Is There Cancer in This PHOTO?

Frederica Perera, DNA-damage detective, suspects that if a mother breathes in pollution, her child may develop cancer

By Jeff Wheelwright

On an early spring day in New York City, a clean wind from the north sweeps down the Hudson River. Cars are backed up on the George Washington Bridge, their tailpipes spewing, yet the air today seems to brush the pollution away. It is so clear I can make out every feature in the rust-colored cliffs of the Palisades across the river in New Jersey. What a terrific view.

Frederica (Ricky) Perera has been a DNA-damage detective for 25 years. She is the 64-year-old professor of environmental health sciences at the Columbia University Mailman School of Public Health, a heavy smoker who has been exploring the long-term, invisible impacts of air pollution on health. An award-winning cancer investigator and defender of the welfare of newborn children, Perera comes from the public-health model of disease, which assumes that most ailments are caused from outside the body and can be prevented. She has pioneered a field called molecular epidemiology, a hybrid science that melds urban surveys with subtle molecular changes. Her work ranges from the noxious tailpipe to the precancerous cell, evaluating all the possible ways stations of disease. It is an extremely complicated task, because it is so broad. Progress in molecular epidemiology has been slow, but Perera is not one who gets discouraged.

Just blocks from her base at the Columbia Center for Children's Environmental Health are the low-income neighborhoods of Washington Heights and Harlem. The poor there tend to live with more pollution than other people do. Some of their own making, like cigarette smoke, but a lot of it they cannot avoid, like lead in old paint and smoggy urban air. The predominantly African American and Dominican subjects of her research live a world apart from Ricky Perera, yet she thinks about their health all the time.

Since it began in 1998, her Mothers and Newborns Study has enrolled 700 women. The project monitors women's exposures to airborne chemicals during pregnancies and tests their babies as soon as they are born. Tracking particles of pollution that pass from mother to child, Perera and her team have connected the process to lower birth
weights and smaller head circumferences in some infants. She suspects cancer could be an outcome as well, although it’s too early in the study to know for certain.

Perera has agreed to take me to a clinic where participants in her studies are recruited. Wearing black slacks and pale makeup, she puts on a black leather jacket and a black-leather backpack. Thin and athletic, she walks at a rapid clip down 10th Street. When we get to the Audubon Clinic, which is supported by low-income patients and is supported by the university, we sit in the corner of the waiting room, trying to be unobtrusive. Perera’s eyes flick about for pregnant women.

An assistant with a bunch of flyers stands in front of the young women waiting in plastic chairs. Because of new rules protecting patients’ privacy, the staffer cannot give them a hard sell about joining the study. Rather, she simply asks women if they would like some information about a research project. It helps that each mother-to-be in Perera’s study receives a series of small payments.

The first research step, she says, is “collecting dust and air samples and interviewing the mom at home.” After the pollutants are recorded, the next step is to look for biological signs of chemical exposure, which she calls markers. Some markers may represent early signs of disease.

The simplest markers show concentrations of foreign substances in blood or fat. Take lead, perhaps the most dangerous of common pollutants. The amount of the metal in a child’s blood has proved to be a reliable indicator of the amount of neurological or cognitive damage following exposure to leaded gasoline or paint chips. Although a mother’s placenta is usually a barrier against many unwanted chemicals, lead, like some other chemicals, passes directly from the mother to the fetus. As Perera notes sardonically, “One way to get rid of lead is to have a baby.”

Her favorite chemicals—favorite in the sense that she has studied them more than any others—are the polycyclic aromatic hydrocarbons in cigarette smoke, power-plant emissions, automobile exhaust, and other sources of combustion. These compounds cause cancer in laboratory animals, and studies of industrial workers strongly suggest they can cause lung cancer in humans too. Near the end of her pregnancy, each woman wears an air monitor, a small pump-and-filter system that records the hydrocarbons she breathes over 48 hours. No smokers are enrolled in the research, but many of the women report they are exposed to secondhand smoke at home or at work.

When a participant goes into labor, she is supposed to notify the Columbia center. A staffer retrieves the placenta and draws a tube of blood from the umbilical cord, in effect taking a sample from the baby. If possible, blood is collected from the mother, too, and the lab later identifies.

