Enzyme-Mediated Resistance to Antibiotics
Mechanisms, Dissemination, and Prospects for Inhibition
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To Rita, to whom I owe everything
—R.A.B.

To Liliana and Ryan
—M.E.T.
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AT THE PRECIPICE

A quick look at contemporary newspapers and journals will reveal startling reports about antibiotic-resistant bacteria, “superbugs.” A large number of common infectious diseases caused by bacteria were once easily treatable with antibiotics. Now many pathogens have become increasingly deadly due to antibiotic resistance. At the present time, vancomycin-resistant *Staphylococcus aureus* (VRSA), community-acquired methicillin-resistant *S. aureus* (CA-MRSA), hospital-acquired MRSA, vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococcus pneumoniae*, and multidrug-resistant (MDR) *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* represent a highly significant threat to children, hospitalized patients, immune-compromised individuals, and nursing home elderly. They are, in fact, a threat to us all. A recent commentary in *Nature* describes MDR *A. baumannii* as “a real danger” (1). Alarming drug resistance phenotypes in gram-negative bacteria like *P. aeruginosa* and *A. baumannii* include resistance to penicillins (piperacillin and ampicillin), extended-spectrum cephalosporins (ceftazidime and cefepime), β-lactam β-lactamase inhibitors (ampicillin/sulbactam, amoxicillin/clavulanate, and piperacillin/tazobactam), and carbapenems (meropenem and imipenem). Even resistance to colistin, a polymyxin-class antibiotic, has emerged. It is highly disturbing to the clinician to be faced with pathogens that have become resistant to all antibiotics. It is like being at the precipice...

The history of our most trusted antibiotic, penicillin, began in 1929 when Alexander Fleming published his seminal paper in the *British Journal of Experimental Pathology* on the “mold extract” from *Penicillium* as a germ-killing compound (8). This serendipitous discovery was further developed by Howard Florey, Ernst Chain, and Norman Heatley at Oxford University. Realizing the potential of Fleming’s discovery, this team developed methods for growing, extracting, and purifying enough penicillin to demonstrate its power against streptococcal and staphylococcal...
infections. The success of the utilization of penicillin was so spectacular that it received the appellation of “miracle drug.” This early work was published in two landmark papers in *Lancet* in 1940 and 1941 (3, 5). Among the first fortunate patients to receive this “miracle” drug were the victims of the devastating Cocoanut Grove fire in Boston in November 1942 (6, 9). The high mortality of infections due to wounds sustained in battle (gangrene) and the burgeoning problem of gonorrhea and syphilis in World War II veterans also enhanced interest in the curative powers of penicillin.

Before this period of amazing discovery, E. P. Abraham and Ernst Chain reported in *Nature* (1940) the presence of an enzyme in *Bacillus (Escherichia) coli* able to inactivate penicillin (2). This significance of this report was not immediately realized. After the beginning of penicillin’s use to combat infections, *S. aureus* was among the first bacteria known to become resistant to penicillin. The clinical impact of this development was staggering. This pathogen not only caused serious illness (such as pneumonia, endocarditis, osteomyelitis, and toxic shock syndrome) but was also once more untreatable. The development of semisynthetic penicillins and the discovery of other natural products stemmed this threat, but our stay was only temporary.

In 1943 Selman Waksman and his group isolated streptomycin from the soil bacterium *Streptomyces griseus* (10). Streptomycin was first tested to be effective against *M. tuberculosis*, the scourge of ancient civilizations. The use of streptomycin and other antitubercular compounds led to a significant reduction of mortality due to tuberculosis in the United States, from 39.9 deaths per 100,000 population in 1945 to 9.1 per 100,000 in 1955 (4). Waksman and his group also created the concept of systematic screening of microbial culture products, developing a technology that has provided the foundation of the early antibiotic industry. Soon, new antibiotics were discovered that provided physicians with a large number of “weapons” to combat bacterial diseases.

In spite of more than half a century of tremendous commercial and scientific investment, bacterial infectious diseases were not completely eradicated by the use of antibiotics (7). Paradoxically, several diseases re-emerged, and many of the bacterial pathogens are becoming more and more resistant to treatment with antibiotics.

