

Magic Bullets, Lost Horizons: The Rise and Fall of Antibiotics

by Sebastian G.B. Amyes

Taylor & Francis Books, 272 pp, £40.00;
2001

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Subsequent to the introduction of penicillins as life-saving drugs 60 years ago during World War II, we take for granted that there will be one or more antibiotic, alone or as a combination, that will be available, safe and curative when we come down with a bacterial infection. In the recent anthrax bioterror campaign in the United States, an almost talismanic role of ciprofloxacin as a life-saving treatment exemplifies the magical qualities attributed to antibiotics in this era. Sebastian Amyes, a medical microbiologist in the United Kingdom, distilling his decades of experience with the development of antibiotic resistance in bacterial pathogens, has written a book whose subtitle, *The Rise and Fall of Antibiotics*, should bring any reader up short.

After an initial two chapters on the discovery of antibiotics in the early part of the twentieth century, Amyes notes that the golden age of antibiotics was in fact quite short, from the mid 1940s to 1961, when the first quinolone, the progenitor of ciprofloxacin, was introduced into human medicine. Since then the widespread use of antibiotics has led to the global spread of antibiotic resistance, detailed in a chapter called "Paradise Lost". The later chapters are even less optimistic with titles or subtitles of "the doomsday scenario", "why we shall lose the battle against infection", and "has resistance switched out the light at the end of the tunnel". The last page warns of the likelihood that "we are going to slip further into an abyss of uncontrollable infection." This is a clarion call to pay attention, or rather a klaxon at high decibels.

Amyes has my attention and he should have yours, as he explains how the past 30 years have seen a complete

switch in our views about bacterial diseases. The optimism of the US Surgeon General in 1969—that the book on infectious disease could be closed due to the power of antibiotics—has been replaced by the current view that the antibiotic cupboard is bare. Amyes surmises, as others have in recent years, that the widespread acceptance of antibiotics by physicians and patients, coupled with their excellent safety and low toxicity, led to an avalanche of use. With wide usage comes both inappropriate prescription and subtherapeutic dosing, resulting in the selection of drug-resistant bacteria and their subsequent global spread. Amyes illustrates his arguments with many clinical microbiological examples including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), lactam-resistant *Streptococcus pneumoniae*, and the currently emerging vancomycin-resistant *Staph aureus* (VRSA). There is also a chapter on the use of antibiotics in agriculture and their consequences for man, a topic of recurrent heated debate.

Amyes brings a lifetime of research and clinical involvement to the subject and is authoritative in personalizing the crisis of life-threatening, antibiotic-resistant bacterial infections. The book is rich with anecdote and information from the practical, such as what antibiotics Amyes travels with, to molecular details of the evolution of mutant genes encoding the β -lactamase enzymes that destroy penicillins and cephalosporins. This is not meant to be a scholarly work; for example, there are no references anywhere in the text. I found almost no errors of commission but would have liked to peruse some subjects further. Also there are very few figures and illustrations, and in general those graphics are rather primitive. This seems a missed opportunity, and the lack of effective visuals makes the textual details difficult for the non-expert reader to grasp.

With the potential microbial doomsday scenarios well framed, I kept reading to see what solutions Amyes might offer as credible and likely. He offers few in-

sights, beyond better infection control procedures and more careful use of life-saving antibiotics. He addresses bacterial genomics efforts to find new targets briefly and rather dismissively. In the end, the book serves as warning for impending disaster, but I had the sense that Amyes did not make extensive effort to put the contemporary searches for new antibacterial drugs into an integrated perspective.

Amyes writes that the quinolones (of the ciprofloxacin family) introduced in 1961 were the last novel structural type of antibiotic. But this misses the oxazolidinone (trade name Linezolid) approved by the US Food and Drug Administration in early 2000, perhaps after Amyes completed his manuscript. It remains to be seen how effective the oxazolidinone scaffold will become, but it represents the emergence of significantly increased medicinal chemistry efforts in antibacterial drugs in the past seven or eight years by pharmaceutical companies. There are also lipopeptide antibiotics in clinical trials that may prove useful and that Amyes could have noted.

There are many bacterial genome sequences now in public databases, including MRSA, VRSA, enterococcal, streptococcal, pseudomonal, tuberculosis and plague genomes. Dozens to hundreds of new genes from these pathogens have been determined to be essential and/or required for virulence, so validated new targets are now available and real-time PCR may soon allow a revolution in pathogen diagnosis for customized treatment. It is a long and uncertain road from a novel validated target to an antibacterial drug, and the utility of synthetic

combinatorial chemical libraries to provide useful starting points that can be turned into drug leads remains in question. It may be that these efforts will be ineffective and Amyes and the rest of us can distribute along the spectrum of dire pessimism to muted optimism as our dispositions permit. *Magic Bullets, Lost Horizons* is another clarion call that we must not take the antibiotic era for granted or it will be a much-admired period of the past.

