committed to helping the public make good environmental health choices through the work of its Community Outreach and Education Program (COEP). The program's wide range of activities is illustrated by some of the artifacts found in its offices. These include artwork created by students living near Chornobyl and brought to the CEEH by visiting Russian teachers, plaster fish used to indicate seafood type and portion size during interviews of non-English-speaking Asian–Pacific Islander communities, and a mercury exposure board game created by school students, the result of a curriculum developed during teacher training workshops.

In its first years, the COEP published a 1999 study of seafood consumption and potential health effects from seafood contamination among Asian–Pacific Islanders through the EPA, piloted an Environmental Risk Information Service hotline, and partnered with the American Lung Association's Master Home Environmentalist Program, which trains volunteers to help local residents reduce the risk of indoor air pollutants in their homes.

The COEP recently joined forces with an existing NIEHS K–12 program titled Health and Environmental Resources for Educators at the University of Washington (HERE@UW). HERE@UW brings to the partnership a variety of curricula, expertise in conducting teacher workshops, and Tox-in-a-Box, an outreach kit in a briefcase that gives environmental health professionals the training and props they need to make successful K–12 classroom presentations.

In addition to K–12 outreach, the COEP was actively involved in planning a 29–30 September 2000 town meeting, "Voices for Healthy Environments, Healthy Communities," hosted by the CEEH [see sidebar, next page]. "The planning process for the meeting has given COEP staff an opportunity to connect with a wide range of community-based organizations," says HERE@UW manager Jon Sharpe. "Future COEP opportunities will no doubt grow out of these new relationships." **–Kris Freeman**

Seattle Town Meeting Targets Environmental Justice

Environmental justice was a key theme of community testimony at an NIEHS town meeting titled "Voices for Healthy Environments, Healthy Communities," held 29–30 September 2000 in Seattle, Washington. Other major themes included concerns about the health effects of pesticide exposures (especially among farmworkers), groundwater contamination from radioactive waste at the Hanford Nuclear Site, and a desire for environmental health researchers to be advocates for disease prevention, not just providers of scientific data. More than 200 people attended the meeting, which was cosponsored by NIEHS and the University of Washington Center for Ecogenetics and Environmental Health along with several community groups and the regional office of the U.S. Environmental Protection Agency.

The NIEHS has held a series of town meetings throughout the country during the past four years in order to solicit public input in setting its research agenda. The meetings also provide a forum in which the American public can speak directly with NIEHS director Kenneth Olden and senior NIEHS staff to express their concerns and local experiences with environmental health problems.

The morning before the meeting opened, Olden and other NIEHS representatives visited Seattle's South Park neighborhood, which has a high percentage of low-income and minority residents, and high loads of air, noise, and chemical pollution from freeways, airports, and industry. U.S. Congressman Jim McDermott (D–Washington) and Washington State Representative Velma Veloria accompanied NIEHS officials on the tour.

The town meeting opened Friday evening with a welcoming ceremony that included dancing and comments from members of the Suquamish Tribe, and presentations by more than 20 community groups, tribal nations, and youth groups. Saturday morning began with addresses from Olden and Washington State Senator Rosa Franklin, a retired nurse, who spoke on environmental justice. Said Franklin, "A growing body of evidence continues to show that low-income people—a disproportionate percentage of whom are people of color—are more exposed to environmental pollutants than the general population."

The theme of environmental justice continued during Saturday's open microphone session, which included Latino farmworkers who testified about the effects of pesticide exposures. "Every time a worker moves a piece of fruit or a leaf, they get exposed to pesticides. They get overexposed," said Guillermo "Bill" Nicacio, a family service worker with the Washington State Migrant Council. "During apple-thinning season we can tell who is thinning because of the redness of their eyes and the rashes on their hands." During his keynote address, Lupe Gamboa, Washington State regional director of the United Farm Workers of America, AFL-CIO, said, "Farmworkers are treated this way because they don't have political power and they don't have economic power." Gamboa also expressed concern about the lack of training for health care workers in detecting pesticide-induced injury and illness.

Kris Freeman

Focused on the problem. Attendees at the NIEHS town meeting in Seattle consider information and opinions on the disparate effects of environmental pollutants on different populations.

Throughout the meeting, participants pressed for more community involvement in research projects, and for researchers to help tackle the environmental health problems that communities identify. "We do need research, but we also need action once we get the information. We need researchers to work with the communities to find solutions to the problems as well," said Yalonda Sindé, executive director of the Seattle-based Community Coalition for Environmental Justice. Carol Dansereau, executive director of the Washington Toxics Coalition, added that researchers should speak out about the limitations of scientific studies to predict exactly where pollutants will end up and how they will affect different populations. "We want to see decisions based not on risk assessment but on prevention," she said.

Saturday afternoon workshops were led by community and labor leaders, center researchers, and representatives of local and federal agencies and industry. Congressman McDermott chaired a session titled "Air Pollution (Indoor and Outdoor) and Asthma." Other workshop topics addressed chemical health risks to agricultural workers and their families and environmental justice issues. A series of smaller groups discussed topics including water quality, contamination of seafood by marine toxins and pollution, toxic waste, children's environmental health, and drinking water quality.

Further information on the town meeting is available at the "Voices for Healthy Environments, Healthy Communities" Web site at **http://depts.washington.edu/townmeet/**. **–Kris Freeman**