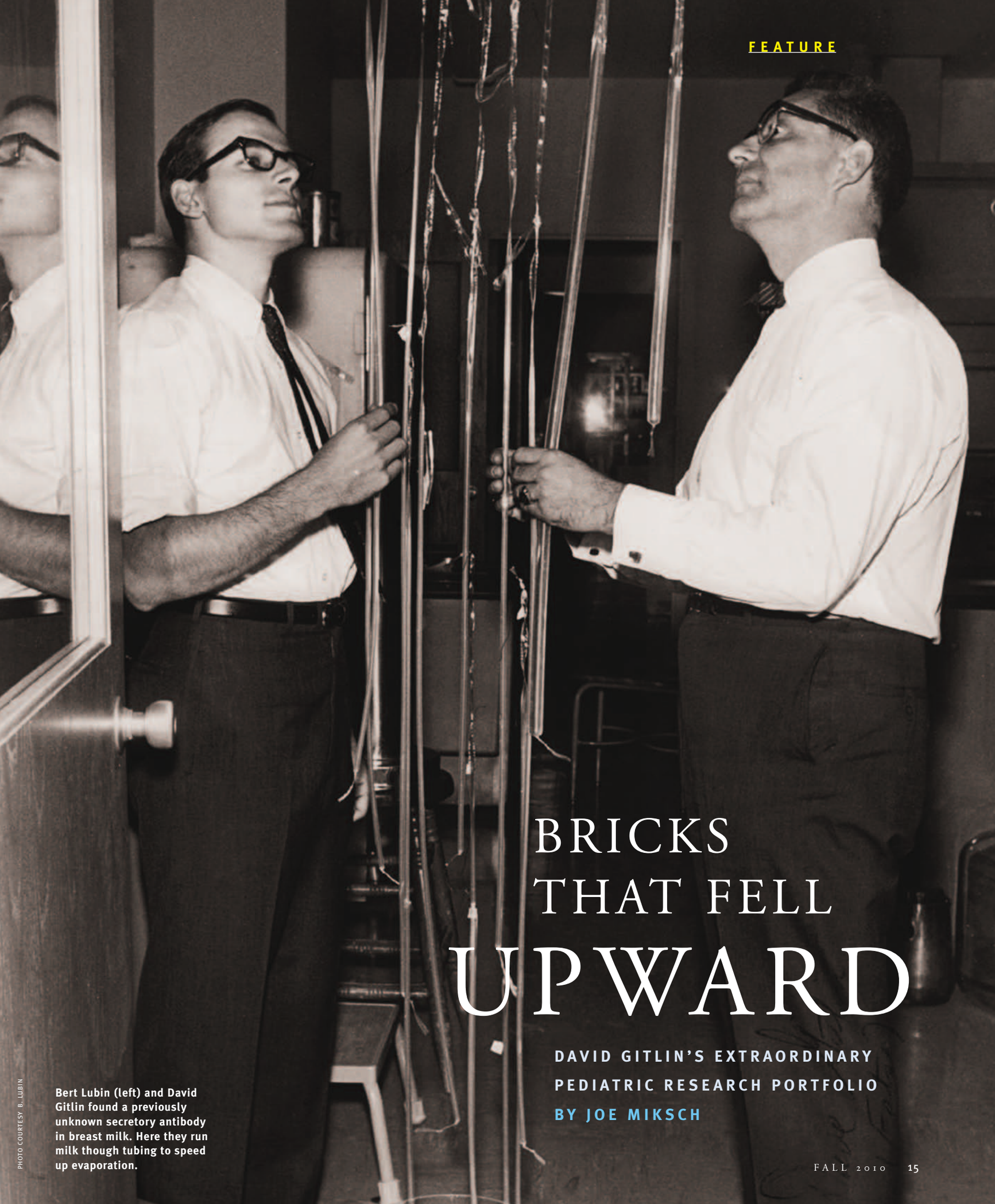


BRICKS THAT FELL UPWARD

DAVID GITLIN'S EXTRAORDINARY PEDIATRIC RESEARCH PORTFOLIO

BY JOE MIKSCH

Bert Lubin (left) and David Gitlin found a previously unknown secretory antibody in breast milk. Here they run milk though tubing to speed up evaporation.

PHOTO COURTESY B. LUBIN

In simple terms, David Gitlin wanted to know why some kids were more susceptible to infection than others.

