

Outsmarting bacteria that fight back

Dr. Stuart Levy cautions that our misplaced faith in “miracle drugs”
has precipitated a worldwide public health crisis.

Designing new antibiotics is only part of the answer.

Ever since the 1940s, when penicillin became widely available, antibiotics have become the first line of defense against bacterial germs. Diseases such as tuberculosis, staphylococcal sepsis, syphilis, gonorrhea, scurvy and strep throat were successfully outmatched by antibiotics, which saved lives by targeting infectious organisms. Yet today a public health crisis is unfolding precisely because of the efficacy of these “magic bullets.” Through our overreliance on and indiscriminate overuse of antibiotics, strains of bacteria resistant to these wonder drugs have emerged, propagated and proliferated to such an extent that they are now found worldwide. Evidence shows that these resistant strains have changed the bacterial flora of our skin and intestines and the bacteria in the environment. In laboratory tests some of these so-called superbugs are able to beat every one of the more than 100 antibiotics on the market.

Are we losing the battle against germs? Antibiotic resistance is a hot topic today, and with increasing frequency, journalists, scientists, public health officials and industry, look to Stuart B. Levy, director of Tufts’ Center for Adaptation Genetics and Drug Resistance and staff physician at the New England Medical Center, for answers. A graduate of Williams College, he received his medical degree from the University of Pennsylvania. After his internship and residency at Mount Sinai Hospital in New York, and a three-year position at the National Institutes of Health, he started a fellowship program in hematology at Tufts and NEMCH in 1970. Recognized as the 1975 Leukemia Research Scholar of the Year, he remained as a physician in hematology and a staff scientist in cancer research. He was fascinated, however, with how bacteria outwit antibiotics—in fact, “antibiotics revealed a feature of bacterial ingenuity that we did not know about,” he recalls. “The excitement for me has been finding new mechanisms for resistance that bacteria have acquired.” At Tufts in 1979, he had his first success, discovering a novel resistance mechanism for tetracycline. The finding that strains of tetracycline-resistant bacteria were actively pumping the antibiotic out of the cell so it never reached its target inside the cell was the first description of a drug efflux mechanism. Such efflux mechanisms, then unique, now are a widely recognized strategy for mediating resistance in other antibiotics and explain the basis for resistance to chemotherapy by cancer cells, fungi and parasites.

In 1981, Dr. Levy was instrumental in founding the Alliance for the Prudent Use of Antibiotics (APUA), an international organization with members in more than 90 countries, and of which he is now president. Convinced that antibiotic resistance called for even more comprehensive efforts, in 1992 he established the Center for Adaptation Genetics and Drug Resistance at Tufts, whose mission combines basic research with public education.

His 1992 book, *The Antibiotic Paradox: How Miracle Drugs Are Destroying the Miracle* (Plenum Press), has had the greatest impact. Its publication just preceded growing alarm over antibiotic resistance in TB, meningitis and ear infections, diseases long considered problems of the past. The public and the media now had clear evidence of the conflict-

ing consequences of antibiotic use: curing disease and selecting for resistant bacteria. Dr. Levy has been featured in major national and international newspapers and magazines, as well as on television and radio, while continuing to garner recognition for his innovative research—in 1995 he won the Hoechst-Roussel Award from the American Society for Microbiology for his work in antibiotic chemotherapy. This year he was elected president of the Society.

In the following interview, Dr. Levy talks with managing editor Laura Ferguson about how designing new drugs is only part of the antibiotic resistance solution; success will ultimately depend on the rational use of antibiotics, and understanding and knowledge about bacteria and the environment.

According to the National Foundation for Infectious Disease, a new group of antibiotic-resistant pneumonia bacteria causes half a million cases in the United States annually, 20,000 of them fatal. How would you describe the scale of antibiotic resistance?

This decade will go down as the decade of multidrug resistance. Bacteria-causing infections of all kinds have finally emerged, at the end of this millennium, with resistance to not one and two antibiotics, but to multiple different antibiotics. In many treatment options, we are left with one or no drugs. This is a far cry from the beginning of the antibiotic era. We have good reason to be worried, for instance, that the strain of streptococcus bacteria that causes strep throat, scarlet fever, rheumatic fever—the one that killed Jim Henson—while still susceptible to penicillin, shows resistance to the second drugs of choice, erythromycin and tetracycline.

What does that say? We’re in a public health crisis and on our way to a disaster when we lose our ability to treat infectious organisms like the staphylococcus or the pneumococcus, which can cause severe infections. We will see many deaths. Resistance is a major problem we must control, but we also need to improve upon hygiene so as to avoid infections, not just rely on antibiotics after the fact.

There are very few data that estimate loss of lives due to resistance. We do know that in this country over 2 million people contract infection in hospitals and about 20,000 people die. Seventy percent of the bacteria are multiresistant organisms. That doesn’t mean that the patients died because of resistance, but it does lead you to ask: “Why should the bacteria be resistant?” There are millions of people carrying multiresistant bacteria. We carry them in our intestinal tract. Why? Because bacteria everywhere are confronted by antibiotics, and of course, the survivors are those which are resistant.

