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The species of
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MARCH 2006

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 fissure in the rust-colored cliffs of the Palisades across the river in New Jersey. What a terrific view Frederica (Ricky) Perera has from her 25th-floor office.

However clear the day, the view is deceiving. For 25 years the 64-year-old professor of environmental health sciences at the Columbia University Mailman School of Public Health has been probing 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 conveyed 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 mo-

lecular changes. Her work ranges from the noxious tailpipe to the precancerous cell, evaluating all the possible way 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 is 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 168th Street. When we get to the Audubon Clinic, which serves 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 strolls 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 fingerprints 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 identi-

'I don't like advocacy without a scientific basis,' Perera told me firmly. 'The passion without the facts won't work'

fies and compares markers in the samples. Perera isn't interested in raw amounts of pollutants in the subjects' tissue or fluids. Instead, she looks for signs of hydrocarbon exposure in the genetic material of the white blood cells, because chemical interference with DNA can initiate cancer.

The National Institute of Environmental Health Sciences, the health agency that pursues the environmental causes of cancer, has been a major funder of Perera's center. The institute has seen its support pay off in 54 publications by Perera's group in the past four years. A paper published just before my visit has caused a stir of media interest. The Columbia investigators analyzed three possible links in the tortuous chain from chemicals outside the mother to cancer inside the child.

One reading measured the levels of harmful hydrocarbons in the air that 60 mothers inhaled in the weeks before they delivered. The other two measurements recorded levels of two markers in white blood cells of the women and their infants. One is a type of molecule, called an adduct, 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 adducts 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 implications—Perera edits her center's releases line 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 isn't 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 this one-two punch—her research points directly to problems she thinks society should resolve.

In her office I question 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, because three measurements lining up in a sequence to cancer are a lot 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,

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 pollution? That definitely needs investigating, she says.

But by now she has picked up the implication of my questions: Do her social concerns taint her research results; is she biased? "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 90 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 Toxic Substances Control Act—epidemiologists hurried to analyze the risks. "The National Institute of Environmental Health Sciences was born out of the notion that we were living in a sea of chemicals," says Gwen Collman, a program manager at the institute who works with Perera today. "There was a lot of pressure to understand what was going on."

By recording who got sick after years in the workplace and who did not, and then comparing their exposures to chemicals,



"We need the environmental side because the Human Genome Project isn't going to give us all the answers," Perera says.

investigators were able to put hard numbers on the carcinogenic potencies of many substances. The most pervasive carcinogen, cigarette smoke, was identified outside the workplace. Exposure to it increased the risk of lung cancer 9 or 10 times over that of nonsmokers. None of this research required any laboratory biology. When researchers compared retrospective studies of smoke exposure and death rates, the impact was unmistakable.

Smoking is voluntary, of course, and Perera began to wonder about involuntary low-dose exposures to other common chemicals. "I'm seeing this research happen, and it's great," she says. "But at the same time hundreds of thousands of others are being exposed. The biggest challenge was air pollution. It's so hard to measure compared with waterborne contaminants. I thought, *That would be the thing to tackle, the air pollution story.*"

In 1976 an environmental advocacy group, the Natural Resources Defense Council (NRDC), hired Perera as a health scientist. Then as now, the council took a tough stance on toxic threats to the natural world and human health. She and a colleague at the NRDC wrote 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 method [of detection] was to weigh the air filters," Perera says, "and these captured only the bigger particles, not the ones down to one or two micrometers [about 1/50 the width of a human hair]. We said that the Environmental Protection Agency should regulate these fine particles and undertake a research program."

To read *Respirable Particles* today is to appreciate how far ahead of her time Perera was, or at least ahead of the regulators. Studies associating urban death rates with air pollution have since drawn a tighter and tighter circle around fine particulate matter. As a result, the EPA began to monitor and regulate particles as small as 10 micrometers, also called microns, in 1987, but did not get down to the level of 2.5 microns, as Perera had urged, until 1997, when standards were tightened. Fine particles are considered especially dangerous because they lodge deeply in the lungs and aren't cleared by coughing. Trapped there, the toxic fractions, including hydrocar-

bons, 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 upped the ante on the kind of information we're seeking."

While at the NRDC, Perera became interested in a hydrocarbon compound called benzo[a]pyrene, or B[a]P for short. It had a long rap sheet in toxicology. B[a]P is found

She wrote a long paper, her first work in a scientific journal, about the compound's harmful properties. She called for the EPA to rein in B[a]P pollution under the Clean Air Act. But by then the general cleanup of America's air had resolved the worst of the problem. The EPA never did regulate the substance.

