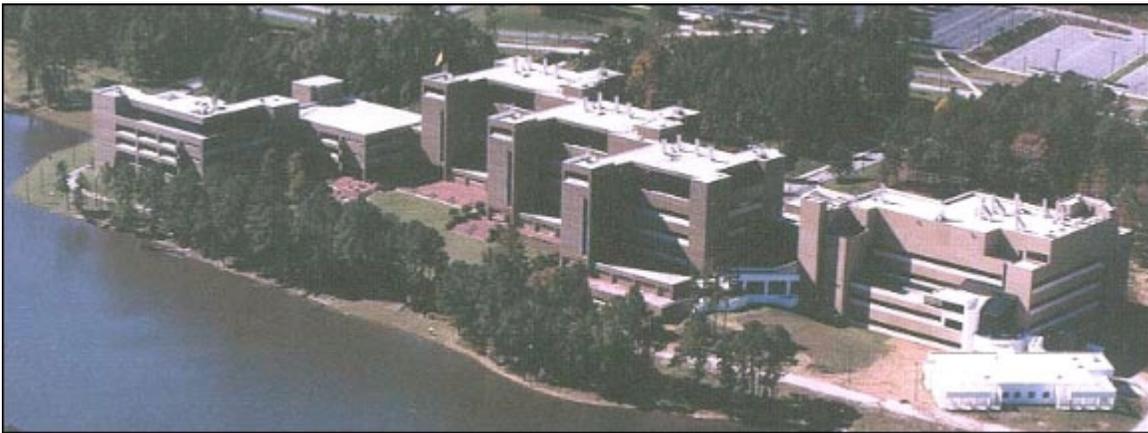




The National Institute of Environmental Health Sciences

# NIH Exposure

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The National Institute of Environmental Health Sciences (NIEHS) is one of 25 Institutes and Centers of the National Institutes of Health (NIH), which is a component of the Department of Health and Human Services (DHHS). The Director of the NIEHS is Dr. Kenneth Olden.

Mission:

**Human health and human disease result from three interactive elements: environmental factors, individual susceptibility and age. The mission of the National Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of human illness and dysfunction from environmental causes by understanding each of these elements and how they interrelate. The NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach.**

**FROM THE DIRECTOR**



The National Institute of Environmental Health Sciences once again gained a sizeable increase in our budget for FY 2001. I believe this illustrates the importance of the work that is conducted at NIEHS and further shows the need for more research to be done in this field.

To realize the public health and economic potential of environmental health research, several critical investments will be required. These critical investments can be grouped into three major categories. First, there is a need to develop high throughput technologies for carcinogenicity and toxicity testing coupled with the establishment of a mechanistic understanding of how the specific environmental agents trigger both processes. The second strategic investment is to incorporate individual susceptibility into risk assessments. This ability will evolve as we define better the genetic basis of individual responses to toxicants, define important gender differences, define the unique vulnerabilities of children, and define the impact of diet, behavior, poverty and ethnicity on environmentally associated diseases. The third strategic investment is to establish a rational basis for testing and regulatory decision making. Such rationality will arise when we are able to base decisions on the actual, real-world exposures of the American public, when we can identify the truly important environmental triggers of disease as they are revealed through ongoing population-based cohort studies, and when the technology is in place to understand the health effects of multiple, complex exposures rather than the single-compound studies upon which current risk assessments are based.

Let me conclude by saying that by employment of new technologies, the power and effectiveness of the science base for environmental health decision-making can now be transformed at a pace that could not have been foreseen a decade ago by even the most astute visionaries. The scientific opportunities for NIEHS develop an entirely new framework to understand how environmental exposures affect human health.

# PREVENTION

## THE RESPONSIBILITY OF NIEHS: PREVENTION

Preventing disease is one of the most important services a government agency can provide to its citizens. Protecting people from avoidable illness and death saves money, spares suffering and improves the quality of life for everyone. Prevention underlies the concept of "environmental health." The premier research facility for this discipline in the U.S. is the NIEHS of the National Institutes of Health (NIH).

