

Nigel Paneth, M.D., '70: Snow job

By Jennifer Durgin

When a pediatric researcher claims to be interested in aging, the apparent oxymoron turns heads. Perhaps that's why Dr. Nigel Paneth, a neonatal epidemiologist, is so fond of stating exactly that.

"I study the aging placenta," he declares. When a baby reaches 40 weeks' gestation—a full-term pregnancy—the infant has no further need for the placenta. So at that point, posits Paneth, "it's an aging organ," whereas "at 28 weeks or 32 weeks, the placenta is still very functional."

This intriguing observation is characteristic of Paneth's unconventional approach to research. For more than 30 years, he has combined the disciplines of pediatrics and epidemiology to study what can go wrong during pregnancy, birth, and early infancy—and what can be done to solve problems when they do occur. Recently, Paneth, a professor at Michigan State University (MSU), has been investigating the association between cerebral palsy and low thyroid hormone levels in premature infants.

To explain this research, Paneth first poses a very broad question: How do premature babies' brains get damaged? "The first thought," he says, is that "they're born so immature and so little and so unable to withstand everything that's going on that they get into trouble—respiratory and brain and so forth. They lack oxygen, they lack this, they lack that." That's the conventional theory.

But Paneth has another hypothesis. Maybe what goes awry, he suggests, is that preemies are separated too early from the placenta and the support that it pipes in from the mother's body. For example, the thyroid hormone thyroxine is essential for proper brain development. In the womb, fetuses draw on their mother's stores of thyroxine, transmitted through the placenta. Once they're born, babies must produce their own thyroxine to develop properly. Twelve hours after birth, healthy, full-term babies double or triple their production of thyroid-stimulating hormone, says Paneth. That surge, he notes, is a "wake-up call: 'Hey, wake up. You're out in the real world by yourself.'"

But in preemies, that surge often doesn't occur. Instead, their thyroid hormone levels plummet and can stay low for weeks. Paneth

Grew up: England, Switzerland, Israel, New York City

Education: Columbia College '68 (A.B.), Dartmouth Medical School '70 (B.M.S.), Harvard Medical School '72 (M.D.), Columbia University School of Public Health '78 (M.P.H.)

Training: Pediatric intern and chief resident, Bronx Municipal Hospital Center; clinical fellow in pediatrics, Albert Einstein College of Medicine

Family heritage: His mother was British and his father was a Hungarian—a Jewish anti-Nazi journalist—who fled to England in 1939

Cherished possession: An 1855 book by German hygienist Max von Pettenkofer, with notes in the margin by London medical officer John Simon; both were dead wrong about how cholera was transmitted

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coauthored a 1996 paper in the *New England Journal of Medicine* which showed that preemies with very low levels of thyroxine were much more likely to develop cerebral palsy and other cognitive and motor problems than preemies who had more normal thyroxine levels. Infants with the lowest levels seemed to have the most severe, long-term developmental problems.

These findings beg the question whether giving these infants thyroid hormone supplements would improve their outcomes. Paneth and other researchers just completed Phase I of an international trial testing just that question; the results were in but not yet available at press time for this article.

However, Paneth is careful not to get too enthusiastic about the idea until it has been fully tested. If supplementation is shown to work, he says, he'll be able to look back on

that 1996 paper "and sound proud of it." But if supplementation does not improve babies' developmental outcomes, then "that paper really didn't lead us anywhere. . . . It could be that the thyroid hormone simply correlates with something else."

In Paneth's field, "one needs a skeptical mind and a good deal of education on epidemiology and statistics," notes Dr. Alan Leviton, a pediatric neuropathologist and neuroepidemiologist at Boston Children's Hospital. Leviton and Paneth have been working together for almost a decade on a study to identify protein biomarkers that can predict early brain damage and later developmental disabilities. The collaborators frequently consult each other for feedback and advice on other projects, too. "We always challenge each other with, 'Might you be wrong?'" says Leviton.

Most recently, Paneth put his experience and skepticism to use as one of the designers of a massive project funded by the National Institutes of Health (NIH). Called the National Children's Study, it will follow 100,000 U.S. children from before they're born until they're 21 years old to examine the effects of various environmental influences. "Environment" is being defined broadly to include social, familial, and cultural influences, as well as physical, biological, chemical, and genetic factors. Paneth is also the study's principal investigator for Wayne County (which includes Detroit), one of