He followed this line of inquiry from his 1947 graduation from the New York University College of Medicine through his years at Pitt, which began in 1963 and never really ended, as he remained an emeritus professor of pediatrics in the School of Medicine until his death, at 88, in January.

Gitlin melded biology, chemistry, and medicine to become a leading immunochemist—one of the first. He helped define and develop treatments for a host of immune disorders including agammaglobulinemia, an inherited disorder marked by very low levels of protective immune proteins called immunoglobulins.

Gamma globulin replacement therapy, which is still in use today, rescues thousands of children with agammaglobulinemia from their susceptibility to serious and repeated infection. Our understanding of how the immune systems of infants develop can be traced to his work involving the transfer of immunoglobulins from mother to fetus.

It's hard to overstate how prolific the scientist was: Gitlin unraveled the secrets of plasma protein metabolism in children with kidney disease, discovered how the intestine absorbs iron, found a biochemical marker for Wilson's disease, advanced the understanding of plasma protein production and distribution, and established that alpha-fetoprotein could be used to detect life-threatening birth defects in fetuses.

He was particularly proud of his alpha-fetoprotein work, says his son, Jonathan Gitlin. The work in plasma protein research initiated the start of a field that has led to the discovery of biomarkers for diagnosing diseases in infants.

"He always had the sense that there were many things you could monitor in maternal plasma that could give you a unique imprint of the fetus," Jonathan Gitlin says.

"He was a basic scientist, but he had a sense that true discoveries make a difference in the lives of children."

David Gitlin also liked to talk about bricks.

"He had this great expression, which I've never forgotten," Jonathan says of his father. "He said, 'Science is like sitting by a window, throwing a brick out the window, and you write down in your notebook, *Brick went down, brick went down, brick went down.*'" What if one day, you throw a brick out, and it goes up?

"'The difference between discovery and pedantic research,' he said, 'is that one person will write in the notebook, *Experiment didn't work; brick went up*. And the other person will stick his head out the window and say, *Where did the brick go?*'" He told me to always stick my head out the window and see where the brick went."

The younger Gitlin earned his BS from Pitt in 1974 and his MD from the School of Medicine in 1978 and is now chair of the Department of Pediatrics at Vanderbilt University and physician-in-chief at Monroe Carell Jr. Children's Hospital of Vanderbilt.

His father's pursuit of the upward-flying brick began in earnest in the early 1950s at Harvard University. There, he found himself in the lab of preeminent pediatrician Charles Janeway. Janeway, who was physician-in-chief at Children's Hospital Boston, had recruited Gitlin, a noted up-and-comer, to join the immunology lab he was starting in the basement of the Farley Building, which housed the hospital's inpatients.

Shortly after joining the lab, which included other pediatrics luminaries such as Fred Rosen, Gitlin played a key role in discovering the cause of and a treatment for agammaglobulinemia.

David Nathan, president emeritus of Boston's Dana-Farber Cancer Institute, was in hematology at Harvard, but regularly visited the lab.

"When I first went to [Gitlin], he was known as a guy who was a tremendous experimentalist, someone who could help you with any problem in the laboratory," Nathan says. "I was trying to measure hemoglobin synthesis, and I was trying to do it with radioactive amino acids. My problem was that I was worried that the glycine was being converted to serine. So I went to see him about that.

"He told me exactly what to do," Nathan says, admiration still in his voice.

In addition to being a savant of the bench, Nathan says, Gitlin possessed a formidable imagination. "He seemed to know exactly where the science would be going. He was such a curious man, like the Elephant's Child in [Rudyard Kipling's] *Just So Stories*."

Nathan says Gitlin—the man who used bricks as metaphors for good science—could also hurl verbal bricks at those he thought weren't making the most of their brain cells.

He remembers that first Gitlin encounter, when he needed help measuring hemoglobin synthesis:

"In this crowded laboratory," Nathan recalls with a laugh, "standing there was Gitlin's trainee, Fred Rosen [who went on to spend 50 years at Harvard, pioneered Boston's pediatric bone marrow transplant program, and made vital contributions to the understanding of immunodeficiency], washing Petri dishes. I'm asking this question, and Gitlin is listening. He looks up at me and says, 'You [idiot]!' And I said, 'What's that you said?' and he said, 'You've got a hearing disorder, too? You're an [idiot]!'"

Rosen, Nathan notes, continued to quietly wash his Petri dishes, "staying out of the line of fire."

But this unusual beginning wasn't an obstacle to admiring the man.