The NIEHS pursues its goals by studying the how a wide variety of chemical and biological agents found in the air, ground, food and water impact human health. This information is acquired by laboratory and field testing done either by NIEHS or by research laboratories at academic centers that receive support from the Institute; and it forms the backbone of many of the important regulations established by the Environmental Protection Agency, the Food and Drug Administration and other government oversight and regulatory agencies. This information is also the scientific basis for many laws passed by the U.S. Congress to protect the health of U.S. citizens.

The most effective way to prevent disease is to understand the cause of an illness and change the conditions that permit it to occur. A key strategy for preventing many diseases or minimizing disease progression is to reduce or eliminate adverse effects of environmental exposures. The NIEHS preventive strategy approach reflects the findings of national surveys, which repeatedly find that reducing exposures to adverse environmental agents is the best way to protect our health and the health of our children. This belief is supported by a continually growing base of knowledge suggesting that environmental chemicals may be important triggers of many human medical problems.

A major component of NIEHS research investigates how exposures to specific agents, such as an agricultural compound or a water contaminant, affect health. The institute conducts and supports such studies both in laboratory animals as well as in epidemiological studies of the disease occurrence and relevant environmental exposures in humans. This work gives valuable insight into the potential of certain environmental agents to cause specific diseases or disabilities. In turn, this insight can lead to an improved understanding of the underlying mechanisms by which these agents act.

The NIEHS is unique within the NIH because its primary focus is to prevent disease rather than to find ways to treat illnesses already afflicting people. The institute does this by approaching health as an integrated response of all organ systems of the body to the environment. Areas of special interest to NIEHS are cancer, birth defects, asthma, diabetes, infertility, neurodegenerative and developmental disorders and autoimmune disease. Thus, rather than focusing on one or two specific organs, like the heart or liver, the NIEHS takes a holistic approach to human health and a preventive approach to medicine.

**NIEHS HIGHLIGHTS**



**Sister Study of Breast Cancer**

The NIEHS is establishing a cohort of 50,000 women whose sisters had breast cancer. Because these women are at increased risk of breast cancer, twice as many breast cancer cases are expected as would be identified in any other similar cohort. Approximately 500 cases are expected after five years. Biologic specimens will be collected and stored prior to disease onset and extensive questionnaires will be regularly submitted. Breast cancer risk could be assessed in terms of exposure to endogenous hormones, exogenous hormone disruptors, growth factors, dietary components, and environmental contaminants such as pesticides and solvents. This study would also assess the importance of gene-environment interactions. Although the effort would target breast cancer, less common hormonally-related cancers such as ovarian and endometrial cancer will also be studied. Additionally, as more breast cancer-related genes and exposures are identified, the databank could be regularly re-evaluated to address this new information. This study group

could also conceivably be used to evaluate other exposures important for female-predominant diseases, such as autoimmune diseases.

**Agricultural Health Study**

The Agricultural Health Study (AHS) is a prospective study of 55,000 licensed pesticide applicators and nearly 35,000 spouses of farmer-applicators. The benefits of this study extend beyond farmers because the exposures under study -- pesticides, solvents, nitrates, metals, mycotoxins, and silica -- are not limited to farmers but are common to rural communities and other settings. Enrollment of the cohort has been completed, with more than 80 percent of eligible applicators in Iowa and North Carolina completing a questionnaire about their exposures and health status. Cohort members are now completing five-year follow-up interviews; cancer incidence and mortality is being evaluated using cancer registries and vital records. The NIEHS has identified possible links between farm exposures and some neurological health endpoints and is examining other outcomes including reproductive health and asthma. The NIEHS is currently working to identify incident cases of juvenile diabetes, autoimmune disease, early ovarian failure, and macular degeneration within this cohort. A nested study of farming-related and other risk factors for Parkinson's Disease is being developed in collaboration with researchers from the Parkinson's Disease Institute.

## Environmental Health Institute Scientists Begin To Unravel Cause Of Blocked Memory In Alzheimer's

Researchers at the [National Institute of Environmental Health Sciences](#) have found a protein in patients with Alzheimer's disease that can disrupt brain signals and therefore may contribute to the memory losses of Alzheimer's disease, the scientists reported in the [Journal of Neuroscience](#), 2001, Vol. 21, RC 120, pp. 1-5.