The central problem is that the use of antibiotics has contributed to the inexorable rise of antibiotic-resistant bacteria. A large number of factors, including human and nonhuman use of antibiotics, have contributed to the emergence, acquisition, and spread of resistance. These factors include the use of antibiotics in food-producing animals, which leads to the development of resistance in bacteria that find their way into the human food chain; the misuse and overuse of antibiotics in humans; the demand for antibiotics by patients when they are not appropriate; noncompliance by patients who often fail to finish the antibiotic prescription; and the over-the-counter availability of antibiotics in a large number of countries. The World Health Organization has estimated that bacteria resistant to antibiotics now account for about 60% of nosocomial infections. The Centers for Disease Control and Prevention estimate that of about 60,000 deaths that occur in the United States every year due to nosocomial infections, 14,000 are the result of antibiotic-resistant bacteria. The number of deaths related to antibiotic-resistant community-acquired infections is also growing.

Years of research demonstrated that bacteria have evolved a wealth of different ways to resist the action of antibiotics as well as to transfer these capabilities. Antibiotic resistance mechanisms include (i) changes in permeability that interfere with the penetration of the antibiotic into the cell; (ii) the presence of efflux mechanisms that expel the antibiotic; (iii) modification or substitution of the target of antibiotic action; and (iv) chemical modification of the antibiotic molecule. In addition, besides vertical transmission, once the resistance trait is acquired there
are several mechanisms of horizontal transfer that accelerate the dissemination of resistance.

An important component of the antibiotic resistance problem is represented by mechanisms mediated by enzymatic processes. Chemical modification of aminoglycosides and β-lactams is of great relevance in the clinical setting and is mediated by a large number of enzymes. These enzymes tend to be coded for by genes that are present in mobile elements (transposons, plasmids, etc.) that favor their quick dissemination. In this book we highlight the enzymatic capabilities of microorganisms to introduce chemical modifications that negate the biological activity of β-lactams (β-lactamases) or aminoglycoside antibiotics (aminoglycoside-modifying enzymes). These chemical modifications include destroying the β-lactam ring of β-lactam antibiotics and introducing acetyl, nucleotidyl, or phosphate groups at different locations of the aminoglycoside molecules. We hope that the chapters describing different aspects and kinds of β-lactamases and aminoglycoside-modifying enzymes will provide the reader with a complete picture of the present state of knowledge about these important mechanisms of resistance. As an example of the existence of other enzymatic mechanisms that result in resistance, we have included a chapter on RNA methylases and resistance to erythromycin. We will illustrate the variety of scientific approaches important to their characterization and, we hope, inspire researchers to take up the still many unknowns that need to be clarified.

To complement this compilation, we will also illustrate the different ways bacteria share resistance determinants. Horizontal transfer is a big part of the problem of antibiotic resistance, and in our view, different mechanisms for dissemination of antibiotic resistance genes need to be included. In some cases, such as “transposable elements” or “plasmids,” the fields have become extremely big and a chapter would not do justice to all the material that needed to be included. Recent books have been entirely devoted to these elements. Therefore, this discussion has not been included here. However, some aspects of these elements can be found through chapters in the section “Dissemination of Antibiotic Resistance and Its Biological Cost” as well as in chapters in other sections of the book. The collection included here will permit the reader to acquire information about the history and recent developments in other areas such as dissemination at the cellular level and integrons. Since the acquisition of resistance does not come free to the bacterial cell, a chapter dealing with the biological cost of resistance has been included.

Finally, one might ask, “Why catalogue these enzymatic resistance mechanisms?” Clearly, rational approaches are needed to control the dissemination of resistance genes and to combat the highly versatile inactivating enzymes. A wide variety of methods are under development, as discussed in the section “Novel Approaches and Future Prospects.” It is our hope that the material included herein will inspire students of enzymology and antibiotic resistance to save us from falling over the edge.

Robert A. Bonomo
Marcelo Tolmasky

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