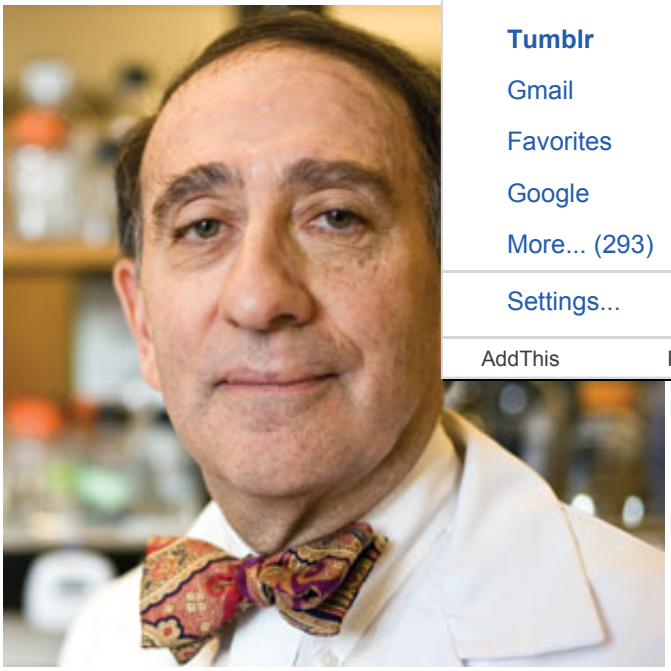
Resistance Fighter

Stuart Levy has spent a lifetime studying mechanisms of antibiotic resistance and crusading to abolish the use of antibiotics in animal feed.

By Anna Azvolinsky | June 1, 2015



STUART LEVY
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ALONSO NICHOLS/TUFTS UNIVERSITY

s a visiting research fellow at the Pasteur Institute in 1962, on leave from medical l, Stuart Levy met a Japanese scientist who uced him to an exciting recent breakthrough searchers from his country. "The Japanese iscovered that resistance to antibiotics could nsferred from one bacterium to another," says—even across species. "This was ard of previously. It was the beginning of s on transferrable drug-resistance genes fectious drug resistance." Inspired, Levy traveled to Tokyo's Keio University in 1964 and spent several months in Tsutomu Watanabe's laboratory, working on the so-called R (resistance) factors. Watanabe is credited with bringing the topic to a wide scientific audience with the publication of a 1963 review in English, highlighting the results of Japanese research on what he called the "infective heredity" of multidrug resistance.

Levy published several papers with Watanabe, including a description of episomal resistance factors of Enterobacteriaceae and an investigation of methods for inhibiting their transfer. "We didn't know at the time about the mechanism, but we knew it was an exciting moment in the history of antibiotics and resistance," says Levy. "Later, transfer was linked to small pieces of DNA—plasmids—that bore different resistances to antibiotics."

Here, Levy talks about the prank he and his twin brother (Jay Levy, who was among the first to discover the HIV virus) executed that earned them a brief spot in the limelight; how science allowed him to travel the world—and befriend Samuel Beckett; and an urgent call to a castle in Prague about chicken eggs.

Levy Learns

Sunday mornings. As young kids growing up in Wilmington, Delaware, Levy and his identical twin brother Jay used to accompany their father, a physician, on Sunday house calls. "House calls were not that common then, but not as rare as they are now," says Levy. His father, who came from a poor immigrant family, would visit patients, many of whom could only pay him with food grown in their gardens or with services. "He would see the Italian gardener who would exchange Dad's expertise for his fruit. He was brought up under that kind of understanding, and the patients respected and loved him. He would sometimes discuss with us patients he was seeing; that is probably how my interest in medicine began."

All in the family. "My twin brother, sister, and I were all interested in biology. We lived in the country near a farm and spent a lot of time outdoors with the animals. All three of us went to medical school, but, unlike my father, we stayed in academic circles rather than going into private practice. My brother, Jay Levy, and my sister, Ellen Koenig, both do HIV research."

"That low-dose antibiotics given as growth promotion will lead to high levels of resistance [in humans] was a surprise. No one has tried to replicate that study to this day."

Foray into football. Both Levy and his twin brother wanted to play high school football, but their parents refused, fearing injury. So the head coach took on both boys as coaches. "We got to be near the team and did things like measurements and statistics of the plays. My parents didn't know then what we know now about concussions, because no one talked about that, but they knew it was a potentially dangerous sport," says Levy.

Playing both sides. At Williams College, Levy majored in English. "My brother knew by sophomore year that he wanted to go to medical school; I only made the decision my junior year. But I had lots of interests, namely literature and arts. I loved the fact that I could keep these interests and still go to medical school. When I could do something and not give up another I loved, I was happy," Levy says.