One resulting measured the levels of harmful hydrocarbons in the air that 64 mothers inhaled to the works before they conceived. The other two measured recorded levels of two markers in white blood cells of the women and their infants. One is a type of genetic code, called an allele, in which a hydrocarbon locks onto a part of the DNA. The other marker is an aberrant pattern in the chromosomes, the DNA shows a greater number of abnormalities than normal, including DNA that is missing or moved. According to other research, both classes of markers—the alleles and the chromosomal aberrations—are associated with increased risks of all cancers.

Perera’s paper in Cancer Epidemiology Biomarkers and Prevention linked the chromosomal aberrations, which were somewhat higher than normal, to air pollution. On average, the higher the hydrocarbons in the mothers’ air, the more frequent the abnormalities seen in the infants’ chromosomes. The research did not claim a cause-and-effect relationship between hydrocarbon pollution and an indicator for cancer. But after the institute and the Columbia group put out press releases addressing the obvious implication—Perera edits her center’s releases by line—the local newspapers connected the dots. “Bad City Air Boosts Kids’ Risk of Cancer” and “Cancer Is Air Born” were two of the headlines.

In a radio interview Perera cautions that the results do not necessarily mean a child will get cancer if the mother breathes polluted air. She says it’s not practical for women to think of moving to the country to escape air pollution. Rather, she says, policymakers should review pollution standards to see if the regulations are protective enough. I notice that Perera likes to throw in this one-two punch—her research points directly to problems she thinks society should resolve.

In her office I asked her about a finding the news media had ignored. The DNA adducts in her study weren’t linked with the other two factors that she measured. This weakened the results, she says, because three measurements lining up in a sequence to cancer are far stronger than two. She is not fazed. “Contrary to our hypothesis,” she replies cheerfully, “the exposures correlated stronger to the chromosomal aberrations than the adducts did. In fact, I don’t like advocacy without a scientific basis,” Perera told me firmly. ‘The passion without the facts won’t work’
the adducts didn't correlate at all. Maybe it was due to the small sample size.

Another puzzle is that the African American newborns showed substantially more aberrations in their blood than the Dominican babies did, given the same range of exposures. Why would the two groups be so different in their responses to low levels of pollutants? That definitely needs investigating, she says. But by now she has picked up the implication of my question: Do her social concerns taint her research results? She dismisses it: "I don't like advocacy without a scientific basis," she says firmly. "The passion without the facts won't work."

When Perera entered graduate school in the environmental health sciences program at Columbia in the mid-1970s, the field had begun to move away from worrying about microbes. In Western societies antibiotics had controlled menaces like tuberculosis and typhus, and the mechanisms of bacteria and viruses were well understood. Environmental health, the study of disease transmitted through the environment, included another focus: industrial toxins.

During the 1970s health officials commonly stated that as much as 10 percent of cancer was environmental in origin, with pesticides and industrial chemicals responsible for half the incidence. Even as regulatory measures were put in place— the Occupational Safety and Health Act, the Clean Water Act, the Clean Air Act, the Safe Substances Control Act—epidemiologists hurried to analyze the risks.

"The National Institute of Environmental Health Sciences was born out of the illusion that we were living in a sea of chemicals," says Owen Colman, a program manager at the institute who works with Perera today. "There was a lot of pressure to understand what was going on."

By the second who got sick after years in the workplace and what did what, and then comparing their exposures to chemicals,
investigators were able to put hard numbers on the carcinogenic properties of many substances. The most pervasive carcinogen, cigarette smoke, was found to be the top killer outside the workplace. Exposure to it increased the risk of lung cancer by 20 to 30 times over that of nonsmokers. None of this research required any laboratory bludgeon. When researchers compared retrospective studies of smoke exposure and death rates, the impact was unmistakable.

Sensing a wave of causation, and Perera began to wonder about the humanity at low exposure to other common chemicals. "I'm seeing this research happen, and it's great," she says. "Not at the same time. Hundreds of thousands of other chemicals are being exposed. The biggest challenge was air pollution. It's so hard to module comparable with environmental conditions. I thought, I'm going to take the thing to scale, the air pollution story.'"

