Understanding Gene–Environment Interactions

Geneticists are making headlines almost daily as they decode the human genome. By the year 2005, it is expected that researchers will have most of the sequence data in hand. Yet genes are proving time and again to be only part of the complex disease picture, as many common diseases such as cancer, Alzheimer's disease, osteoporosis, and asthma are being shown to have crucial environmental elements.

Now the NIEHS is launching a $60 million Environmental Genome Project to elucidate the intricate interactions between genes and environment. Relying heavily on technology developed by the Human Genome Project, the Environmental Genome Project seeks to determine genetic sequence diversity data for the U.S. population on more than 200 genes known to control susceptibility to environmentally linked diseases, and to develop a central database of polymorphisms for these genes. Then, on the basis of subsequent epidemiological studies, extramural researchers at centers nationwide will determine how the polymorphisms account for increased risk of or resistance to disease upon exposure to specific toxins or carcinogens. In addition, the project will look at environmental factors ranging from diet (including what people eat and how they prepare food) to effects of exposure to chemical mixtures, which is another NIEHS priority.

"This is very different [from] the Human Genome Project, which is much more focused on disease genes," says Karl Kelsey, a molecular epidemiologist at Harvard University. "This will enable us to develop better intervention strategies for individuals and populations," Kelsey says.

Disease prevention is more complex than just targeting genes. Few diseases are the consequence of a single genetic or environmental event, says NIEHS Director Kenneth Olden. For example, only a small percentage of all cancer cases can be attributed to a single defective or mutant gene, typically identified from familial clusters of disease. Instead, common allelic variants of susceptibility genes with relatively low penetrance account for a higher percentage of cancers and other chronic diseases overall. Thus, properly controlling environmental, occupational, or lifestyle exposures could prevent more diseases than just those caused by rare, highly penetrant alleles that lead to familial clusters, explains Jack Taylor, head of the NIEHS molecular and genetic epidemiology group.

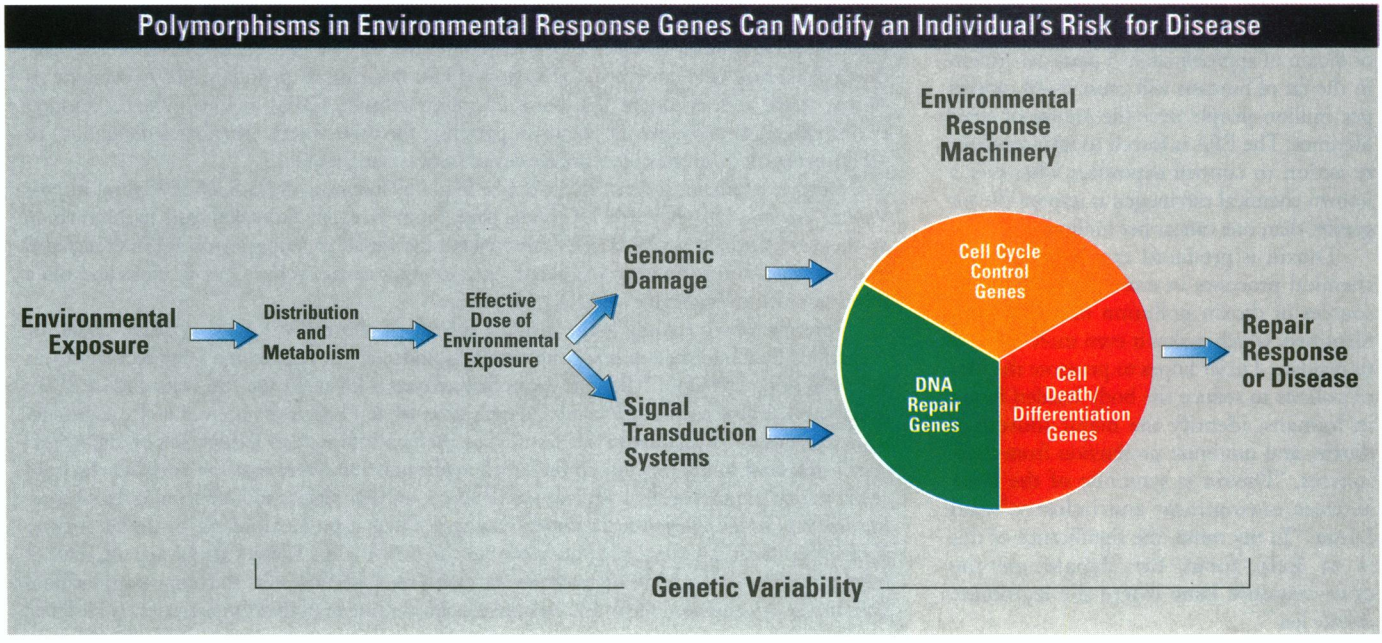
To get a more accurate picture of risk from exposures, researchers need to understand the nature, significance, and distribution of susceptible genotypes in the general population, NIEHS officials contend. Molecular and genetic techniques advanced by the Human Genome Project now make possible studies of individual differences in susceptibility to diseases and dysfunction linked to environmental exposure. It is hoped that the Environmental Genome Project and the Human Genome Project will complement each other, Olden says. "We can take advantage of and build on what [the] other is doing."

