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Introduction: Antibiotic Resistance

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One of the central themes of success in human therapeutics in the 20th century was the discovery and development of antibiotics and antibacterial agents, for the treatment of bacterial infections. The introduction of antibiotics helped drop the death rates from infectious disease from 797 per hundred thousand in 1900 to 36 per hundred thousand in 1980, a 20-fold improvement. Two lines of chemical investigation proved fruitful: the isolation of natural products with antibiotic activity from microbial sources and the purposeful synthesis of antibacterial agents by medicinal chemists.

The first line of discovery, the isolation of microbial metabolites from Nature, was initiated by Flemming's discovery of a penicillin-producing fungus and was closely followed by systematic search of antibacterial producing microorganisms by pioneers such as Dubos and Waksman. This strategy produced many of the famous classes of antibiotics. These include both the cephalosporin and penicillin branches of the β-lactams, the aromatic polyketides of the tetracycline class, the aminoglycosides represented by streptomycin, the polyketide macrolactones exemplified by erythromycin, and the glycopeptides of the vancomycin and teicoplanin family. The search by medicinal chemists for antibacterial magic bullets by synthetic efforts has produced the sulfa drugs, the dihydrofolate reductase inhibitors, the fluoroquinolones, and most recently the oxazolidinones.

In the course of these discovery efforts, the active natural products and synthetic antibacterials have proven to be valuable probes for deciphering the identity of targets in pathogenic bacteria. Historically, this has turned out to be a target poor therapeutic area with only four robust targets for widely used groups of antibiotics: bacterial cell wall biosynthesis; bacterial protein biosynthesis; DNA replication and repair; and folate coenzyme biosynthesis.

The golden age of antibiotic discovery in the 20th century was actually quite short (Table 1). The two decades from 1940 to 1960 saw isolation of most of the major classes of natural antibiotics. The sulfa drugs were introduced in the 1930s and have been in continuous use for 70 years. The first versions of the quinolone synthetic drugs were introduced in 1962.

Much subsequent activity has involved refinement of existing antibiotic structures to deal with the onset of resistance. For example, the first generation penicillin V was replaced by second generation versions, methicillin and ampicillin, which in turn were superseded by such extended spectrum molecules as piperacillin. A parallel effort at semisynthetic modification of cephalosporins has led from first generation (cephazolin) to second (cefoxatin) to third (ceftriaxone) and now fourth (cefipime) generation versions where the bicyclic lactam core scaffold is maintained and the periphery tailored to deal with succeeding

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Table 1. History of Antibiotic Classes in Clinical Use

year	antibiotic	class	natural product	synthetic
1929 (activity) 1940 (purification)	penicillin	β-lactam	√	
1932	sufapyridine	sulfonamide		√
1944	streptomycin	aminoglycoside	√	
1945	cephalosporin	β-lactam	√	
1947	chloramphenicol	phenypropanoid	√	
1948	chlortetracycline	tetracycline	√	
1950	erythromycin	macrolide	√	
1955	vancomycin	glycopeptide	√	
1955	virginiamycin	streptogramin	√	
1955	amphotericin	polyene (antifungal)	√	
1955	lincomycin	lincosamide	√	
1959	rifamycin	ansamycin	√	
1962	nalidixic acid	quinolone		√
1969	fosfomycin	phosphonate	√	
2000	linezolid	oxazolidinone		√
2003	daptomycin	lipopeptide	√	

waves of resistant bacteria. In the macrolide lineage, the fully natural product erythromycin was tailored to give the second generation semisynthetic azithromycin and clarithromycin and now the third generation ketolides such as telithromycin.

There was a 38-year interval between introduction of the fluoroquinolone class of antibiotics in 1962 and the next new structural class, the oxazolidinones, in 2000.

This innovation gap is directly relevant to the current situation where the antibiotic cupboard is rather bare for meeting the challenges of new outbreaks of resistant bacteria.