According to the report, the characteristic plaques seen by scientists and physicians in the brains of Alzheimer's patients may not be the result of the disease but a cause. (At autopsy, these characteristic plaques -- first noted in 1906 -- are used to confirm Alzheimer's.)



Dr. Jerrel Yakel

The NIEHS scientists said they had demonstrated in animal models that the major protein of these plaques binds to a receptor in the brain, thus blocking the signals, or currents, that are thought to be involved in learning and memory. The protein is called Beta-amyloid peptide and is found in the brains and plaques of humans, as well as animals.

Many researchers have speculated that the protein had memory-blocking properties but, according to the authors, this work for the first time establishes this functional link between the plaques seen at autopsy and the failure in brain functioning.

The senior NIEHS scientist on the study, [Jerrel L. Yakel, Ph.D.](#), said that better drug therapies could result from finding chemicals that prevent the chemical binding and thus keep the brain signals flowing. "Knowing how the disease process works," Dr. Yakel said, "makes it more likely that medical science can find ways to slow, halt or even reverse the process."

Dr. Yakel, Diana L. Pettitt, Ph.D., and Zuoyi Shao, Ph.D., showed that the Beta-amyloid peptide blocks the function of a key signaling receptor, the nicotinic acetylcholine receptor, in the hippocampus -- the seat of memory, motivation and emotion in the brain. For the text of the scientific report, see the full [Yakel/Pettit/Shao report](#) at <http://www.jneurosci.org/rapidcomm.shtml>

Alzheimer's is the most common form of dementia -- a medical condition that disrupts the way the brain works -- in older people. It is characterized by confusion, profound forgetfulness and, often, anger. Seldom diagnosed a few decades ago, the disease appears to be increasing as the U.S. population ages and currently affects an estimated four million Americans.

In rare cases, the disease begins to develop before age 50 but most cases develop after 65. Alzheimer's Disease, or AD, is named for the German physician Alois Alzheimer. In 1906, he noticed abnormal clumps (now called senile or neuritic plaques) and tangled bundles of fibers in the brain tissue of a woman who had died of a then-unusual mental illness. These plaques and tangles in the brain are now considered to be hallmarks of AD.

Alzheimer's may begin as mild forgetfulness about recent events, activities, and the names of people and things. Simple math may become hard.

As the disease progresses, people may forget how to do such tasks as combing their hair or brushing their teeth. They may no longer think clearly: Speaking, understanding, reading and writing become difficult. Patients may become anxious or aggressive as the disease continues to progress, and they often wander from home. AD patients eventually need total care.

Because such problems may result from other conditions as well, doctors can only make a probable diagnosis of Alzheimer's - though in specialized centers this is correct 80 to 90 percent of the time. Since it is risky to remove brain tissue from a live person, doctors cannot confirm AD with total accuracy unless they do an autopsy after death to determine if there are plaques and tangles in the brain.

Several drugs have been approved for temporarily relieving some symptoms of Alzheimer's but there is no cure or drug that can stop the disease.

## **Air Pollution Slows Lung Function Growth in Children**

Common air pollutants slow children's lung development over time, according to results from the [University of Southern California-led Children's Health Study](#). The 10-year-long study is considered one of the nation's most comprehensive studies to date of the long-term effects of smog on children. The study was initiated with support from the [California Air Resources Board](#) and was funded by the [National Institute of Environmental Health Sciences](#), the [Environmental Protection Agency](#) and the Hastings Foundation.

"This is the best evidence yet of a chronic effect of air pollution in children," says John Peters, M.D., D.Sc., USC professor of preventive medicine and one of the study authors. "Long-term exposure to air pollution has long-term effects on children's lungs, and the effects are more pronounced in areas of higher air pollution."

The report, released in the October issue of the [American Journal of Respiratory and Critical Care Medicine](#), covers smog's health effects on children over the first four years of the study. Normally, children's lung function grows steadily as they grow up. Females reach their greatest potential lung function when they are in their late teens, while males reach their maximum lung function when they are in their early 20s. After that, lung function stays level for awhile before slowly declining as a person ages.