Information gleaned from the Environmental Genome Project could refine current risk assessment capabilities to better protect sensitive subgroups such as children or people who are immunocompromised, and to potentially reduce regulatory costs. Although today's risk assessments and resulting chemical regulations do a pretty good job given the data that are available, "they make the assumption that there is an average individual and an average exposure," Olden says. "There may be an average exposure, but not an average individual." As it stands, he continues, "whether we're actually protecting the health of the American people is uncertain. We may be underregulating or overregulating," as the deviation from the norm can be enormous.

Variances in the responsiveness to exposures caused by susceptibility genes have made the definition of environmental disease components difficult. The Environmental Genome Project may shed light, for example, on disease caused by exposure to the nerve gas sarin or other organophosphates used during the Persian Gulf War, Olden says. People with certain polymorphisms produce variants of the enzyme paraoxonase that have difficulty breaking down such nerve agents and related pesticides while people with other allelic variations are more resistant to disease.

"The project has tremendous public health implications and will have a tremendous public health impact," Olden says. "If we can understand how these agents interact, we'll be in much better shape to prevent and not just treat end-stage diseases."

Project researchers anticipate collecting blood samples from approximately 1,000



Americans from five ethnic groups—Asian American, African American, Hispanic, Caucasian, and Native American—in order to learn what the allelic variations and frequencies of these "environmental disease" genes are in the U.S. population overall and within ethnic groups. Exons and regulatory regions of these genes from different age groups will also be sequenced to study genetic variability. "Getting the proper informed consent is important," Taylor adds, "because this group of samples will become a national resource for future studies."

To date, only a handful of susceptibility genes have been explored for genetic polymorphisms, Taylor says. For instance, some alleles may increase risk for one disease and decrease the risk for another disease, while other alleles only increase the risk of disease if a person has an environmental exposure.

Currently, more than 200 candidate genes are under consideration for the core study from five broad classes: genes controlling the distribution and metabolism of toxicants, genes for the DNA repair pathways, genes for the cell cycle/cell death control system including apoptosis, genes for metabolism of nucleic acid precursors, and genes for signal transduction systems controlling expression of the genes in other classes. Olden plans to convene a conference in the early fall of about 30 key geneticists, epidemiologists, and policy makers to determine which genes should be included in the project and to establish a study group to provide peer review for all aspects of the project. Researchers from six DNA sequencing centers selected through

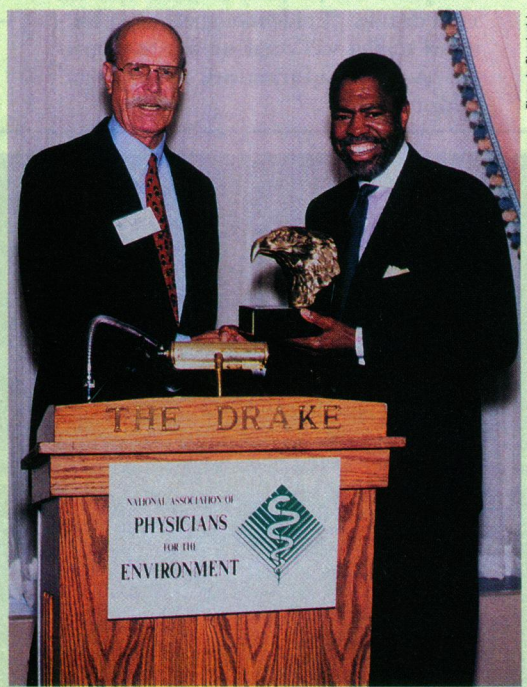
NIEHS Director Receives Inaugural NAPE Award

On May 23, the National Association of Physicians for the Environment (NAPE) presented its inaugural award for public policy leadership in protecting health and the environment to Kenneth Olden, director of the NIEHS. John Grupenhoff, executive vice president of the NAPE, said that Olden's dedication and leadership had advanced the 1,000-employee institute to new prominence and had brought environmental health to the forefront of public concern. "He's putting environmental health on the map . . . and that's something we wanted to recognize him for," Grupenhoff said.

Olden was chosen as the third director of the NIEHS and the second director of the National Toxicology Program (NTP) on 18 June 1991. Since that time, the institute has grown in size and reputation, improving its intramural research programs and supporting extramural environmental health science centers at universities across the nation.

Olden said that one important change he has made since becoming NIEHS director has been to increase the institute's emphasis on human health. "In the past," Olden explained, "the public knew us more for our toxicology work and animal studies. The public didn't understand that the work we do here is relevant to human diseases like osteoporosis [and] Parkinson's disease. But, in reality, almost all diseases have an environmental component. I've tried to focus the institute on human diseases and the preventive measures related to the environment that can be taken to protect human health. . . . I want the NIEHS to be known as the institute of the NIH that focuses on prevention."