Mistaken identity. After exchanging identities for a day in high school, the Levy brothers took the prank even further in college. As sophomores, the twins swapped identities for an entire week and each wrote an essay about the experience. Stuart lived life as Jay at Wesleyan University and Jay as Stuart at Williams. "This was our first taste of being in the limelight." The brothers had received permission from the presidents of their respective colleges to switch spots, but then played a prank on those authorities—telling them the wrong week for the intended swap. "We wanted to see if we could even fool the presidents and had a few friends help us play along. When classmates suspected a change, we answered by stating our wish to be considered individuals and not a single entity."

Levy Launches

Medical school travels. Stuart Levy started medical school at the University of Pennsylvania in 1960. His brother, in medical school at Columbia University, received a Fulbright scholarship and studied at the Sorbonne Institute in Paris. "Our relationship was such that we wanted the other to have what we had, so when my brother was successful in getting a position in Paris at the Sorbonne, he told me, 'You have to do this, it's fantastic to be here on your own! There is never anyone directing you,' " says Levy. The following year, he followed Jay to Europe, first as a research scholar in Milan and then at the Pasteur Institute in Paris. There Levy worked on a model of viral resistance in a mammalian cell line in Raymond Latarjet's laboratory. "To tell you the truth, I didn't care what I was doing, I just wanted to have a new experience, and Latarjet was a wonderful mentor. He loved golf, which is what I was raised on. We had wonderful times golfing together at dusk," Levy recalls.

For the love of literature. "When my brother was first in Paris, he met Samuel Beckett. Jay had written his thesis at Wesleyan on Beckett and sent it to Sam's address, which everyone said you could not get through to. Beckett liked what [Jay] had written. Beckett was not a snob, he was shy. So Jay introduced me to Beckett when I was in Paris and every four to six weeks we would have lunch together in the Latin Quarter. I'd tell him what we were doing in the laboratory, and he would share with me accounts about the production of his new play. It was such a unique opportunity."

Tangents. Levy did his residency in medicine at Mount Sinai Hospital in New York City. While there, he spent much of his free time working in the laboratory of Charlotte Friend, a microbiologist who had discovered a virus that caused a leukemia-like disorder in mice. "She took me under her wing—I was always looking for something else to do other than look at pathology slides. Jay did the same. We weren't interested in the status quo. We did what was needed to get the degree, but also pursued our own interests," says Levy. Although his clinical focus was officially hematology, Levy continued to pursue his interest in antibiotic resistance. "I was so interested in infectious diseases that I used to go on the rounds with the infectious-diseases group in addition to my regular clinical duties."

A system to call his own. Levy became a staff scientist at the National Institutes of Health (NIH) in 1967, working for two years in Loretta Leive's lab on synthesis of the lipopolysaccharide that populates the outer membrane of *E. coli*. As an independent researcher on R plasmids and chromosomeless minicells, Levy developed a way to purify large amounts of these *E. coli* minicells, which form from an aberrant cell division site and possess no bacterial chromosome—what he calls the plasmid-in-minicell system. "The NIH brought me together with senior scientists in the field, but no one was interested in tetracycline resistance. They wanted to understand enzymatic resistance," says Levy. In 1970, Levy demonstrated that the tetracycline resistance gene is found on plasmids that are transferred to minicells.

Mechanism of resistance. In 1971, Levy moved to the Tufts University School of Medicine as an assistant professor of medicine and of molecular biology and microbiology; he has remained ever since. There, his lab went on to show that an R plasmid encoded a protein associated with tetracycline resistance and that no other positive regulation was required for the bacterium to synthesize this protein. "There could be several hundred genes on the plasmid, and in the 1970s, we were not that sophisticated yet to identify the specific gene," says Levy. In 1978, his lab determined that the plasmid-derived resistance to tetracycline involved a novel transport system for tetracyclines. Levy's lab then discovered the first active efflux mechanism, showing that *E. coli* resistant to tetracycline actively pumped the drug out of the cell and that this mechanism of resistance was encoded by a single R-plasmid gene. Levy also showed that a nonefflux mechanism was present as well. Others subsequently demonstrated that this second mechanism for tetracycline resistance involved a ribosome protection protein. "The use of minicells and the discovery of the mechanism of tetracycline resistance is what really put me on a clear path to a successful career," says Levy.