Researchers with the Children's Health Study have monitored levels of major pollutants in a dozen Southern California communities since 1993, while carefully following the respiratory health of more than 3,000 students. Each year, USC scientists tested lung function by having each child take a deep breath, then measuring how much air the kids could blow out and how fast. The researchers showed that as children grow up, those who breathe smoggier air tend to lag in lung function growth behind children who breathe cleaner air. Children with decreased lung function may be more susceptible to respiratory disease and may be more likely to have chronic respiratory problems as adults.

The air pollution effects were most evident in fourth graders, followed from age 10 to 14. On average, over the four years, the lung function growth rate of children in the most polluted community was about 10 percent lower compared to children in the least polluted community. Similar effects on lung function were observed in boys and girls, and in asthmatic and healthy children.

"The association we see with air pollution also is stronger in children who spend more time outdoors," says W. James Gauderman, Ph.D., USC assistant professor of preventive medicine and the study's lead author.

**"That is consistent with what we would expect from a detrimental effect of outdoor air pollution."**

**One surprising finding of the study, Gauderman notes, is that ozone did not appear to play a major role in the pollution's effects on children's lungs. Instead, the offenders were nitrogen dioxide, microscopic particles known as particulate matter, and acid vapors. All come directly or indirectly from the burning of fossil fuels (the exhaust from a car or truck, for example), as well as from emissions from industrial plants and other sources.**

**Millions of Southern Californians breathe polluted air every day, especially on days when levels of pollutants exceed state and federal standards for air quality. The area's layout as a basin, as well as the typical sunny weather and omnipresent vehicle traffic, combine to keep high levels of pollutants in the air. Although polluted air has long been known to cause immediate uncomfortable symptoms such as eye irritation, coughing and chest tightness, long-term or chronic effects have been less clear. In the current research, though, scientists have begun to demonstrate effects over time.**

**The researchers recruited 150 fourth graders, 75 seventh graders and 75 tenth graders in 1993 from each of the 12 communities. For this study, the California Air Resources Board routinely tests air in the 12 communities, from [Atascadero](#) in the north to [Alpine](#) in the south. Locations in the Inland Empire were chosen because they were known to have relatively high levels of pollutants, while northern communities were chosen because they have lower pollution levels.**

**Researchers found that on average, lung function growth tended to be higher in cleaner communities and lower in areas with more air pollution.**

**The USC team released [preliminary results](#) of the Children's Health Study in 1999, which provided an initial hint that lung function is lower in children who breathe the most polluted air. The researchers will continue monitoring students into their teens and possibly into adulthood. They also are following students who have moved away to lower pollution areas, to see if their lung function rebounds.**

**In general, air quality in Southern California has improved over the last two decades. Says Gauderman, "Our results indicate that continued reduction of air pollution, through the efforts of both regulators and the public, will lead to improved health in our children."**

**For more information about the Children's Health Study, please visit the [researchers' website](#).**

RESEARCH ADVANCES



**Parkinson’s Disease - Identifying the Environmental Triggers**

Background: Parkinson’s Disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer’s Disease. Most cases begin after the age of 50 and its incidence increases as a function of age. Like most diseases, PD appears to arise from the interaction of three events -- an individual’s genetic, environmental exposures, and his/her age. Recent studies in twins indicate that genetic susceptibility is the primary determinant for early onset PD, but late onset PD (after age 50), which accounts for the majority of cases, arises from some other factor, possibly of environmental origin.

Important insights into environmental triggers of PD were gained in the early 1980s when a synthetic heroin elicited severe Parkinsonism in addicts who injected it intravenously. The initiating agent was found to be 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a compound with structural similarities

to some herbicides and pesticides. Subsequent case-control studies have found increased incidence of PD associated with pesticide use, rural environments, consumption of well water, exposure to herbicides, and living near industrial plants, printing plants, or quarries.

The defect that is a hallmark of the disease is the loss of brain cells that produce a chemical -- dopamine -- that helps direct muscle activity. Neurotoxicants that act on this system are obvious candidates for setting the stage for PD. Recent work by an NIEHS-supported researcher showed that a multi-neurotoxicant exposure scenario might explain some PD cases.