Is the frequency of resistance accelerating?

Yes. We’re seeing more and more resistance yearly in the national statistics from the Centers for Disease Control and in hospital and community data. We haven’t seen what we hoped for, that is, a plateau in resistance frequency. Only where deliberate interventions have been made has resistance gone down. We are trying to get the message out to the public at large to help in this effort to clean up the environment.

Does that mean that if I were to catch an infection today, there would be a good chance that my prescription might not work?

Unfortunately, yes. Neither you, as the patient, nor we, as physicians, can take it for granted that the antibiotic will work because resistant strains are so much a part of our environment. That is the core of the problem. Resistance is ecologic. We want to get the message out to physicians and patients—use antibiotics prudently. Only in this way can we restore the susceptible strains of bacteria. Then the chances that your infection will be treatable by antibiotics will be assured.

Does the biological basis for drug resistance make this problem difficult to solve?

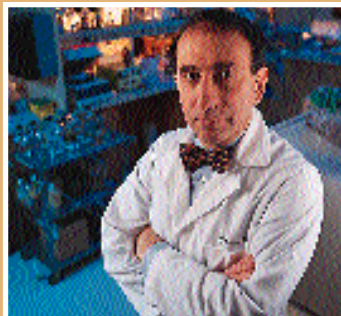
The problem reflects a combination of things. All around us bacteria are exchanging genetic information. That exchange is inconsequential unless it serves as an advantage to the bacteria, and this clearly occurs when it involves a trait which distinguishes between life and death. If bacteria exchange a gene for a slightly altered metabolic process or a membrane component, it might help them a little, but if the bacteria contain a gene mutated for resistance to antibiotics, and your antibiotic is delivered at that time, the resistance makes a big difference. The susceptible bacteria die out and the resistant organisms take over. Bacteria can replicate in less than an hour.

At the same time, bacteria travel constantly—in the air, in soil, on skin, or on uncooked foods such as salads. We have gathered some strong evidence in studies we performed here at Tufts. In the mid-1970s we established a close relationship with a farm in Sherborn, Massachusetts, where we did some early studies on the effect on chickens of feed laced with tetracycline at subtherapeutic levels. We examined the intestinal tract bacteria of the chickens and the people living on the farm. Within 24 to 36 hours, the chickens fed the tetracycline-laced feed began excreting tetracycline resistant intestinal *E. coli*. In two months following introduction of the feed, the *E. coli* excreted were also resistant to ampicillin, streptomycin, and sulfonamids, even though they had only been fed tetracycline! After five to six months, we saw an increase in tetracycline- and multidrug-resistant *E. coli* in family members. We traced *E. coli* from chicken to chicken and from chickens to farm dwellers. In later studies we traced the same bacteria from a calf to pigs, flies, mice, and people.

Just recently a study showed that family members of people taking antibiotics for acne had much higher levels of resistant skin bacteria than control families where no antibiotic was being taken. It's "secondhand smoke" in a different form.

You could be very paranoid about germs.

There are many people who are. I believe that is what has led to this mania for antibacterial-containing household products. Antibacterial agents are in everything—plastics, deodorants, detergents. But like antibiotics, we want to reserve these antibiotic-like products for the care of sick patients. They are not needed for everyday use. They too



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create environments of surviving resistant strains. Their use runs the risk of creating new kinds of microbial environments in our homes, like hospitals. And I am concerned about this, because as we send patients home from hospitals earlier, we expect the home to be reliably free of resistant bacteria. But if the home is being subjected to antibacterial products that change the bacterial environment, is the home actually being converted to a hospital?

Cleanliness and personal hygiene are important in preventing infection. But soap and water are a fine combination to do the job, perhaps adding to ammonia, chlorinated compounds, or alcohol—products that do not leave residues for the selection of resistant bacteria. It is only when caring for the sick that we need special treatments with antibacterial ingredients. The important thing to remember is that bacteria are our allies. We need them to regenerate life, to protect us from the rare disease-causing kinds. Their resilience is what we rely on. At the same time, they are under the same laws of nature as all creatures—survival. Without bacteria, we would be in a worse situation than we are in now. They help our immune system mature. We have evolved with them, as have many of our physiological processes. To remove them could lead to greater danger. Still, we have to control them. However, to overtreat them will only get us into trouble, since antibacterial products destroy the good as well as the bad bacteria.

You've become a nationally recognized expert in antibiotics and have been increasingly called upon by the media. Do you detect an undercurrent of panic?

No. But for the first time since we've been warning about antibiotic resistance, both professional and lay people, are beginning to listen. No one wanted to believe resistance was an issue. Miracle drugs cause miracles, not problems. It is delightfully surprising and rewarding to see organizations that previously skirted the issue now becoming involved.

So there is not panic, but there is mounting concern. The United States AID just released \$50 million for control of emerging infections in through their missions; \$15 million is designated for antibiotic resistance. WHO officials call resistance one of the three major public health problems of this and the next decade. The Alliance for the Prudent Use of Antibiotics has never been busier, with chapters in some 15 countries. Pharmaceutical companies have refined their search for new antibiotics. It is a game of catch up. Still, it would have been nice to have stayed ahead of the bacteria instead of now racing to get back on top. It often takes a crisis to turn things like that around.