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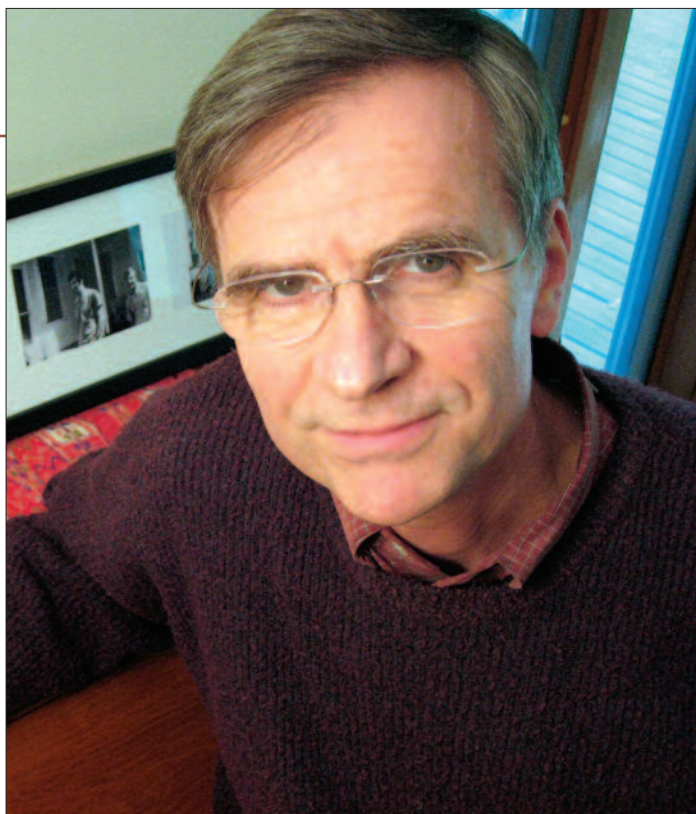
26 counties nationwide in the first wave of the study.

Paneth has lots of experience with big, long-range observational studies. In the 1980s, he got NIH funding for a project called the Neonatal Brain Hemorrhage Study, which has followed more than 1,000 low-birth-weight infants for more than 20 years. It has revealed many risk factors for brain damage in preemies, including how the baby is delivered, and it has helped to identify the best predictors of long-term outcomes for such infants.

Many of Paneth's colleagues have expressed doubts about the wisdom of his devoting so much time to the National Children's Study, given its unusually long timeline. "I won't see a paper out of this for 10 years," he says. "If you're at my age, that's possibly beyond retirement." But, he continues, "how can you not be involved in something so ambitious and so potentially powerful? Even if you have some hesitations about the details, you have to go for it."

"We see opportunity where others do not," says Leviton of himself and his Michigan collaborator. For example, when Paneth arrived at Michigan State in 1989, he saw an opportunity to start a program in epidemiology from the ground up. In 1997, that program became a department. By 2005, Paneth had established the only NIH-funded training program in the country that's devoted exclusively to perinatal epidemiology. The program accepts one predoctoral and two postdoctoral fellows each year. Leviton, who serves on the advisory board for the program, recently asked one of the trainees if the fellows actually get time with Paneth, given his numerous commitments. "He's too busy for everybody else, but for us he's available," Leviton recalls the graduate student saying.

"There are so many arrogant people in our field," says Leviton. He clearly does not put Paneth in that category, adding, "Nigel's refreshing that way." Perhaps Paneth's humility and skepticism stem from his wide-ranging intellectual curiosity. For example, to better understand the historical roots of his field, Paneth has long studied the life of Dr. John Snow, a pioneer in epidemiology and anesthesiology. Snow is famous for having pinpointed the source of an 1854 cholera epidemic in London. When local authorities insisted that cholera was caused by "miasma," or disease-causing vapors, Snow figured out that



Alumnus Nigel Paneth is one of the leaders of the massive NIH-funded National Children's Study, which will follow 100,000 children from before they are born to age 21.

the disease was actually being spread by contaminated water from a public pump. In 2003, Paneth and four other MSU professors coauthored a biography of Snow titled *Cholera, Chloroform, and the Science of Medicine: A Life of John Snow*; it was published by Oxford University Press.

"Snow didn't allow an education to get in the way of his genius," Paneth noted during an interview on National Public Radio shortly after the book came out. "He left school at 14. He was virtually entirely self-taught." Some of Snow's ideas, particularly about cholera, were not accepted during his lifetime, even after they had been proven accurate.

Snow's original writings are "exquisitely rare," says Paneth,

who collects old medical books. Paneth once purchased an uncatalogued box of 19th-century books about cholera from a dealer in Great Britain, hoping a volume by Snow might be among them. What he ended up with instead was "pretty much the entire repertoire of government reports on the [London] cholera epidemics in 1848 and 1854," says Paneth. "It was fascinating to contrast what John Snow was doing on his own, without any resources, and what the officials, who were paid [to investigate the epidemics], were finding."

What Paneth admires most about Snow is his originality. "What he understood that other people did not understand . . . [was that] of all the things you need to know about a disease, the single most important . . . is its mode of transmission."

Remembering that principle helps Paneth keep an eye on the big picture in his own research. Lack of thyroid hormone may indeed be the agent, or direct cause, of some forms of brain damage in preemies. But, he admits, thyroxine deficiency may be just one piece of a larger problem he calls "placental withdrawal syndrome."

Although he would likely balk at such a comparison, Paneth seems to embody several of the characteristics he so admires in Snow: unconventional thinking, cross-disciplinary training, an ability to see the forest for the trees, and a preference for research that can be readily applied. "I'm not interested really in research that just finds out enjoyable things to learn," says Paneth.

Only in research that improves people's lives. ■