Medical School alumnus and bacteria researcher Dr. Stuart Levy warns against the overuse of antibiotics, a potential public health nightmare for the 21st century.

By Tom Nugent

In nearly 30 years of playing cat-and-mouse with his "amazingly adaptable" bacterial adversaries, Dr. Stuart Levy M'65 has developed a "great deal of respect" for their ability to quickly change their form to fend off their antibiotic pursuers. "Bacteria do what they do very well: he says. "They can afford to lose millions and millions of their numbers, and they certainly do. They take huge losses, over and over again. But then they suddenly adapt, and they come back with a vengeance."

"It seems to me that bacteria represent a basic feature of this present world, which is 'survive and propagate.' And they do just that. It's very clear that they've been here much longer than we have — we entered their world, after all. And as far as they're concerned, we may be just a 'passing feature' in their history, which reaches back millions and millions of years. It's a little disturbing to think about — but then, dinosaurs come and go, don't they?"

With the wide availability of antibiotics starting in the 1940s, it seemed that bacteria had met their match in human ingenuity. But the victory was shortlived, and the comeback is now in full force — helped along, ironically, by those very antibiotics. Combined with bacteria's protean nature, rampant overuse of these drugs, by eliminating both vulnerable strains of disease bacteria and other, benign types of bacteria (innocent bystanders caught in the battle against disease), has created an environment in which drug-resistant strains of bacteria can develop and flourish as never before.

Levy directs the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine, where he is also a professor of medicine and of molecular biology and microbiology. As a researcher, he has made major contributions to understanding the mechanisms of drug resistance in bacteria; he has also become a leading voice in educating the public about the "major world health threat" posed by antibiotic-resistant bacteria. He expressed his message succinctly in the title of his influential 1992 book: The Antibiotic Paradox: How Miracle Drugs Are Destroying the Miracle.

Much of Levy's public education work centers around the Alliance for the Prudent Use of Antibiotics (APUA), an international group dedicated to curbing antibiotic resistance which he co-founded in 1981. Currently, he is president, APUA's Web site (www.healthsci.tufts.edu/apua) offers a wealth of information for physicians, researchers and consumers, from notices of relevant international meetings, to news reports about antibiotics and drug resistance, to instructions on proper handwashing technique.

At 61, Levy swims daily laps at a downtown Boston pool and favors bow ties ("I tie my own — it's a point of personal pride with me," he says) with his white labcoat. A former president of the American Society for Microbiology, he was awarded the Society's prestigious Hoechst-Roussel Prize in 1995 for his research. A major theme of his work has been how bacteria alter their genetic structure to build stronger cellular defenses against antibiotic drugs. In The Antibiotic Paradox, he describes how, through a variety of transfer processes, pieces of DNA or genes can move from one bacterial cell to another, including bacteria of very different types. "We now know that bacteria exchange genes readily in nature. Antibiotic resistance has allowed us to see just how extensive these transfers can be, because resistance genes are so easy to identify and follow."

Several factors are involved in these new forms of resistance, but the most important "is that antibiotic use is out of control," Levy says. Since 1954, the amount of antibiotics produced in the United States annually has increased from two million pounds to 50 million pounds. Research suggests that about half of these antibiotics aren't medically necessary.

"Everywhere you look these days, doctors are prescribing antibiotics for colds and earaches. But if all you've got is a common cold, you definitely don't need an antibiotic," Levy says. "Remember, colds are caused by viruses, not bacteria, and viruses are completely unaffected by antibiotics. If you use one, all you'll get
are side effects, resistant bacteria, and no help on the virus! Instead of resorting to the antibiotic, you need to eat well and drink lots of liquids. Get plenty of sleep, and take Tylenol or other anti-inflammatoryatories that you can buy over the counter.”

He also urges parents not to demand an antibiotic from their pediatrician at the first signs of a child’s earache. “Most earaches in kids don’t require an antibiotic, at least not at first; he says. “And in many parts of Europe right now, 95 percent of kids are not given an antibiotic when they present with an ear infection. Instead, they wait 24 to 48 hours, and then there are only 10 or 15 percent who actually require it, because most earaches will just get better on their own. In the U.S., our best assessment is that two-thirds of earaches are caused by bacteria, but of those two-thirds, more than half will cure themselves. So I’d say that no more than one in five really needs an antibiotic.”