"He was amazing," Nathan says. "He was into everything from copper metabolism, to iron metabolism, to the turnover of immunoglobulins. His work on the absorption of iron

is such a famous paper. He clearly showed that there were two separate receptors for iron in the gut, and this precedes our knowledge of the receptor biology of iron by 40 years. It was an amazing paper. It just predicts everything we now know about iron absorption."

Nathan's stories—of David Gitlin's brilliance and prickliness—don't much surprise Jonathan Gitlin. He says his father had the kind of intellect that simply couldn't process how someone would make a mistake, in or outside the lab. "He could take some getting used to," Gitlin says with a chuckle. "The typical story is when we went on summer vacation, and he ordered ice cream with sprinkles. It came with chocolate covering instead of sprinkles. It was incomprehensible to him that it happened. His world was black and white in every possible way."

Gitlin's dedication to science was a direct function of this bichromatic way of living. Science was important, everything else, less so. When he needed a piece of equipment, David Nathan says, Gitlin wouldn't order it and wait for delivery, despite having the funding to do so. He'd rather make whatever he needed himself at home in his workshop. This was quicker, Gitlin thought, and the faster he could get back to his investigations the better.

Gitlin brought his black-and-white worldview to the University of Pittsburgh in 1963. While he was in great intellectual company at Harvard, the move to Pitt presented Gitlin with three great benefits: a promotion to full professor, the prospect of better funding, and a more collegial environment.

Richard Day was the chair of pediatrics at Pitt at the time. He, like Janeway at Harvard, wanted to invest money and intellectual capital into building pediatric immunology at Pitt. What better way to do so than poaching one of the earliest recruits to Janeway's lab?

Jonathan Gitlin says his father was in love with Pitt from the very beginning.

"He found the University of Pittsburgh to be a very collaborative environment for a university researcher."

Even when he didn't work directly with them, the younger Gitlin says, his father was thrilled to be able to bounce ideas off of investigators like Klaus Hofmann, the famed protein chemist. These were the sorts of things that didn't happen at Harvard, Jonathan Gitlin recalls his father saying.

"Pitt was ahead of its time in that way," Jonathan Gitlin says. "It was contiguous and integrated and was what everyone is talking about having these days: one university where the medical school wasn't divorced from the rest of the institution."

Because of this and the facts that Pitt had a freestanding children's hospital and put as much stock in teaching as in other aspects of medicine, the school was a comfortable home for Gitlin.

"More than anything he loved being a professor at this university," Jonathan Gitlin says. "If he met someone on a plane, he'd tell them he was a professor, not a doctor, not a scientist."

But a scientist he was. At Pitt, operating on the hunch that there were unique proteins made by the fetus transferred to maternal plasma—that might have a story to tell about fetal development and could be useful for diagnosing disorders in the unborn child—Gitlin delved into the world of protein synthesis.



COURTESY J. GITLIN

The Gitlins collaborated on research projects before celebrating Jonathan Gitlin's 1978 graduation from the University of Pittsburgh School of Medicine.

His hunch was spot on. That's when he began making critical advances in the understanding of alpha-fetoprotein. Studies resulting in papers in *The Journal of Clinical Investigation* (*JCI*) in 1966 and 1967 earned Gitlin the Medal of the University of Helsinki and the first Federico Gómez award from the Hospital Infantil de México in 1968. What Gitlin learned in terms of where, when, and how alpha-fetoprotein is synthesized led to its use as a tool to identify potential issues with fetal development.

(Gitlin also played a key role in developing the research arm of the Hospital Infantil de México. The relationship began during his time at Harvard and his main collaborator in Mexico City was the aforementioned Federico Gómez.)

Jonathan Gitlin considers the '67 paper a sign of things to come in medicine. "My father always looked at that one as the tip of the iceberg," he says. "I think what he did was very prescient. At that time, people were just beginning to think about [biomarkers]."

The level of alpha-fetoprotein is commonly used as a marker of risk for many birth defects during pregnancy, including spina bifida, and can indicate multiple births. Greater-than-normal levels can point doctors toward liver disease or certain cancers in adults.

David Gitlin was particularly proud of another *JCI* paper he authored while at Pitt. His co-author was a first-year medical student

named Jonathan Gitlin.

"Protein Binding by Specific Receptors on Human Placenta, Murine Placenta, and Suckling Murine Intestine in Relation to Protein Transport Across These Tissues," by Gitlin and Gitlin dealt with how proteins crossed the placenta, addressing the issue of passive immunity.