The pattern of introduction of successive generations of β-lactam antibiotics and of macrolides, tetracyclines, and aminoglycosides is strong testimony to the almost inescapable correlation that introduction of a new antibiotic into widespread clinical use induces the rise of resistant bacteria. Given the vast numbers of bacteria, their short generation times, and typical gene mutation frequencies of 1 in 10^7 bacteria, resistance is inevitable. Antibiotics select for those very rare bacteria in a population that are less susceptible and allow them to become dominant in the populations as susceptible bacteria die off. For all the major classes of antibiotics noted above, both natural and synthetic, clinically significant antibiotic resistance has ensued after introduction into human therapeutic use. The time frame has been as short as one year for penicillin V and as long as 30 years for vancomycin. The resistance kinetics reflect a range of intrinsic and acquired molecular mechanisms and the extent of dissemination of the antibiotic.

Three major mechanisms of antibiotic resistance reveal a few common themes used by bacteria to fend off antibiotics. One mechanism is destruction of the antibiotic by bacterial enzymes, and this is the quantitatively significant route for disabling β-lactams by hydrolysis of the drug lactam warhead. A second mechanism is bacterial reprogramming of the antibiotic target to lowered susceptibility, and this is the path vancomycin resistant enteroccci (VRE) take to escape vancomycin action. The third major route, especially prevalent in pseudomonads but common to all bacteria, is to pump out antibiotics via transmembrane efflux pumps, keeping antibiotic concentration within the bacterial cell below toxic threshold concentrations.

Thus, the expectation in the first decade of the 21st century is that as a new antibiotic is introduced to combat pathogenic bacteria, resistant organisms will be selected and will vitiate the utility of that antibiotic. New antibiotics will therefore be required periodically as waves of resistance follow. The anticipated cyclical need for new antibiotics raises key questions of where new antibiotics will come from and whether monotherapy will continue to be an effective practice for many life threatening infections.

To optimize the discovery and development time for new antibiotics requires both sources of new molecules and understanding of the molecular mechanisms of resistance. This thematic issue of *Chemical Reviews* collects in one place reviews by experts both on the mechanisms of action of the major classes of antibacterial drugs and on the major resistance mechanisms.

Articles 1−3 deal with cell wall biosynthetic targets, starting with the β-lactam antibiotics and then discussing the glycopeptides of the vancomcyin and teicoplanin class. The glycopeptides are substrate binders for un-cross-linked D-Ala-D-Ala termini of peptidoglycan biosynthetic intermediates. The ramoplanin class of lipodepsipeptide antibiotics also functions by substrate binding but targets the Lipid II molecules that act as carriers for the nascent peptidoglycan units.

Articles 4−7 deal with antibiotics that target different facets of bacterial protein biosynthesis. The first two articles in this cluster take up aminoglycosides, which bind at sites on 16S ribosomal RNA on the small subunit of bacterial ribosomes, and macrolides, which bind to 23S ribosomal RNA near the peptidyl exit tunnel. Article 6 evaluates the newer streptogramins and oxazolidinones for their mechanism of ribosome inhibition. Article 7 reviews the knowledge base for polyketide biosynthesis and combinatorial biosynthesis approaches to novel structural and functional activities for third generation antibiotics in this polyketide class.

Articles 8−10 address antibiotics that act to interdict information flow from DNA to RNA in bacterial

cells, discussing fluoroquinolones that target type II DNA topoisomerases, antifolates that block provision of monomers for DNA synthesis, and rifamycins that block DNA-dependent RNA polymerases.

Articles 11 and 12 take up two variants of peptide antibiotic classes, the ribosomally generated lantibiotics and the nonribosomal thiopeptide antibiotics. Article 13 takes a broader look at the biosynthetic logic for nonribosomal peptide assembly line machinery responsible not only for thiopeptides but also the glycopeptides and the depsipeptide classes. The antibiotic class most recently approved by the FDA is the nonribosomal lipodepsipeptide daptomycin.

Article 14 examines the biosynthesis and mechanism of additional nonribosomal peptide and polyketide natural products, originally identified as antibiotics, but with special potency and utility as antitumor agents. These include bleomycin, the enediynes, and mitomycin, all of which target DNA.

The last article addresses the pressing and continuing need for new antibiotics by reviewing how new targets for antibiotics are discovered in bacteria by genetic and genomic approaches. It also summarizes contemporary approaches for screening of leads in antimicrobial drug discovery.

This comprehensive collection of reviews on the major classes of antibiotics in human clinical use should be a central resource for scientists to grapple with the questions of how antibiotics work, why they stop working, and how the molecular insights into molecules and their targets condition strategies for much needed new antibiotics.

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