Levy Leads

Ahead of his time. The Animal Health Institute of New York asked Levy to study growth-promoting antibiotics in farm animals. "They were looking for scientists who had not spoken negatively about this use of antibiotics," says Levy. Still a young investigator, Levy fit the bill. His lab found a farm outside of Boston that was willing to have scientists come in and raise chickens. Levy's students raised 150 control and 150 experimental chickens fed regular and tetracycline-spiked feed, respectively. "There is a funny story about me at a castle in Prague and not remembering that I had placed an order for 300 eggs, one-half male and one-half female. Someone was looking for me all over the castle so that I would confirm [over the phone] that we should order the eggs anyway. There is no way to identify if eggs are male or female!" The study, published in 1976 in the *New England Journal of Medicine*, showed the ecological effects of feeding farm animals low-dose antibiotics: not only did the antibiotic-resistant bacteria replace the microbiota in the animals' intestines, they also altered the gut microbiome of the humans who lived and worked on the farm. Through contact with the chickens and their tetracycline-laced feed, resistance was in turn transferred to the microbiome of the animal handlers. Levy's lab also demonstrated that animals can transfer antibiotic-resistance plasmids to humans and other animals. "That low-dose antibiotics given as growth promotion will lead to high levels of resistance was a surprise," says Levy. "No one has tried to replicate that study to this day."

Multidrug-resistance find. Levy's laboratory also identified a chromosomal operon found in different bacterial species that results in drug resistance to different classes of antibiotics, including tetracyclines, penicillins, and fluoroquinolones. "[The discovery] was serendipitous. I was trying to get a chromosomal mutant to tetracycline, and when the bacteria grew, they were multidrug resistant from the start, which meant there was a single locus that controlled multidrug resistance and that emerged with selection from a single drug exposure," says Levy.

Antibiotics and politics. Levy has testified many times before Congress on the subject of antibiotic resistance. "Our study from 1976 was [and still is] the only prospective U.S. study on this, and industry didn't want more studies. They were upset that our data showed them to be wrong. This was highly political." Levy says he is now more optimistic about prudent antibiotic use, as this issue has garnered more and more attention, especially since this past March when the White House announced a national action plan, allocating $1.2 billion to combat antibiotic-resistant bacteria. "I think the moment has come for new antibiotics and better use of antibiotics so that people are not as subject to resistance emerging through animal use of other drugs. We won't see real change until there is a genuine commitment to improve antibiotic use, and I think it's coming."

Banding together. In 1981, Levy founded the Alliance for the Prudent Use of Antibiotics (APUA), an international nonprofit with chapters in 65 countries. The idea started at a meeting in the Dominican Republic in the early 1980s because of concern about rising antibiotic resistance in the developing world. The organization provides funding for countries in the developing world to study antibiotic resistance. "I've learned a lot from being part of the APUA. The science is one thing, but you need to package the science with good politics to get what you want," says Levy.

Up to the challenge. "We did the first study that took a patient-by-patient analysis of resistance in a [single] Chicago hospital and what the cost was," says Levy. The analysis showed a cost of about $21,000 per antimicrobial-resistant infection patient, producing a cost to the hospital of about $4 million and a total societal cost of as high as $15 million including the loss of productivity. "[The study] came from a challenge that Ted Kennedy gave me. He said that if you are not going to save money you won't get much interest in [antibiotic resistance], and we took him up on the challenge."

Dream experiment. If money were no object, Levy says, he would design an experiment that would definitively and quantitatively demonstrate the link between subtherapeutic use in animals and the emergence of antibiotic-resistant infections in people.

Influential mentor. "I think the biggest training I received was with Watanabe, and that was just for a summer! He was patient, methodical, and a master."

Greatest Hits

- Discovered the first active efflux pump involved in tetracycline resistance in Enterobacteriaceae
- Identified the *mar* operon, a bacterial regulatory locus that results in multidrug resistance to different antibiotics as well as to disinfectants
- Provided some of the first evidence that feeding animals low doses of antibiotics leads to high levels of resistant bacterial strains that can spread to other animals, people, and the environment
- Established the international Alliance for the Prudent Use of Antibiotics
- In 1993, published *The Antibiotic Paradox: How Miracle Drugs Are Destroying the Miracle*
- Served as an advisor on antibiotic resistance to multiple organizations, including the National Institutes of Health, the World Health Organization, the FDA, and the Environmental Protection Agency

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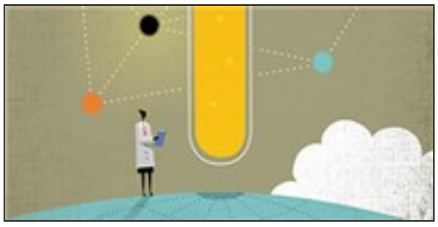

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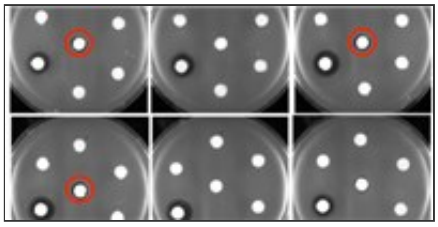

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