Slow Movement on Antibiotic Resistance

Could inspiration to trigger real action on the global medical problems caused by bacterial drug resistance come from a musical source?

Bernard Dixon

I had just started telling a friend how regrettable it was that many doctors prescribe antibiotics for trivial infections, even for minor troubles that might be virus infections or not even infections at all, when he interrupted—pleading agreement with every word. “You’re quite right,” he insisted, “I would never dream of troubling my doctor for trivial complaints. I go to the Internet and find the antibiotics I want there. Years ago, every time I went to a country where the stuff was available across the counter, I used to stock up.”

Whenever I have this sort of experience, or read of the latest horrendous problems created by antibiotic-resistant bacteria around the world, I think above all of one man—E. S. (Andy) Anderson, head of the Enteric Reference Laboratory in London in the 1970s, who did more than anyone to warn of encroaching disasters unless action were taken to stem the tide of resistance. Writing in the *Journal of Hygiene* (74:289, 1975) and elsewhere, he warned how vital it was to restrict any increase in the population of bacteria invulnerable to antimicrobial drugs. This was a tough message, on a planet where astronomical quantities of antimicrobials were deployed without reason or responsibility—by people buying them across the counter; by doctors satisfying patients’ expectations or being thoughtless and sloppy; and by farmers, veterinary surgeons, and feedstuff manufacturers, all of whom connived at the misuse of these potent agents in animal husbandry.

Again and again, Andy pointed out both the immediate and long-term hazards caused by invulnerable pseudomonads that were so feared in burns units, the ampicillin-resistant *Haemophilus influenzae* strains that were beginning to cause untreatable meningitis among children in the United States, and the chloramphenicol-resistant *Salmonella typhi* that had already infected some 100,000 patients in Mexico and killed 14,000 of them. These were not nuisance species of concern only to one country, Andy observed. They were part of the world population of bacteria, and action to prevent their emergence or limit their spread needed to be taken on a correspondingly international basis.

Much of Andy’s paper described laboratory and epidemiological work with chloramphenicol-resistant isolates of typhoid bacilli from Mexico, India, Thailand, and Vietnam—countries without any restrictions on the sale of antibiotics, and where indiscriminate drug usage led to a high incidence of resistance factors in the nonpathogenic enterobacteria of humans and animals. Moreover, the Mexican epidemic in particular was not limited to the indigenous population. British, Swiss, and many American visitors also became infected. The R factor responsible conferred not only an unusually high level of resistance to chloramphenicol but also insensitivity to streptomycin, sulfonamides and tetracyclines. A closely related R factor had been isolated from cultures of *S. typhimurium* from Portugal, Belgium, Canada, and Israel. Other closely related problems included epidemic drug-resistant dysentery caused by *Shigella disenteriae* in Central America and intractable, virulent outbreaks of infection with multiply resistant salmonellae in pediatric units in South America.

As Anderson pointed out, such developments were predictable and provided yet another warning that rationalization and reduction of the use of antibiotics and other antibacterial drugs were necessary not only in developing countries but throughout the world. “The time has clearly come,” he concluded, “when international cooperation at legislative and professional levels is needed to attempt to reverse the change in the ecology of the enterobacteria and other organisms that has resulted from the indiscriminate use of antibacterial drugs.”

Although his voice was arguably the strongest
to call for real, global action on drug resistance, Andy was not alone. And in the intervening years, many other individuals and committees have taken up the cause—most recently Britain’s senior medical officer, Dame Sally Davies, who recently argued that “antimicrobial resistance risks a health catastrophe to rank with terrorism and climate change.” Yet the situation remains grim, leading to repeated warnings that we are in danger of returning to the dark ages when bacterial infections were literally untreatable.

And of course, microbial evolution has continued apace—based not only on the mutation and selection that would have been familiar to Charles Darwin but also on the transferable resistance that makes matters (from a human perspective) considerably worse. One of the latest, alarming developments is the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae. Writing in The Lancet Infectious Diseases (16:161, 2016), Yi-Yun Liu and other investigators in China point out that this heralds the breach of the last group of antibiotics by plasmid-mediated resistance. “Although currently confined to China, MCR-1 is likely to emulate other global resistance mechanisms such as NDM-1,” they write. “Our findings emphasise the urgent need for coordinated global action in the fight against pan-resistant Gram-negative bacteria.”

How grimly familiar those words would sound to E. S. Anderson, more than half a century after he first enunciated similar sentiments. Andy did at least have the satisfaction of stirring up a political storm on the subject in the UK, supported by several influential figures in the media. Eventually, this triggered off a government inquiry into the (mis)use of antimicrobials in animal husbandry. Despite stiff opposition from some sectors of the pharmaceutical industry, that committee’s deliberations and recommendations did lead to a total ban on the inclusion of penicillins and cephalosporins in feedstuffs for pigs and poultry, to promote their growth.

Aside from real but limited initiatives of this sort, however, the general picture remains bleak. What on earth can be done now, after decades of a worsening scenario and countless research papers, reviews, newspaper articles, warnings, Web activity, committees of inquiry, and inaction by the individuals and bodies that could actually help to alter the situation?

Even last year’s call by the WHO’s annual meeting in Geneva was deeply unimpressive. True, the representatives of 194 countries approved a new global plan with five main objectives—to improve awareness and understanding of resistance, strengthen surveillance and research, reduce the incidence of infection, optimize the use of antimicrobial drugs, and ensure sustainable investment in the countering of resistance. But these seem little more than worthy, familiar words. And the agreed target of 2017 for every country to have in place a system to monitor drug resistance is pathetic.

Perhaps the requisite inspiration to encourage real action may come not from science alone but from music. The very idea may sound crazy at first, yet I do discern possible help from that quarter. Andy Anderson’s son, Julian, is a composer—currently a professor at the Guildhall School of Music and Drama in London and before that professor of music at Harvard University. Moreover, Julian has written a piece of music, Transferable Resistance, which portrays the very phenomenon his father spent a lifetime studying. Commissioned by the Royal Society in London, it is dedicated to the memories of Andy and of two other distinguished microbiologists, Max Delbrück and Bill Hayes. It is played by four groups of brass players located in different parts of the concert hall.

Could it be that someone, somewhere, some time, is so stirred by Julian’s expression of the molecular genetics of antibiotic resistance transfer, and its human consequences, that he or she is emboldened to ensure real progress?