PERERA'S THESIS ADVISER AT COLUMBIA WAS a molecular biologist named Bernard Weinstein. "My lab was interested in DNA adducts, how B[a]P bound to



Reading medical detective stories influenced Perera's interest in public health. She now studies pollution exposure

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 benzo[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, Wow, 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 benzo[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

development 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,

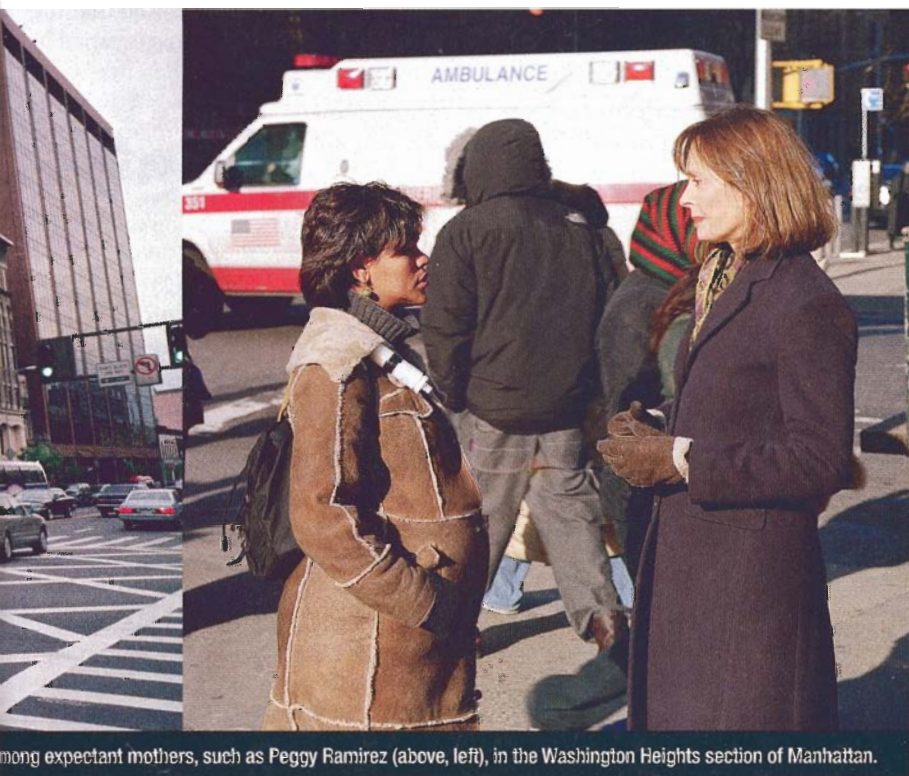
found new urban sites abroad, first in Finland and then in Poland, where she could pursue hydrocarbons and their biological signatures. The opportunity to work in Poland came after the collapse of Soviet Communism. U.S. health officials offered to help their counterparts who were struggling with rampant, 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. Exhibit 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 Whyatt pointed out in a 1995 paper that children have "higher breathing 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 risk from adults to children and added markers for cognitive development and asthma to her molecular toolbox.

"The value of a susceptible subpopulation like children," says Gwen Collman 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 psychosocial stressors as well as polycyclic aromatic hydrocarbons, cigarette smoke,



Among expectant mothers, such as Peggy Ramirez (above, left), in the Washington Heights section of Manhattan.

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 de-

velopment 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 Groopman of Johns Hopkins University. Groopman 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

insecticides, toxic metals, and indoor allergens. The Columbia center not only collects health data from its subjects but also offers health instruction.

Counting staff and scientists, about 50 people are employed full- or part-time on projects. Perera has teamed economists and psychologists with toxicologists and analytical chemists. "I'm an interdisciplinary figure," she said, smiling at the grand description. "I like bringing together juxtapositions. As one of my advisers said, to be 'interdisciplinary' is to have several skills in one skull."

Perera has people skills in spades. Christopher Dickey, one of her graduate students and later a research assistant, recalled going to scientific meetings with Perera in the early 1990s, when molecular epidemiology was new. Dickey would watch in admiration as his boss picked the brains of potential partners. It wasn't just advice on biological markers she sought, it was also help in paying for the analyses. "She is a master of those collaborations," he said. "She's phenomenal at it. She gets people with different agendas to work together."

Dickey gave two reasons for her persuasiveness: "Sensitivity—I haven't seen it honed in other people as finely as it is in Ricky. Also, she's physically striking and extremely polished. It's a little intimidating even. There aren't that many with that charisma."

When I visited, Perera was confident enough to open all her staff meetings to me. She ran the agenda and dealt with problems and interruptions with an unflinching calm, her voice relying on a softly rising tremolo for its effect rather than a boost in volume. She penned a note to herself on a fingernail—"Wed at 9"—for the next meeting.

No edges were evident, nor any abrasions from the harder climb a woman has to make in the largely male world of science. The closest she came to a feminist statement was when I referred to the DNA adduct, in use for more than 20 years, as the granddaddy of biological markers.

"It's the grandmother, don't you think?" she says, arching an eyebrow.

On the last day of my visit we went to see her latest collaborator, Benjamin Tycko, a cancer geneticist at the Colum-

bia-Presbyterian Medical Center with much fancier digs than her own. Perera had sent him cord-blood samples for a trial run of their project.

Tycko studies a phenomenon called gene silencing, in which one of a person's two copies of a gene is shut off. Normally a person's gene-silencing patterns are inherited from one parent or the other. But chemicals, including those in cigarette smoke, can shut genes off, too, or turn inactivated genes back on. Sometimes, when genes regulating growth are switched on

'Chemicals can shut genes off or turn inactivated genes back on. When genes are disrupted, a cell can turn cancerous'



Peggy Ramirez, a study participant, is close to her due date. She will wear the white cylinder, which monitors airborne chemicals, for 48 hours.

or off, a cell turns cancerous.

Tycko is examining gene silencing in *PEG-1*, a growth-factor gene that's active in the placenta and in the development of the fetus. Perera would like to know if 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 cord-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 exposures," 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, hard blue, clean 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, accommodating 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." ❏