Are we approaching the end of the antibiotic era? Editorial overview

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Just over a half a century ago a major international effort, stimulated by the on going second world war, resulted in the introduction of penicillin into medical practice. This, together with the earlier sulphonamides, ushered in the 'antibiotic era'. No longer were bacterial infections the scourge of the military personnel (and of civilians). Physicians finally had weapons to direct against bacterial causes of life threatening infections. We can estimate the impact of antibiotics on Western society because life expectancy increased by about eight years between 1944 and 1972. No other single treatment has had such an impact on human medicine.

The two decades following the introduction of penicillin were the glory years of antibiotic discovery, as one after another new antibiotic classes were introduced and found a place in our pharmacopoeia. These new and diverse antibiotic classes were largely the products of the systematic screening of natural product libraries for compounds with antibacterial activity, an approach which appeared to run out of steam in the late 1960s. This was probably inevitable since any scientific question asked repeatedly (in this case 'What can we find that prevents bacterial growth?') will generate fewer and fewer new answers over time. Even in those days we were learning about antibiotic resistance — the ability of bacteria to acquire the capability to grow in the presence of an antibiotic — and its consequences on effective treatment (see the review by Morris *et al.*, pp 524–529).

In the absence of new antibiotic classes, the response by the pharmaceutical industry over the past 30 years has been to focus on semisynthetic modifications of existing antibiotic classes and to exploit biochemical knowledge of the antibiotic molecular targets to devise far more sensitive screening strategies (most importantly of the β-lactams). Antibiotic resistance has continued to be the major driving force for antibiotic discovery and although major successes were achieved, it is of great concern that no new chemical classes of systemically active antibiotics have been successfully introduced into the clinic for over 30 years. The oxazolidinones and the antimicrobial peptides (see the reviews by Chopra, pp 495–501 and Piddock, pp 502–508) are the only the novel classes that have recently undergone clinical trials. The 'new' fluoroquinolones are structurally and mechanistically related to an antibacterial agent (nalidixic acid) first used over 30 years ago and Synercial, an agent currently in Phase III clinical trials, belongs to a class of compounds discovered in the 1950s which hitherto have found little clinical utility (Chopra, pp 495-501). Furthermore, the mechanisms by which bacteria have acquired resistance to these various new derivatives, are fundamentally similar to the original resistances experienced by members of the given drug class (see the reviews by Chopra, pp 495–501, Piddock, pp 502–508 and Bush and Miller, pp 509–515). As a result, bacteria have learned a variety of sophisticated methods for becoming resistant, and even for acquiring resistance to multiple classes of antibiotics simultaneously through multidrug efflux (see the review by Nikaido, pp 516–523). Indeed we now observe resistance problems for a given set of novel antibiotic derivatives much earlier than had been seen previously (and often during clinical trials). Thus, while recent antibiotics have offered much needed improvements in potency and in pharmacokinetics, they have provided no really novel challenges for the bacterium.

This situation is worsening. Bacteria resistant to all or most available antibiotics, termed 'superbugs', are becoming more prevalent and, for these bacterial infections, antibiotic resistance is rendering existing antibacterial agents obsolete (Morris *et al.*, pp 524–529). This is occurring, not just with feared hospital pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), but also with community acquired infections such as the pneumococcus. If we do not reverse the current trends by judicious use of existing and new antimicrobial agents, we stand the risk of seeing the antibiotic era as a footnote in human history. It has, therefore, become a major priority to develop fundamentally novel therapeutic approaches to combat infectious disease. Thankfully, this worsening medical situation is occurring during something of a renaissance in both biological and chemical sciences, being driven principally by revolutions in genomics and medicinal chemistry, respectively. As a consequence, pharmaceutical and biotechnology industries, which have made major investments in the development and application of a vast array of associated technologies, may now have the means to break the apparent deadlock in the discovery of radically new anti-infective agents. To do this, two principle technical hurdles, at the very beginning of the discovery process, need to be overcome. These relate to the paucity of new molecular targets and to the relatively limited diversity available for screening.

The genomics revolution, which has already seen the DNA of several significant pathogens fully sequenced (see the review by Allsop, pp 530–534), provides us with all possible targets for antimicrobial intervention and leads potentially to a third paradigm in antibiotic discovery. This encompasses the advantages of the two previous paradigms, namely, diversity from empiric screening (screening for active agents regardless of their chemical nature and mode of action), and potency from the molecular-target based approach (synthesis/screening for agents with a particular mode of action). For example, comparative genomics enables the identification of many conserved genes which currently have no known function. Thus it is possible that we can screen for inhibitors of some of these gene products even before we understand how they work (Allsop, pp 530–534). New screens, for example based on the phenotype of mutants in these candidate genes, can be readily harnessed to expanded chemical libraries [1] generated by new combinatorial approaches in medical chemistry.

Although our experience of microbial drug resistance began with bacteria, we are already seeing major problems with effective therapy of viral and fungal infections (see the reviews by Balzarini *et al.*, pp 535–546 and Georgopapadakou, pp 547–557). Nowhere is this seen more clearly than with AIDS, a disease caused by the HIV virus, where resistance to even the most recently introduced anti-virals is threatening their continued utility (Balzarini *et al.*, pp 535–546).

If we are correct in our assumption that new approaches will result in the discovery of new agents, a note of caution is still in order. It may well be that the next decade will see most or all of the possible molecular targets screened. Therefore it is possible that the next group of agents to be introduced into the clinic will be the last. The lessons to be learned with drug resistance to all infectious diseases need to be assimilated and applied to the continuing development of appropriate prescribing practices, particularly as the choice of therapies expands. Therefore, despite the hope offered by the genomics approach, it wi'l be very important to observe and learn from the lessons of the past half century in order to prolong the antibiotic era into future generations.

Reference

1. Knowles DJC, King F: **The impact of bacterial genomics on antibacterial discovery.** In *Resolving the Antibiotic Paradox: Progress in Drug Design and Resistance.* Edited by Rosen BP, Mobashery S. Plenum Press; 1998:in press.