You've raised the point that antibiotics set up a troubling paradox: miracle drugs are actually destroying their own miracle. Would you say, then, that antibiotics became too popular for their own good?

Yes. The concept that these drugs were miracles became a myth.

People believed they could cure all illnesses; there were no consequences. The idea took over public opinion. The result today, probably best seen in this decade, is represented by the statistic that the chance of a pneumococcus infection in a child being resistant to penicillin is now up to 20 percent, whereas in past decades, this chance was tiny. That is a dramatic and unsettling change. It has come out of our overuse of penicillin in children for viruses, not bacterial infections. Day care centers have become breeding grounds for these resistant bacteria.

The sense I get is that you have to tackle the resistance problem globally.

The international perspective became clear to me during my travels in developing countries as a consultant for WHO. But it was certainly evident after the 1981 meeting we organized in the Dominican Republic on bacterial genetics and antibiotic resistance. Out of that meeting came the Antibiotic Misuse Statement. We had widespread international news articles of the statement, including half-page coverages in *Newsweek* and *Time*. Out of the statement and media response came the Alliance for the Prudent Use of Antibiotics. We began to raise awareness to the problem. It was a challenge. We learned early on that one cannot tell another country how to run its health policy. The best bet is to empower local people with information and let them know they are part of a global effort. The appearance of AIDS crossed our path at the same time. No country wanted to say they had an AIDS or a health problem for fear of its effect on tourism. Once established, however, the Alliance provided a reason for grassroots groups to work with us. What we learned from linking up with these groups was that the problem was global, but it was also different in different places and even in different hospitals in the same city. Why? While not totally clear, it reflected different uses of antibiotics, different sanitation conditions, different bacteria and different attitudes.

What international situations do you find most compelling in their response to the problem?

A task force in Spain released a report stating that Spain's misuse of antibiotics led to resistant strains it "exported" to other countries. The same bacteria could be traced by their genetic sequences. A pneumococcal strain spread from Spain to other parts of Europe, Iceland, Africa and the United States. The statement was a kind of mea culpa: "we are responsible for the public health of Spain and the rest of the world; we need to improve antibiotic use." Finland recognized a problem with the organism causing Strep throat. Strains had become resistant to erythromycin to frequencies of about 20 percent. So the public health team organized a countrywide effort to reduce and improve the use of erythromycin. It took a few years, but they reduced resistance to below 9 percent and it is still falling. In the early 1980s, Eastern Australia faced a problem of *Staphylococcus aureus* resistant to methicillin. Hospital infection control teams looked at the issue and saw that they were using antibiotics inappropriately. So they established an antibiotic review committee and wrote *Antibiotic Guidelines*, a booklet now in its ninth edition. They are doing great work there.

Talk a bit about the Center's role in stemming the tide.

The Center has as its mission to perform basic research in the area of drug resistance in bacteria and cancer and to define its relevance to the public and to the clinical fields. We're making great strides in research: we discovered a regulatory locus which controls how bacteria sense environmental hazards, including antibiotics. We are focusing on this as a novel way to treat infections by preventing bacteria from surviving potentially hazardous events involved in causing infection. We are also working to restore tetracyclines—their renaissance—to their previous level of success. Our approach is to block the efflux protein and thus allow tetracycline to enter the cell and do its job. We have described new resistance mechanisms in cancer cells.

While laboratory research is important, what we also try to get across is the importance of public education. If there are opportunities to speak on these issues, we respond. With APUA, we work to produce educational materials. We recently produced a video, *Confronting Antibiotic Resistance* with the Tufts Continuing Education office at the School of Medicine.

Is the Center unusual in its mission?

In some sense, yes. While we focus on research using a combination of molecular biology, genetics and biochemistry, our broader aim is to strengthen public health by producing new products for clinical use and materials for public education. Most recently, for example, we helped perform a pilot program at Cambridge Rindge and Latin High School. The 9th-grade students chopped up vegetables and plated them on agar to find bacteria and then showed how many were resistant to antibiotics. They learned about microbiology, antibiotics and resistance. The project was so successful that we were asked to increase the two classes last year to six this year. We have requested funding through the National Science Foundation to help support this effort and to write a curriculum for dissemination to other schools. If we begin teaching about the value of antibiotics early, before children have formed wrong opinions, we get a payoff later. Look how long it has taken to change attitudes about smoking or seat belts.

You've said you sometimes feel like you're "speaking to the wind." How do you feel now that the issue of antibiotic resistance has become much more widely acknowledged?

I'm starting to hear a delightful echo and it's great. People are joining in who never accepted the problem before. The future of our children relies on our ability to understand the resistance problem and come up with answers. Antibiotics are among our most important therapeutics, but they have to be given more respect. They offer great benefits to public health. But when we misuse them, we alter the microbial world with the emergence and propagation of resistant bacteria, which prevent our successful treatment of infectious diseases confronting people throughout the world.

For more information, write the Alliance for the Prudent Use of Antibiotics, P.O. Box 1372, Boston, MA 02117.