Another frustrating recent development is the proliferation of “antibacterial” cleaning agents in household products. “I think many people are paranoid about germs, and that’s what has led to this mania for antibacterial-containing household products,” Levy says. “Antibacterial agents are in everything these days — plastics, deodorants, detergents. But like [medicinal] antibiotics, we want to reserve these products for the care of sick patients. They are not needed for everyday use. They, too, create environments of surviving resistant strains — and their use runs the risk of creating homes that are like hospitals [containing many resistant bacteria].

While cleanliness and personal hygiene are important to preventing infection, “soap and water are a fine combination to do the job, along with ammonia, chlorinated compounds or alcohol. These products do not leave residues for the selection of resistant bacteria,” he says. “The important thing to remember is that bacteria are our allies. We need them to regenerate life, and to protect us from the rare, disease-causing kinds. Their resilience is what we rely on. They help our immune system mature, and to over-treat them will only get us into trouble.”

Needlessly “killing off” bacteria with superfluous antibiotics gives a “selective advantage” to those which survive the assault, Levy explains. “When an antibiotic such as penicillin attacks a group of bacteria cells, those that are highly susceptible to the medicine will quickly die. Those cells that have had some resistance from the start, or that have acquired it through mutation or gene exchange with other bacteria, may manage to survive. Those same cells now face reduced competition from susceptible bacteria, and they will go on to proliferate. And so they become increasingly resistant to our drugs.”

The consequences can be dire. In numerous published studies, Levy has demonstrated a link between human overuse of anti-bacterial drugs and increasing resistance among such formidable pathogens as tuberculosis, which, after being nearly eradicated, is now making an alarming comeback in the industrialized world. He also points to reports from the United States, Japan and Europe in recent years of vancomycin-resistant strains of Staphylococcus aureus, an often-deadly bacteria found in some hospitals. “Vancomycin is a powerful antibiotic, and it’s the last line of defense against a few strains of S. aureus,” he says. “The problem is that those strains now appear to have become resistant to all other antibiotics. So far, there have been four confirmed deaths in the world from drug-resistant forms of S. aureus, and that’s quite troubling. These organisms can cause failure of treatment, and if we don’t keep finding new drugs to stop them, they could emerge as a disaster for patients.”

Son of a family-practice M.D. in Wilmington, Delaware, Levy never doubted that he would eventually become a physician, but he majored in English at Williams College — the result of some “very good advice” from his father, he says. “My dad really understood the value of liberal arts for a doctor, and he helped convince me to major in English as an undergrad.”

After graduating with honors, Levy went directly to medical school at Penn — though some highlights of his education occurred far from campus. He spent the summer after his second year studying in Italy, for example. “I found Penn to be really open-minded and tolerant toward its students,” Levy recalls with a laugh. “When I told them I wanted to spend a summer studying at the Istituto di Microbiologia in Milan, the people at the med school didn’t go up in arms, shouting: ‘You can’t do that!’”

“They gave me a nice stipend, and I went off — this was 1962 — to work under the late Dr. Giulio Maccacaro, who was a great teacher and a great researcher. What a summer. An assistant professor would pick me up at my dormitory each morning, and I’d climb onto the back of his Vespa, and together we’d go roaring into Milan, to the laboratory.

“We worked hard. But at the end of the day, Professor Maccacaro would often take us to one of the bars in the neighborhood, and he’d buy us a little bit of vermouth. Cinzano, red, with a twist of lemon. The Italians would quickly chug it up, like the Russians with their vodka. And I’d be sitting back, drinking it slowly, and they’d all say: ‘Hey, Stuart, andiamo! Andiamo!’ ”

Levy was enchanted by the way the med school helped me arrange those two fellowships,” he says. “That was a terrific year, on many different levels. I’ve always felt grateful for the opportunities I received at Penn.”

Levy completed his internship and residency training at New York’s Mount Sinai Hospital, and by the late 1960s was studying “bacterial genetics” — a growing interest during medical school — on a three-year fellowship at the National Institutes of Health in Bethesda, Maryland. He joined the faculty at Tufts University medical school in 1971, becoming a full professor in 1980. Meanwhile, his research into drug resistance among bacterial species was gaining international attention.