In 1976 an environmental advocacy group, the Natural Resources Defense Council (NRDC), hired Perera as a health scientist. Then in 1977, the council took a tough stance on toxic threats to the natural world and human health. She and a colleague at the NRDC were a book, "Respirable Particles," in 1979, which warned that the government's air pollution standards for American cities and industries were failing to curb the very smallest particles. "The basis of the defense was to weigh the air filters," Perera says, "and these covered only the larger particles, not the ones down to about two micrometers (about 1/5 the width of a human hair). We said that the Environmental Protection Agency should regulate these finer particles, and no one listened to us."

To read "Respirable Particles" today is to appreciate how far ahead of her time Perera was, and how little research to the point of particles. Studies associating urban air pollution was a chronic effect of increased and tighter control around the particulate matter. As a result, the EPA began to monitor and regulate particles as small as 10 micrometers, also called "micros," in 1987, but did not get down to the level of 2.5 micrometers, as Perera had wished, until 1997, when standards were tightened. Fine particles are considered more dangerous because they lodge deeply in the lungs and aren't easily filtered out. Trapped there, the toxic fractions, including hydrocarbons, can pass into the lung tissue.

"Evidence came out that fine particles could be more dangerous than believed," says Raymond Werner, chief of air programs for the New York and New Jersey region of the EPA. "We're able to home in more, and more, based on what we've learned from her studies and others' studies. We've updated the ante on the kind of information we're seeking."

While at the NRDC, Perera became interested in a hydrocarbon compound called benz(a)pyrene, or B(a)P, for short. It had a long shelf life in toxicity. B(a)P is found in coal tar, and coal tar was linked to cancer in English chimney sweeps as long ago as the 1700s. B(a)P is a constituent of the sooty yellow emissions of coke ovens (coke, derived from superheated coal, is used in steelmaking). Workers tending coke ovens were at high risk of developing lung cancer, according to the occupational health research, and the workers who smoked were at even more risk. Cigarette smoke also contains B(a)P. In 1981 the National Institute of Environmental Health Sciences declared that benz(a)pyrene was "reasonably anticipated" to cause cancer in humans.

When Perera returned to Columbia in 1979 for her doctorate in public health, she was eager to close the case on B(a)P. DNA, Weinstein recalls. "My group in 1979 showed the molecular structure of the B(a)P adduct. We thought, What's that tells you the DNA has been clobbered by a carcinogen. It was a carcinogen on a critical molecule. We could use that as a marker."

Perera began working with Weinstein on a small study comparing two groups of hospital patients. One group was suffering from lung cancer; the other was a group of orthopedic patients as a control sample. Perera and Weinstein detected the benz(a)pyrene adduct in some of the cancer patients but not in the control group. Although the patients' exposure to cigarettes and other hydrocarbon sources...
was not integrated with the results, the idea of a marker for lung cancer held up.

"We showed it could be done," Perera said. "There was a suggestion of risk in humans. Epidemiology can be done without markers, and it can be very elegant, but to me it was important to know where and when to intervene, before the tumor is locked in and inevitable."

Next, she and Weinstein wrote a conceptual paper that would become the founding document of molecular cancer epidemiology. The paper laid out four categories of markers according to what Weinstein called "a continuum of causation."

The first type of marker simply measures a dose. A foreign chemical, like lead, is detected in fat or blood or urine, but the body hasn't done anything special to it except to retain it or eliminate it. The second type of marker has been transformed through a "biologically effective" reaction. A DNA adduct is an example, because the toxic agent has bonded, at least temporarily, with genetic material. Individuals differ greatly in the amounts of adducts that their blood and tissues will express in response to an exposure. The range can be 100-fold or more.

The third kind of marker Perera calls "preclinical," meaning that a medical diagnosis may be in the offing. Examples are chromosomal aberrations or a mutation in a gene that has been implicated in the formation of a tumor. Finally, there are innate markers of susceptibility. Certain genetic variations make certain people more likely to succumb to an illness. Over the last 20 years, genetic research has provided many markers of susceptibility, just as Perera and Weinstein predicted.

