Inside the womb, a fetus seems buffered from the outside world. Her mother’s sturdy pelvis holds her in place, the placenta filters her blood and nourishes her growth, the amniotic sac cushions her against bumps. Yet even before her neural tube formed in the days following conception, her cells already had a memory. Incorporated within her DNA, the child’s cells carry the biochemical legacy of her mother’s past and ongoing interactions with the environment.

More than chromosomes pass from mother to child, then. Indeed, the very air a woman breathes and the chemicals with which she has come into contact become her child’s legacy, leaving marks that may be carried across the generations.

For decades, Mailman School researchers have worked to unravel the connection between toxic exposure—secondhand smoke, combustion-related air pollutants, flame retardants, insecticides, chemicals in plastics—and physiology. Animal models have long served as the gold standard for investigating how mammals respond to different chemicals. In recent years, powerful new tools have emerged to augment what those experimental models have revealed. Using a growing body of epidemiological evidence and a better
grasp of how insults to human DNA are expressed, these scientists are painting an increasingly detailed picture of the mechanisms by which environmental exposure affects human health over a lifetime.

**TOXIC FOOTPRINTS**

Frederica Perera, MPH ’76, DrPH ’82, PhD ’12 founding director of the Columbia Center for Children’s Environmental Health (CCEH), began delving into the effects of air pollutants on fetal and childhood development as a graduate student at Columbia in the late ’70s.

Perera decided to analyze the effects of polycyclic aromatic hydrocarbons (PAHs), a class of air pollutants found in vehicle exhaust, cigarette smoke, and other products of incomplete combustion. She wanted to know whether it was possible to detect PAHs latched onto DNA in the blood and lungs of humans and use that biomarker to predict the risk of lung cancer—questions no one had investigated before. Scientists at the time believed that the placenta was impervious to the outside environment, so for her PAH-free control, Perera collected samples from newborns and their placentas. She planned to compare those clean samples with DNA from adults exposed to PAHs. What she found surprised her.

“We were seeing damage from PAHs in these supposedly pristine control samples, and clearly the contaminants were getting into the fetus from the mother and being transferred across the placenta,” she says. “That’s what raised my alarm and turned my focus to this susceptible life stage.”

Building on this work, in the early ’80s Perera and her mentor, Bernard Weinstein, MD, proposed a new way of studying the causes of human disease. Now known as the field of molecular epidemiology, their technique integrates biomarkers—the footprints left in blood, urine, and tissues when chemicals are absorbed by the body—with epidemiological data. With their new tools, scientists could investigate the continuum between exposure and clinical outcomes months and even years later and use those findings for prevention. “Epidemiology,” she says, “has become more powerful with the use of biomarkers, ‘omics,’ and sophisticated imaging, which weren’t available in the past.”

In the intervening decades, Perera and her colleagues at the CCEH have extended their studies to include over 2,000 at-risk children in the United States, Poland, and China, looking for clues to the effects of prenatal exposure to a wide array of compounds on neurodevelopmental disorders, asthma, and obesity, as well as potential risk of cancer. Many investigators are involved, sharing and enriching the Center’s resource of large
prospective cohorts, lab and data cores, and biospecimen and data banks.

A NEW DIMENSION

Epidemiologist Virginia Rauh, ScD, professor of Population and Family Health, also uses biomarkers to measure clinical disturbances among children exposed to pollutants in the womb. For two decades, the center has collected data on more than 700 children. Analyses by Rauh and Perera with Professor Emeritus Robin Whyatt, DrPH, have documented a correlation between high levels of exposure to PAHs—and to the organophosphate insecticide chlorpyrifos—with brain anomalies and adverse cognitive developmental effects in childhood, as well as motor changes through adolescence.

Many of these findings, says Rauh, fly below the radar; they appear only subclinically in most children. To detect such subtle signs, Rauh developed what she calls a “dimensional approach,” a combination of data points, to see at-risk children as a whole and predict their developmental trajectory.

“In psychiatry, clinical problems are defined by meeting a threshold,” says Rauh. “For example, one would have to have five out of eight possible symptoms. But sometimes there is variability in all of these different areas, and they miss clinical significance. The dimensional approach enables us to make a comprehensive profile of a child across four or five different domains that may not meet the clinical standard for a single diagnosis but may well reflect a unique picture of a child who has been highly exposed.”

Rauh starts with good old-fashioned epidemiological data to identify the most vulnerable populations and home in on the time and place associated with particular symptoms. Then she layers in biomarkers, neuropsychological tests, and even brain imaging—all tools that can help piece together the typical phenotype of a child who has been exposed to high levels of pollutants.

This approach, says Rauh, allows for a more sensitive examination of toxic effects on the brain and on childhood behavior, further identifying links between exposure and mental health symptoms that might otherwise be missed.

HOW CAUSE BECOMES EFFECT

For regulators in the United States assessing a particular chemical, however, even the most robust associations rarely suffice. American policymakers demand a detailed explanation of how a chemical works in the body before they take it off the market, says Andrea Baccarelli, MD, PhD, chair and Leon Hess Professor of Environmental Health Sciences. “It’s usually hard to convince policymakers that certain chemicals are toxic unless you understand the mechanism—how the chemical acts to cause the disease.”

Enter “omics,” shorthand for the myriad data generated by the genomic revolution. Genomics refers to the sequence of genes within our cells; epigenomics, how genes are expressed; proteomics, the particulars of the proteins encoded by our genes; and mitochondriomics, the role of genes unique to the mitochondria, the cell’s power plant. With emerging biochemical and sequencing techniques, a wealth of opportunities have emerged for investigators to drill down into the molecular changes that occur within a person’s lifetime.