The NAPE also noted that the NIEHS and the NTP maintain their position at the forefront of research in the field by continuously undertaking bold new projects. Recently, Olden announced the institute's plan to map the "environmental genome" to determine how heredity affects a person's susceptibility to environmental insults. Another new project will use large-scale blood and urine testing to determine pollutant levels in U.S. residents.



Photos by Chamberlain

The natural choice. John Grupenhoff (left), executive vice president of the NAPE, called NIEHS director Kenneth Olden (right) "the natural choice" for the group's inaugural award for public policy leadership to protect the environment and health.

However, Grupenhoff said, one of the most important accomplishments of the NIEHS under Director Olden is the new communications channels that have been forged between the institute and others who are concerned with environmental health. "Immediately upon becoming director of the institute, Ken Olden began a dialogue with representatives of professional and scientific organizations, with industry groups, with environmental advocacy groups, with labor unions, and with economically disadvantaged groups who suffer the preponderance of environmental exposures," Grupenhoff noted in a press release. Said Olden, "When I came here, I made a commitment that I was going to make the institute responsive to the American people. We are identifying issues that people think are important and we are doing research that people are excited about." In this vein, the NTP recently invited the public to nominate substances for inclusion in its Biennial Report on Carcinogens.

Olden said that he was very pleased to be recognized by an organization of health professionals and that he looks forward to a prosperous relationship between the NIEHS and the NAPE. "This award further elevates the institute to a leadership role and increases our visibility. It shows we've taken our place among other institutes as a health organization," he said.

The NAPE, which was formed in 1993, is the designated U.S. member of the International Society of Doctors for the Environment. Its mission is to distribute information and build consensus among health professionals on environmental issues, to act as a forum for debate, and to educate the public. The NAPE's headquarters are in Bethesda, Maryland.

a competitive funding process will evaluate polymorphisms that affect 1% or more of the population, rather than rare mutations that affect less than 1% of the population. In addition, a center will be formed to store and standardize the core data.

"There are many more genes than we can test," says NIEHS researcher Douglas Bell. Yet the list of catalogued genes and the size of the database will likely grow over the next decade as additional environmental susceptibility genes are discovered and related epidemiological studies completed.

About 100 of the candidate genes are metabolism and detoxification genes that regulate cytochrome P450s, NATs, GSTs, glucuronyl transferases, sulphotransferases, methyltransferases, metallothioneins, and paraoxonases. The GST genes, for example, code for enzymes such as glutathione *S*-transferases, which help the body dispose of carcinogens known to be involved with lung, brain, and bladder cancers, among other diseases. Similarly, variations in ADH and ALDH genes have been linked to alcohol-related diseases, including cancer.

There are about 50 DNA repair genes and 50 toxicant receptor genes under consideration as well. The DNA repair genes correct mistakes that occur during DNA matching, nucleotide excision, base excision, and recombination. Inability to repair such mistakes can cause skin and other cancers, Bell explains. Toxicant receptor genes include those that modify pathways related to toxic response, such as Ah receptors, estrogen receptors, progesterone receptors, and endocrine disruptor pathways. Variations in genes in the main toxicology classes—neurotoxicology, reproductive toxicology, and developmental toxicology—are also strong candidates, Bell says.

Genes involved in nutrition pathways or the metabolism of nutrients such as vitamins and minerals account for another 25 candidates. Certain polymorphisms in nutrient pathways contribute to diseases such as hemochromatosis (an iron imbalance), cirrhosis, and liver cancer. Steroid metabolism genes involved in the synthesis of estrogen, progesterone, and testosterone account for an additional 25 or so candidates.

Olden estimates that the first phase of the project—collecting and sequencing the core genetic data and establishing the sample storage and distribution center—will be completed in about five years. The second phase of the project, which comprises determining the functional significance of the identified polymorphisms and conducting population-based studies of associations among alleles, exposures, and disease rates through a mix of investigator-initiated, extramural, and intramural research, will overlap with the project's first phase and probably continue into the next decade. "Epidemiological and functional studies will come on line as soon as we have the information to do that," Olden says.

The third and final stage of the project entails developing, on the basis of the new findings, improved risk assessments and regulations for environmental exposures, better protections for susceptible subgroups, and targeted disease screening for high-risk groups, according to NIEHS officials. Some of these improved guidelines, prevention strategies, and medical treatments can be implemented along the way as well.

Although gene–environment interactions may prove to be more complicated than what the Environmental Genome Project can initially or alone unravel, "it's the next logical step to better identify and protect susceptible populations," Taylor says.

Olden estimates that the cost to sequence the "environmental" genes in 1,000 people will be about $60 million, and he has already committed $10 million from the NIEHS's 1998 budget to the plan. "It's a project we can afford," says Olden, who hopes additional funds will come from other branches of the National Institutes of Health, including the National Cancer Institute and the National Human Genome Research Institute. "We'd like to see every institute involved in some way," Olden says. "This is one of the most important databases to have."

Julie Wakefield Albers

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SUPERFUND XVIII

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For additional information contact: Susan Cantor or Shane Poblete, E.J. Krause & Associates, Inc.
7315 Wisconsin Avenue, Ste. 450N, Bethesda, MD 20814 Phone: (301)986-7800 Fax: (301)986-4538