Overall, the environment's suspected role in provoking cancer is becoming less prominent as genetic and other predispositions are uncovered. Lifestyle factors, like diet and smoking, still weigh heavily, but professionals say that pollution and industrial carcinogens account for 5 percent or less of cancer incidence. Of Perera's peers in molecular epidemiology, perhaps the best known is John Goopman of Johns Hopkins University. Goopman doesn't study industrial toxins at all. He examines how aflatoxin, produced by mold on grains, peanuts, and other crops, leads to liver cancer in Asia and Africa.

The Secret of Perera's Success: I concluded, was adaptability, both personal and professional. When air pollution declined in American cities in the 1980s, Perera found new urban sites abroad, first in Finland and then in Poland, where she could pursue hydrocarbons and their biological signatures. The opportunity to work in Poland came after the collapse of Soviet Communism. U.S. health officials offered to help their counterparts who were struggling with rampant, unrestricted coal burning by factories and homes.

The pollution in Poland jolted Perera into thinking about children as study subjects. "The air stung my eyes," she said. "I was alarmed—well, not alarmed, but I was concerned. I thought about the children. Let's go into the womb, I thought."

In the 1990s health officials and researchers converged on the view that children were more sensitive than adults to pollutants and so merited additional protection. Exhibition A was lead, which set back children's mental development without appearing to harm adults. Pesticides in foods and contaminants in air and water posed extra hazards, if only because children absorb relatively more of these substances. Perera and her associate Robin Wyno pointed out in a 1995 paper that children have "higher breath- ing rates, ingest more drinking water, and consume more calories of food per unit body weight than do adults." So the researcher adjusted her sights for cancer research to children and added markers for cognitive development and asthma to her molecular toolbox.

"The value of a susceptible subpopulation like children," says Gwen Colman of the National Institute of Environmental Health Sciences, "is that it helps you get away from the mean, which may cloud the truth. Why waste your efforts on protecting everybody when not everybody is affected?" When the institute and the EPA awarded funding in 1998 to create children's health research centers around the country, Perera set up shop as director of the Columbia Center for Children's Environmental Health. Her assumption was that if air pollution is bad for mothers and infants, it's worse in communities where mothers and infants are poor. Perera's team analyzes housing conditions and psycho-social stressors as well as polycyclic aromatic hydrocarbons, cigarette smoke, and the effects of lead and pesticides on children's health.
Chemicals can shut genes off or turn inactivated genes back on. When genes are disrupted, a cell can turn cancerous

Peggy Rasmussen, a study participant, is close to her dye stain. She will wear the waist sash, which indicates she is a cell with cancer. She told Perera that the dye stain was a visual representation of her cancer cells. She also told him that the study was important because it could help find new ways to treat cancer.

Tycko is examining gene silencing in PEG-1. The growth factor gene that's active in the placenta and in the development of the fetus. Perera would like to know how the gene's activity can be switched on and off by environmental toxins. If so, Tycko's PEG-1 marker might be paired with one of her own. Ideally, the markers would lie on the same path in the maze connecting the mother's environment, the placenta, and the newborn.

Perera turned the full beam of her attention on Tycko as he explained how the cool-blood samples showed that the gene's activity varied and that it varied in ways that suggested the differences were not random but environmentally influenced. In other words, the project that she had in mind, to test PEG-1 as a marker, was feasible.

"What's this gene's relation to cancer?" Perera asked.

"It's not clear-cut," Tycko said cautiously. "It's related to growth. They began to discuss a joint venture. "You're the one who knows how to measure the exposure," Tycko said. Perera left the meeting encouraged, saying, as she strode briskly back toward the Hudson River: "We're very poor compared with the 'hard' sciences. On the other hand, the hard sciences are saying they need the environmental side."

The sky was a high, blue, clear as a whistle. If there is a single cloud hanging in the way of molecular epidemiology, it's called "validation." A validated marker can be used precisely, accommodation whatever question is asked of it, so that scientists and policymakers can take it off the shelf, plug it into their risk calculations, and have confidence in the results. Blood levels of lead predict neurological deficits far better than any DNA adduct or aberrations can predict a cancer. The day for cancer markers will come, but it will take more spending, and it will take a much deeper understanding of carcinogenesis.

"It's slow," Perera said, "but I'm patient." She read from notes she had written, so as to be clear. "The picture has become more complex. It won't be solved in my lifetime. I won't solve these problems, but I hope to establish methods for others to follow."