Advance: An NIEHS-supported researcher was studying the herbicide, paraquat, which acts adversely on the dopamine system. When paraquat and the fungicide, maneb, were jointly administered to mice, the combined exposure decreased motor activity, increased dopamine turnover, and reduced other measures of dopamine effect at levels far greater than when the same chemicals were administered singly. The fact that combined exposures, such as would be found in real-world applications, can potentiate the adverse effects on the dopamine system raises important possibilities for multiple environmental risk factors being associated with PD development.

This work is complemented by another group of federally-supported

researchers. They found that the organic pesticide, rotenone, produced symptoms of PD in laboratory animals.

***Implications:*** These studies support the hypothesis that agricultural exposures might well play a role in initiating or triggering many cases of PD. They help refine some of the research questions that NIEHS-supported researchers can investigate in their long-term study of pesticide applicators in the Agricultural Health Study. Equally important, these findings call into question the adequacy of current risk assessment guidelines for these chemicals which are based on effect levels derived from exposures to single agents

### **Firefly Gene Lights Up to Detect Dioxin**

***Background:*** Dioxin is a toxic byproduct of chemical manufacturing and combustion that increases risk for diabetes, cancer, and reproductive disorders. It was a contaminant of Agent Orange, the herbicide used during the Vietnam War, and was also found at Love Canal.

***Advance:*** A gene from a firefly was added to mammalian cells so that they glow when exposed to dioxin. The cells glow brighter as the level of dioxin increases, thus providing a way to assess both the presence of dioxin and its amount.

***Implications:*** This novel system is more rapid and less expensive than

current test methods, providing a more useful means of environmental monitoring of this important pollutant. It can analyze 50 samples per hour at \$400 per sample, compared to one sample per hour at \$1500 per sample using existing techniques.

### **Effects of Dioxin on Gender Ratios in Offspring of Exposed Men**

***Background:*** Dioxin is a highly toxic byproduct of some common commercial processes. It can cause cancer and can disrupt multiple hormonal functions. Although its formation is inadvertent, the multiplicity of processes that lead to its production has led it to be widely distributed in the environment.

On July 10, 1976, an explosion occurred at an herbicide manufacturing facility in Seveso, Italy. Approximately 30 kg of dioxin was released into the environment. It contaminated the soil of the surrounding area and many people were exposed. Many of these people have been followed for adverse health effects following the accident.

***Advance:*** NIEHS-supported scientists did a follow-up study on previous work that demonstrated a significant increase in the number of female births after the accident. Serum samples taken at the time of the accident were analyzed for dioxin. The data indicate a positive correlation between increased probability of female births with increasing dioxin concentration in the

sera of the fathers. The effect starts at concentrations less than 20 ng/kg bodyweight--a level about 20 times higher than the normal dioxin concentration in people. This level of contamination is similar to doses that cause certain reproductive impairments in rats.

*Implication:* Dioxin is a ubiquitous toxin in that all human beings have some exposure. The Seveso incident occurred over 20 years ago and the effects on offspring gender ratios are still present. This fact demonstrates the persistence of dioxin and its adverse effects following exposure. Also, the level of exposure compared to “unexposed” populations is relatively low, suggesting that these effects may also be seen in the general population or susceptible individuals. These observations could have profound public-health implications.

### **Gene-Environment Interactions - A New Clue with Implications for Asthma**

*Background:* Most diseases arise from the complex interaction of underlying genetic susceptibility and environmental exposures that occur over time. Although most people think of environmental exposures in terms of synthetic chemicals, some of our most important exposures are from the natural world. These exposures would include the nutrients in our food, the pathogens normally found in soil and air, and the by-products produced by insects and mites in our homes.

One such exposure is endotoxin. Endotoxin is produced by molds and is commonly found in household and grain dusts. Inhalation of endotoxin has been implicated in asthma and other respiratory diseases and has been shown to cause chest tightness, wheezing, and difficulty in breathing. Endotoxin-induced asthma is a particular problem in farming occupations that involve handling grain and subsequent exposure to grain dusts. Researchers have recently discovered an important genetic component underlying susceptibility to endotoxin that has implications not only for asthma, but potentially for other airway diseases such as acute lung injury, cystic fibrosis, and pneumonia.