The author or editor of five books and more than 200 scientific papers and journal articles on antibiotic use and resistance, he is credited with achieving several breakthroughs in his field. These include the discovery of the “efflux pump” resistance mechanism in bacteria, along with major new insights into the ways in which antibiotic-resistant bacteria are transferred from animals to humans and the location of the “protein master switch” that controls bacterial resistance.

At the Center for Adaptation Genetics and Drug Resistance, Levy leads a team of genetics
Tufts scientists were startled to find the re-"we shut down the pump, so that the tetra-derstood how the efflux mechanism worked, we asked ourselves: ‘How could that would be carried into the cell mem-brane along with the tetracycline.

Levy, whose English-major back-ground comes out in a love of metaphor, describes the working of the ‘stickly tet’ this way: ‘Think of the bac-terial-cell membrane as a revolving door. The molecules of tetracycline flood in, but then they get swept right back through the revolving door by the pump. What we did, in biochemical terms, was to attach the ‘sticky mole-cules’ to the pump. Now the pump isn’t working so well. Fine! Because lots of [tet] molecules can get into the cell now, and they can target the ribosomes in there, and in this way they will suc-cceed in inhibiting the cell’s growth.’

Laboratory research is important, but Levy places at least as much empha-sis on public education. “Whenever we get a chance to speak out publicly on the issue of drug resistance and the con-tinuing misuse of antibiotics, we respond,” he says. “So I have to spend a lot of time traveling, both here and abroad, in order to attend scientific conferences and make presentations on this topic.”

We studying the complex dynam-ics of bacterial resistance to antibiotics, Levy spent much of the late 1970s dis-cussing the problem with scientific ex-perts in more than 20 developing countries around the world, where such resistance has caused a growing health threat in recent decades. One major out-growth of those discussions was the founding of the APUA. “We decided that when it came to bacterial drug resis-tance, our constituency would have to be global,” he says. Today the APUA is active in research and advocacy in more than 90 countries.

Though his views were initially seen as highly controversial, Levy says, by the mid-1990s most of the U.S. sci-entific and medical community had come around to his vision of antibiotic resis-tance as a growing health menace. Early on, his toughest opponents were re-searchers in pharmaceutical companies, some of whom accused him of exagger-ating the problem. “They were a pretty strong counter-group at first,” he says, “but I think even the executives who run the pharmaceutical houses have now understood that this is a very sig-nificant medical issue.”

Levy says he actually feels “quite op-timistic about the fact that doctors and patients alike are now waking up to the health dangers from increasing bacterial resistance to drugs. “We’re at a very im-portant fork in the road, and we have to take the right route. And that has to be the prudent use of antibiotics,” he says. “I’m quite confident we can do it. It’s just a matter of understanding what’s at stake, and then putting our minds to it. But it has to start with the patients. You aren’t going to get the doctors to stop prescrib-ing needless antibiotics until you get the patients to stop demanding them.”

On the technological front, Levy was also encouraged by the announcement in mid-April that the U.S. Food and Drug Administration had approved for public use the first new synthetic antibi-otic in more than 20 years, called Zyvox—which may be arriving just in the nick of time to help prevent runaway proliferation of such newly resistant bac-terial strains as S. aureus.

“I think that FDA announcement sounded a very hopeful note,” he says. “For more than two decades, we have not had a new structure in an antibiotic. So this is good news. But at the same time, let’s not get carried away by it. For one thing, if you read the fine print, you’ll see that it only works in two-thirds of the patients who take it.

“Still, it’s a brand-new drug and most bacteria haven’t seen it before. I’m sure it can help—provided that we use it right. If we use it rationally, we can keep it around for a long time. But if it’s pushed to its limits, you can be sure that bacteria will emerge with resistance to it as well.”

He pauses for a moment, to let his message sink in—the same one he’s been preaching throughout most of his professional career. “Somehow, we’ve got to stop thinking of antibiotics as ‘miracle drugs’ that can cure every illness overnight, and without consequences. They are not magic bullets. Instead of re-sorting to antibiotics at the first sign of illness, we need to use them sparingly, and only when they’re truly needed he says. “We need to remember that ‘resis-tance is ecologic’—and to find a better balance with the bacterial world that surrounds us.”

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