Take, for instance, epigenomics (aka epigenetics): Rather than relying on the sequence of DNA, which stays fixed in every cell, epigenetics focuses on gene expression—how chemicals intertwine themselves into the DNA and affect which genes are turned on or off. “Gene expression is much more interesting than just looking at the genome,” says Baccarelli. “It’s a function of the DNA that changes during our lives. It’s flexible and can be shaped and reshaped by the environment.”

“THOSE MOST AFFECTED BY TOXIC EXPOSURE ARE OFTEN SOME OF THE MOST VULNERABLE.”
Like the annual rings in a tree’s trunk, changes in gene expression take time to emerge. But once they manifest, they persist. “Our cells and tissues remember our past environments, positive or negative,” says Baccarelli. “What disrupts our cells ends up having effects in our bodies many years later.”

Baccarelli, who joined the Mailman School faculty in June, has made such delayed reactions—including those transmitted across generations—a centerpiece of his research. He’s used the epigenome to link lifelong exposure to air pollution and heavy metals with age-related cognitive decline in the elderly. He’s also examined the intergenerational effects of an industrial disaster in his native Italy in the ‘70s and how the children of women exposed to the chemical cloud when they were girls have been afflicted with thyroid dysfunction. “This formal memory, this gap in time, is particularly interesting,” he says, “especially for fetal exposures and neurodevelopmental disorders.” By identifying what happens in the gaps, Baccarelli sees a chance to change or even prevent aberrant gene expression before diseases develop later in life.

“We’re bringing epigenomics to the next level,” he says, “by doing studies that are epigenome-wide, so we can measure hundreds of thousands or even millions of epigenetic clues at once.”

**BY DESIGN**

For policymakers, the bottom line boils down to this: Can scientists make the leap from establishing correlation to proving causation?

Before biomarkers, omics, and big data, epidemiologists testing their hypothesis that a particular exposure led to a specific health outcome labored for decades to reveal even a correlation of risk—that is, statistical evidence that two events were associated by more than chance. They identified and measured chemicals, assessed nutritional factors, documented features of the environment, and estimated exposure through monitoring, food samples, and questionnaires on behaviors, diets, and occupations.

“We still do those things,” says Perera. And more. At the Mailman School, environmental scientists team up with biostatisticians to develop rigorous techniques for integrating epidemiological methods with the wealth of data from biomarkers, omics, and imaging.

“Using new methods to analyze these new kinds of data,” says Associate Professor of Biostatistics Shuang Wang, PhD, “makes results more valid and helps assure us that the conclusions are based on sound methods.”

**EVIDENCE-BASED POLICY**

As investigators meld scientific methods to flesh out their understanding of prenatal toxic exposure, regulatory bodies like the Environmental Protection Agency are rethinking how they craft evidence-based policy to protect public health. Consider, for example, the body of evidence available to the EPA on the safety of the pesticide chlorpyrifos, a compound whose effects Rauh, Perera, and Whyatt have investigated in multiple studies.

Farmers and urban housing authorities alike rely on pesticides to kill insects and rodents that threaten crops, make living environments uncomfortable or risky, and exacerbate diseases like asthma. Among them, the organophosphates—a class of neurotoxins, including chlorpyrifos, that interrupt enzymes vital to nerve function—have been prized for their efficacy. In recent decades, they’ve been scrutinized due to concerns about their effects on children. In 2000, the EPA banned chlorpyrifos for residential use, significantly reducing exposure in urban areas.

Large farms, however, retained the option to include chlorpyrifos in their pest-control arsenal. Now the EPA is weighing whether to further restrict its use. Among the findings under consideration are the results of three epidemiological studies—including one conducted by
Rauh and colleagues—all funded by the National Institutes of Health and jointly named 2011 Paper of the Year by the journal Environmental Health Perspectives.

Each study was designed and conducted independently, with a unique roster of participants and investigators. Yet all three confirmed similar neuropsychological disturbances in 7-year-olds whose mothers had positive biomarkers for exposure to chlorpyrifos during their pregnancies. While each study looked at different biomarkers—in maternal urine and in blood collected at birth from the umbilical cord—all of the participating children were assessed with the same developmental test. “What’s really powerful,” says Rauh, “is that while these studies were all observational, not experimental, they corroborate one another’s conclusions.”

As the EPA considers potential safeguards to prevent adverse exposure, the role of epidemiological data in the regulatory process remains contentious, with stakeholders and scientists raising concerns about how to proceed. Others in the scientific community, including many public health advocates, point out that epidemiological analyses supplement experimental data gleaned from animal models, furnishing a more complete picture of how environmental exposures affect people’s health. “We’ve entered an age when the EPA and other regulatory agencies can look at findings from epidemiological and molecular epidemiological studies, as well as experimental studies, whether they be in vitro or using laboratory animals,” says Perera. “They can take all of the data and do a full strength-of-evidence evaluation.”

Ultimately, says Baccarelli, scientific rigor offers the greatest promise to those who are most vulnerable—the pregnant women living in impoverished urban neighborhoods or working in fields of vegetables doused with pesticides. It is their children who will bear the legacy of prenatal chemical exposure. “We in environmental health are lucky that what we publish and what we do is monitored very carefully by policymakers,” he says. “Hopefully, policies will be geared toward protecting those who are most susceptible, so the levels of acceptable exposure will be lowered to the point of being safe.”

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