*Advance:* These investigators studied the response of 83 healthy human participants to increasing concentrations of endotoxin equal to the amount a grain handler or farmer would be exposed to during a normal work-day. The results demonstrated differences in the constriction of the airways between the participants--some exhibited normal constriction while others were affected to a much lesser degree. Further genetic testing led the investigators to attribute the difference in response to mutations in the toll-like receptor-4 (TLR4) gene. These findings were further substantiated by *in vitro* experiments conducted on cell cultures obtained from people with the mutation. By adding a normal copy of the TLR4 gene to the cells in culture, the normal cell response to endotoxin was recovered.

Implication: These findings may have future implications on the treatment of asthma and other respiratory diseases. Scientists may be able to capitalize on these findings by designing drugs that will bind to normal TLR4 receptors and thus prevent the bronchoconstriction seen in asthmatics. However, the researchers warn that people with the TLR4 mutation may be more susceptible to blood-borne infections because they may not respond as readily to early signs of infection.

### **Role of Diet and Genetic Mutation in Preventing Lung Cancer**

Background: It has long been noted that diets high in vegetables reduce cancer risks in people. Of particular benefit are the cruciferous vegetables such as broccoli, cauliflower, cabbage, watercress, bok choy, and others. These vegetables are high in precursors of an important class of anticancer agents, the isothiocyanates (ITC). A recent study has shown an important gene-environment interaction that influences the benefit of ITC in reducing cancer risks.

Advance: Everyone has metabolizing enzymes that are responsible for breaking down and eliminating the different compounds to which we are exposed. These compounds would include beneficial substances such as ITC and harmful substances such as tobacco carcinogens. One such enzyme is GSTM1. It is thought that people who lack this enzyme are at increased risk of lung cancer

because they are unable to inactivate carcinogens and, thus, would have a higher exposure than people with active GSTM1 who would quickly excrete cancer-causing substances.

But researchers have recently shown that having active GSTM1 can also be a risk factor in certain circumstances. That is because this enzyme also breaks down and eliminates beneficial dietary ITC. Thus, people with high levels of GSTM1 would have lower levels of the critical ITC anticarcinogen, a condition that could increase their cancer risk.

A unique aspect of this study is that the researchers used a marker they had previously developed for ITC so that levels could be assayed in urine. Questionnaire assessment of ITC requires detail on many dietary items not included in many frequency questionnaires. In this study 18,244 men in China were evaluated. Those with detectable levels of ITC had a 40% decrease in lung cancer risk. Of those lacking the ITC-eliminating enzyme, GSTM1, the lung cancer risk was reduced 64%.

Implications: Understanding how diet and underlying genetic factors interact to reduce disease risk is vital in helping people improve their health. This study demonstrates a key component of the complex gene-environment interactions that control our health. It also represents the first time that a biologic marker for ITC consumption has been used to assess reductions in cancer risks. Use of these more refined methods

over traditional reliance on patient  
recall will greatly improve our

understanding of the true impact of  
diet in improving health.

SCIENCE CAPSULES



**Diet and Health**

Studies continue to validate the importance of nutrition in maintaining health and preventing disease. Whole grain foods, for example, have been identified in NIEHS rodent studies as being protective against breast cancer (Rao, 2000) and have been shown in a NIH-supported longitudinal study of nurses to protect against stroke (Willett, 2000). Nutrition is a major environmental risk component of many diseases. For this reason the NIEHS has partnered with the NIH Office of Dietary Supplements (ODS) to fund a Center for Phytochemical and Phytonutrient Studies. This center is currently investigating the ability of phytochemicals to prevent or treat prostate cancer, the role of phytoestrogens in altering immune response and possibly predisposing some women to autoimmune diseases, and the capacity of bioflavonoids to protect brain tissue from oxidative damage.

NIEHS scientists are also analyzing several existing databases to assess the role of vegetable intake in reducing breast cancer risk, the role

of alcohol intake in increasing breast cancer risk, the relationship of eating frequency to risk of colorectal cancer, and the possible protective effects of antioxidants in modifying risk for amyotrophic lateral sclerosis (ALS).

