FOREWORD

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FOCUS CONTENTS

The end of an era?

The final years of the Second World War saw the development of the first commercial antibiotic, penicillin, as a result of a transatlantic collaboration. A poster from this time showed a soldier and proudly declared that "Thanks to penicillin he will come home". One of the perhaps less romantic realities of war in that era was that many more people succumbed to infections, secondary to other injuries and ailments, than from all of the direct deaths from bullets, bombs and other applications of military might. Penicillin started to tip the balance and in many senses launched the 'antibiotic era'.

Now we tend to take antibiotics for granted. But consider how essential these drugs are to today's society. They underpin all of modern medicine. Without them people would be threatened by the slightest injury, births of early-term infants would be near impossible, major surgeries and transplantations would be unfeasible, cytotoxic therapies for cancer would invite deadly infections, and hospital wards would become focal points for infectious diseases. In short, without antibiotics we would reverse the gains in life expectancy that were so hard won in the past century.

But antibiotics are under threat. There is an explosion not just of antibiotic resistance but of multidrug resistance. The word 'superbugs' is commonly used to describe organisms — emerging at an alarming rate — that are resistant to most or all clinically used antibiotics. Methicillin-resistant *Staphylococcus aureus* now causes more than 100,000 recalcitrant infections each year and has insidiously started to spread into community-acquired infections. For virtually every organism and every antibiotic we are observing a steady decrease in susceptibility over time. Meanwhile, there have been no new classes of antibiotics developed to fill the gap. The discovery of new antibiotics has plummeted over the past 12 years, with few new drug approvals. Except for the very recent development of two narrow-spectrum drugs — linezolid and daptomycin — there have been no new structural classes of antibiotic drugs introduced into human medicine since 1963, when the quinolone nalidixic acid was approved. Is this the end of the antibiotic era? Could antibiotics really be assigned to a rather brief footnote of medical progress?

We are at a significant crossroads in human history. The development of new antibiotics is a difficult endeavour, but to abandon this goal could be potentially catastrophic. The Infectious Diseases Society of America (IDSA) in its 'Bad bugs; No drugs' campaign[1] is publicizing the issue and has asked governments to seek solutions. Working groups of the National Academy of Sciences and others have also reported many potential solutions to the lack of new antibiotics[2,3], including not just new antibacterial drugs but also novel approaches based on new understanding of the human immune system and resident flora.

In this special print and web Focus on Antibacterials some of the leading researchers in the field consider prospects for antibiotic drug discovery in greater detail. The huge optimism engendered by the availability of hundreds of bacterial genome sequences, and the unanticipated lack of success of genome-based discovery efforts, is just one of the disappointments experienced to date. However, there is also considerable optimism from a variety of new approaches, ranging from new screening methods to the exploitation of new cues from nature, including natural products, polyketides and lipopeptides (modified through genetic engineering), antimicrobial peptides (optimized through protein engineering), and riboswitches. In my opinion we should also be thinking beyond our current comfort zone. Are antibiotics the only answer? Alternative approaches, such as exploiting and enhancing host defence systems[2] as a vehicle to attack microbes, could prove promising.

A colleague once suggested that the reason for the dearth of fundamental antibiotics research could be attributed to the perspective of grant funding agencies — believing that antibiotics were largely successful, and that funding and promoting antimicrobial research should be the aegis of large pharma (who profited from these drugs), funding agencies withdrew support for antibiotics research. In hindsight this philosophy has failed society. We are left with a legacy of a few new drugs with diminishing efficacy and relatively few 'experts' in the academic sector. For this reason I join IDSA and my colleagues in urging granting agencies to make the discovery of new antibacterial therapies one of their highest priorities. The alternative of doing nothing is unthinkable.

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1. Infectious Diseases Society of America. *Bad Bugs No Drugs. As antibiotic discovery stagnates a public health crisis brews* [online], < http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf > (2004).
2. National Research Council. *Treating Infectious Diseases in a Microbial World: Report of Two Workshops* (The National Academies Press, Washington DC, 2005).
3. Canadian Institutes for Health Research. *Novel approaches to Antibiotics; Is time running out?* Workshop Report [online], < http://www.cihr-irsc.gc.ca/e/27879.html > (2005).