The paper was important, the younger Gitlin says, but not as important as what he learned while working on it. "The terrific thing for me was that I got to learn to do science from someone who was extraordinary at it," Jonathan Gitlin says. "I had the chance to sit with him and see how he thought through things and how he imagined the next set of experiments."

The education paid off—the younger Gitlin received the prestigious E. Mead Johnson Award for Pediatric Research in 1998, the same award his father won in 1956.

Bertram Lubin (MD '64) also trained with David Gitlin. Now president and CEO of Children's Hospital and Research Center Oakland, in California, Lubin had decided as a third-year medical student that he wanted to gain some research experience in a pediatrics lab.

"I was having a discussion with [Pitt immunologist] Richard Farr," Lubin recalls. "In our discussion, he said, 'We have this really brilliant pediatric immunologist coming from Harvard to Pittsburgh named David Gitlin. Don't be afraid of him!'"

Lubin wasn't, though he came to understand what prompted the warning, "[Gitlin] had a reputation for being rough and critical and not afraid to say anything he believed in regardless of the audience."

While in Gitlin's lab, Lubin was assigned a project that involved seeking answers to why breast-fed babies suffered fewer gastrointestinal problems than their bottle-fed counterparts. "So [Gitlin] said to me, 'I'd like you to go to Magee [Womens Hospital], collect breast milk, and pool it. We'll see if there are the same antibodies in breast milk that you see in plasma.'

"So I was walking around Magee with a breast pump asking for milk," Lubin says laughing. "He realized I knew nothing about what was going on, so he coddled me. But lo and behold, we found a new secretory antibody that could kill bacteria, *E. coli* in particular."

Working with Gitlin was a transformative experience, Lubin says. "The man was just brilliant, and I loved him. He treated me like one of his kids. I called him before I took this job [in 2008], and he said, 'I'm very proud of you.'

"I'm thankful to him for all the things he taught me—creativity and innovation and to not give up on something you believe can be done."

Dorothy Becker, an MD, absorbed the same lessons when she landed her first faculty position at Pitt in 1976. Now professor of pediatrics in the School of Medicine and chief of endocrinology and diabetes and director of the diabetes program at Children's Hospital of Pittsburgh of UPMC, Becker was given lab space near Gitlin as she launched her career.

Though their scientific foci differed, Becker says, Gitlin taught her a great deal about lab techniques and gave her equipment and materials she couldn't afford on her own as a young investigator.

She, like seemingly everyone who met him, thought Gitlin a brilliant scientist and was well aware of his prickly side. She benefited from the former but, unlike many, avoided the latter.

"I think quite a few people were nervous about him, but he was very supportive of me when I was young," she says. "He really helped me establish my lab and, actually, when he retired (in 1978), he donated everything he had to me."

Doing science was everything to him, Becker says, and sharing that passion was a key part of his personality. "He not only talked to me, but he listened to me," she says. "He would bounce ideas off of me and listen to mine, which for a very junior person was wonderful. I would say that his best attribute, though, was bringing me into his excitement."

What didn't excite Gitlin was anything at all related to institutional politics. This aversion, Jonathan Gitlin says, is why his father never sought a department chairmanship or any other formal leadership role.

Becker agrees that such a role wouldn't have suited her early mentor. "He didn't have patience for fools," she says. "But if you could argue with him intelligently, he was great. He was a mentor and a champion of science."

"My father was either upset about parking or about [lab] space or—" the younger Gitlin says of how his father vexed his higher-ups. "I told him once, 'You're the 5 percent of faculty that's a nightmare to any chair.' But scientifically, he was an extraordinary mentor. When he passed away, people called me to tell me that. He was a scientist's scientist."

"More than anything he loved being a professor at this university," Jonathan Gitlin says. "If he met someone on a plane, he'd tell them he was a professor, not a doctor, not a scientist."

After David Gitlin's retirement, Jonathan lent a hand cleaning out his father's office. Although it's not unusual to find a filing cabinet full of manila folders lurking about at the end of a career, the contents in one cabinet were something of a surprise to Jonathan.

"There were about 40 folders in there," he says. "I looked through them and said, 'Pop, I never saw these published.' Forty papers over 15 years! And he goes, 'Yeah, I never felt completely comfortable with these.'

"These were papers which I imagined most people would have published."

Putting aside those not-quite-good-enough papers, Jonathan Gitlin says, was emblematic of his dad's expectations of himself, his science, and everyone around him: Care enough to ask why a brick went up and never be satisfied until you understand.