**Herbal Medicine**

Botanical, or herbal, formulations continue to be a major focus of NIEHS interest in the dietary arena. Over one-third of the adults in the U.S. population use herbal medicines or herbal products; the majority of the users are women. The herbal industry has grown substantially over the last ten years, and it is now a multi-billion dollar industry. Of the nearly 2,000 herbal products in use, only a few have been adequately tested for efficacy and toxicology. Since the FDA is not permitted, by law, to require pre-market testing by producers, herbal medicines are poorly standardized, and consumers are not aware of potential adverse effects, particularly those effects that might arise following long-term use. Of particular concern are developmental and reproductive effects since herbal products are used frequently by women of childbearing age. Other concerns include immunological responses, cardiovascular diseases, cancer, and interactions among the many constituents of herbal medicines or with prescribed pharmaceuticals.

The NIEHS Center for Phytonutrient and Phytochemical Studies will identify and characterize a large number of botanical species,

varieties, and cultivars used as source material for producing commercial herbal preparations. Their plan is to provide an authenticated reference manual for the herbal industry to use in verifying plant shipments prior to their use in over-the-counter formulations. To augment these efforts, the NIEHS and ODS are sponsoring a workshop on ways to employ DNA technology to identify and quantitate botanicals in dietary supplements.

A number of rodent studies are also being conducted at NIEHS, under the auspices of the National Toxicology Program (NTP). These studies will focus on characterization of potential adverse health effects of herbal medicines, including reproductive toxicity, neurotoxicity, and immunotoxicity, as well as those effects associated with acute high dose exposure and chronic exposure to lower doses. In addition, special attention will be given to the potential for herb/herb and herb/drug interactions and the responses of sensitive subpopulations (e.g. pregnant women, the young, the developing fetus, and the elderly). Herbs presently under study, or about to be studied, are golden seal, comfrey, ginkgo, echinacea, aloe vera, ginseng, kava kava, and milk thistle.

### **Asthma**

From 1982 to 1994, asthma prevalence increased in the general population by 61 percent; and it increased by 72 percent among young people age 18. Overall, deaths from asthma increased by 40

percent throughout the 1980s. Moreover, asthma is not just a major public health problem, it is also a major health disparity problem because the disease is more common in poor, inner-city households. Identifying the environmental triggers of asthma and reducing or eliminating them offers one of the most promising approaches for dealing with this public health menace.

The NIEHS continues to work with the National Institute of Allergy and Infectious Diseases (NIAID) on the Inner-City asthma study, as well as supporting other research that evaluates prevention and intervention strategies for childhood asthma. It has also completed the initial sampling of its National Allergen Survey done in partnership with the Department of Housing and Urban Development (HUD) that will evaluate the real-world exposures to eight allergens in American homes.

Asthma rates vary widely with generally low rates in developing countries and high rates in developed countries. NIEHS has developed a program to investigate childhood asthma in three areas with a spectrum of asthma prevalence -- Southern California (high), Mexico City (intermediate) and Wuhan, China (low). The study of populations with varying rates of asthma rates can help to shed light on which risk factors are causal. Further, there may be protective factors in low incidence countries that are no longer prevalent in high incidence countries.

While this trilogy of international studies provide a valuable resource for examining genetic susceptibility to asthma, it is increasingly clear that timing of exposure during development is a critical issue not easily addressed in these studies. For example, endotoxin exposure may protect against asthma in children but produce airway reactivity in adults. Thus, the optimal way to study the etiology of childhood asthma is to follow a cohort of children starting as early as possible. To this end, NIEHS is developing a birth cohort in Mexico City. This setting provides a unique blend of asthma risk factors and environmental exposures, with the opportunity to investigate protective factors still prevalent in Mexico City such as exposure to certain infectious agents and a more traditional diet rich in fresh vegetables and fruits. Plans for a pilot study are underway.

The international studies will complement ongoing studies that NIEHS is conducting in Southern California. These studies have found a definite association between air pollution and delayed lung development in children. Normally lung function grows steadily as children grow up, with maximum lung function being achieved by the late teens for females and early twenties for males. In this study of 3,000 children, lung function growth was reduced by 10 percent in those living in more polluted environments. This deficit could have future implications because decreased lung function may increase susceptibility to

respiratory diseases such as asthma.

