Taking a World View of Asthma

The incidence of asthma is increasing around the world, particularly among children. According to the Centers for Disease Control and Prevention, almost 5 million American children have been diagnosed with asthma. In spite of active research and prevention efforts, the asthma-related death rate for U.S. children increased by 78% between 1980 and 1993. The picture elsewhere is every bit as troubling. About 1 out of 4 Australian children are now diagnosed with the disease, and the childhood asthma rate has doubled to greater than 11% in Israel. Costa Rica, Panama, Brazil, Peru, and Uruguay all now have childhood asthma rates of greater than 20%.

To an epidemiologist, asthma poses a tantalizing set of questions. Geographic regions that differ in their relative rates of this debilitating disease also differ tremendously in economic status, nutrition, and ethnic makeup, customs, and habits. In an unusual turnabout, people in developed countries are more affected than those in poorer nations.

For some asthma patients, the triggers are everywhere and seemingly unavoidable. Among the culprits responsible for launching asthma attacks are vehicle exhaust, cigarette smoke, cold air, pollen, and mold spores. Exposure to allergens ranging from bacterial toxins to salivary and fecal antigens from cockroaches has been implicated, and using wood, coal, or gas to heat or cook indoors is also known to trigger attacks. The disease also appears to run in families, although little is known about why this is so.

Understanding asthma will require analyzing all these factors to find out how they work, separately and together, to produce the disease. Stephanie London, a senior investigator in the Epidemiology Branch of the NIEHS, is working to understand how genetics and the environment interact in asthma.

One focus of London's work is approaching asthma's causes by studying how and why different populations have such vastly different prevalences of the disease. She began her work in this area as part of a small team that established a cohort study of health effects of air pollution among children in Southern California, where asthma rates are high (as they are in most of the United States). She subsequently added a genetic component to that study. London is now studying populations in Wuhan, China (where asthma prevalence is low) and Mexico City (where prevalence is a bit higher than in China but still lower than in the United States) to answer important questions about how life patterns, as well as exposures to known asthma-promoting factors, are implicated in the complex causation of the disease.

Worldwide wheeze. Studying populations in areas with varying asthma rates, such as Mexico City and Wuhan, could help clarify whether—and which—genetic factors influence prevalence. For example, the continent's highest ozone levels, found in Mexico City (above), may contribute to asthma in genetically susceptible children there.

The Ozone Connection

At the heart of London's work are ongoing studies in Mexico City, where she is investigating the link between ozone exposure and asthma. London's hypothesis is not that ozone is the root cause of asthma. Rather, she looks at ozone as *one* of the potential factors involved—one to which the children of Mexico City are especially highly exposed.

Ozone, an extremely reactive form of oxygen, is found naturally at low levels in clean environments, but builds up to dangerous concentrations when heat, sunlight, and hydrocarbons from fuel exhaust combine. Due to its significant air pollution plus its high altitude, Mexico City has North America's highest ozone levels. In 1995, the average atmospheric concentration of ozone in Mexico City was 0.15 parts per million, nearly twice the current U.S. Environmental Protection Agency daily maximum average.

London is recruiting a group of asthmatic children aged 6–13 years and controls.

Left to right: Digital Vision; EyeWire

The study is unusual because it includes not only the children but also both their parents, forming subject "triads" that can lend insight into the genetics of asthma as well as its environmental triggers.

Children enrolling in the study are tested for lung function and given allergy skin tests. Blood samples are taken from the enrolled child and both parents. Parents fill out questionnaires detailing the child's and family's medical history and exploring potential allergens in the child's home environment: Are there pets? Does someone in the home smoke? Is the child's bedroom dusty, and is it shared with other family members or pets? What is the source of fuel for cooking? The data from the questionnaires will shed light on each child's environment as his or her asthma history unfolds, allowing researchers to understand which environmental factors may be involved in a given child's asthma.

The Genetic Factor

The genes involved in ozone response in humans are not yet known. However, there are data on single nucleotide polymorphisms (SNPs)—sequence differences in a single DNA base pair—for three human genes that are known to be highly conserved versions of ozone-sensitive mouse genes (that is, they are passed down especially accurately, compared to other genes). The mouse ozone-sensitive marker genes encode toll-like receptor 4, an element involved in control of innate immunity; tumor necrosis factor alpha, a cytokine involved in a number of inflammatory diseases; and myeloperoxidase, an enzyme involved in phagocytic cells' responses to immune stimulation.

The SNPs themselves constitute differences that could cause increased susceptibility in some people but not others. London and her colleagues are investigating the distribution of these SNPs in the Mexico City families. By tracing the inheritance of ozone-related SNP factors, London may be able to identify genes that play an active part in determining whether a child becomes sick or remains well when exposed to asthma triggers.

The inclusion of genetic samples from both parents of each child in the group makes these SNP studies extremely valuable. The work establishes a foundation for understanding additional genes involved in the disease, as well as for understanding how ozone may be involved in asthma. Knowledge of ozone response also sheds light on other potential candidate genes in humans.

These results may also lead London back to further molecular analysis of genetic resources from other asthma studies she launched in other communities, such as a cohort of 5,000 seventh-graders in Wuhan. Together, data from these studies will provide a powerful resource—a panel of data linking asthma's incidence in the context of the genetic and environmental conditions of these very different regions.

Branching Out

Data from China may provide new insights into how asthma ties in with another important lung health problem: smoking. The China cohort was originally assembled to study risk factors for initiation of smoking and was expanded by London to include the relationship of environmental tobacco smoke exposure and other sources of air pollution (such as indoor coal burning) to respiratory health outcomes. "In China," London says, "men smoke, but it's rare for mothers to smoke during pregnancy or at all." Smoking is more common among Mexican and U.S. women. In addition, indoor coal burning for cooking and heating is common in China.

London's previous studies have focused on school-aged children, but asthma starts very early in life. For this reason, London is at work putting together a new parent–child triad birth cohort in Mexico City. The new cohort will follow more than 4,000 children from birth to age 6. The birth cohort will allow analysis of how critical early-life nutrition affects children's chances of developing the disease, how common infections such as respiratory syncytial virus and bacterial diarrhea correlate with asthma, and how allergens and different kinds of air pollution may help trigger respiratory inflammation.

"It's important that [London is] going to do these genetic assessments," says Fernando Martinez, an asthma expert and director of the Arizona Respiratory Center at the University of Arizona in Tucson. Martinez calls her studies "the right approach." He adds, however, that it will be very difficult to pinpoint the factors involved in asthma because there are many symptoms of asthma, and not every asthma patient has the same symptoms as other patients or the same symptoms all the time.

But London is optimistic. "The international studies are the key," she says, "because they give us a way to ask what kinds of things might make the difference between places where risk is low and high."

–Victoria McGovern