### **Carolina Lupus Study**

Systemic lupus erythematosus (SLE) is an autoimmune disease that can cause severe damage to the kidneys, joints, and other tissues. Ninety percent of SLE patients are women, and compared to whites, African-Americans are three to four times more likely to develop the disease. Mortality is also higher among black, compared to white, SLE patients. Reasons for the African-American excess risk are not known. The NIEHS and the NIH Office of Research on Minority Health have joined to create The Carolina Lupus Study, a population-based, case-control study in eastern North Carolina and South Carolina designed to examine hormonal and environmental influences on the etiology of SLE. This study offers the opportunity to examine hormonal, occupational, and environmental risk factors in a previously understudied population

The Carolina Lupus Study includes 265 recently diagnosed SLE patients and 355 controls. Ninety percent of the patients are female and 60% are African-Americans. Analyses are currently being conducted concerning reproductive and hormonal factors and medical conditions as risk factors for developing SLE. Contrary to our expectations based on animal studies, we found little evidence that estrogen-related or prolactin-related exposures are associated with an increased risk of SLE. There was

little association between SLE risk and history of implanted medical devices, hepatitis B vaccination, eczema, hay fever, or other allergies, but associations were seen with history of medication allergies, herpes zoster and vascular occlusions (stroke, pulmonary embolism, or blood clots).

These efforts may help illuminate etiologic pathways and develop prevention strategies for susceptible populations. Environmental exposures under study include silica dust, solvents, heavy metals, and pesticides. The influence of genetic susceptibility to disease risk will also be assessed.



### **New Center for Toxicogenomics**

The National Center for Toxicogenomics (NCT) of NIEHS was established in June 2000 to combine the Institute's unique expertise in analyzing environmental effects of toxic substances on humans with recent advances in sequencing the human genome.

NIEHS and NCT define Toxicogenomics as the collection, storage and interpretation of information about:

*Genomic activity* - Expression of specific groups of genes in response to stressors, such as drugs and environmental toxicants.

*Proteomics* - Identification of proteins made by genes responding to toxicants.

NCT will accomplish this mission through a combination of financial support to scientists at academic institutions around the country, in-house research and collaborations with public agencies, private healthcare and biotechnology companies.

### **Support of Minority-Serving Institutions**

The NIEHS has an intense interest in building research capacity of institutions that serve minority students. Since 1996 we have been partners with the University of Maryland and the National Science Foundation to support the Meyerhoff Scholars Program. In 1999 NIEHS initiated the Advanced Research Cooperation in Environmental Health (ARCH) Program for capacity-building in minority-serving institutions. The first recipients of these grants were Xavier University of Louisiana, partnered with Tulane University, and Southern University at Baton Rouge, partnered with the University of Texas Medical Branch, in Galveston. Work at Xavier University will focus on the alteration of gene regulation by environmental compounds, including interaction with steroid

receptors. Research at Southern University at Baton Rouge will concentrate on the occupational compound, butadiene, and its effect on reproductive and neuroendocrine responses, on p53-mediated cellular responses, and on DNA damage and DNA repair. This program was reannounced in FY 2000 and another six applications are being reviewed this year.

### **NTP Center for Evaluation of Risks to Human Reproduction**

The National Toxicology Program (NTP), a toxicological testing program consisting of several federal agencies with the NIEHS as the focal and principal agency, has established a center for studying adverse environmental effects upon human reproduction.

The Center's responsibilities include

- Providing information to the public regarding environmental exposures to reproduction or to the health and welfare of children;
- Provide regulatory agencies with objective and scientifically sound assessments of data related to reproductive/developmental health effects associated with exposure to specific chemicals;
- Identify knowledge gaps to help establish research and testing priorities.

This center was established in 1998 and assesses individual chemicals through rigorous evaluations by independent, scientific panels. The Center's first expert panel was formed in the summer of 1999 and the expert panel completed its review of seven phthalate esters in 2000. (Reports are available on the Center's homepage, <http://cerhr.niehs.nih.gov>)