PREFACE

Bacterial infection remains a leading cause of death in both the Western and developing world. Although the discovery of penicillin heralded the beginning of the age of antibiotics, the phenomenon of resistance emerged almost immediately. Since that time it has become clear that the effective pharmaceutical treatment of bacterial infection will never be complete, but rather, will continue as a complex fight on the ever-shifting battlefield of bacterial evolution and gene transfer. Bacterial drug resistance is most often the result of one of four broad mechanisms: metabolic inactivation of the active species, mutation of the drug target, the emergence of alternate metabolic pathways that obviate the effect of antibiotic action, and removal of active drug agent by active transport. Because of the extraordinary importance of antibiotic resistance in modern medicine, this volume represents the first of a series on the biochemical basis of antibiotic resistance.

Although it had long been imagined that the complex cell wall of gram-negative organisms was responsible for the resistance to antibiotic treatment so commonly observed, it became apparent through the 1980s that the resistance was the result of a complex series of multidrug efflux transporters. Indeed, nearly 40 such transporters have been identified to date, and at least 20 are proposed to act as multidrug efflux pumps. Efflux pumps are divided broadly into five families, based on sequence homology: the ATP-binding cassette family, which harnesses the energy of direct ATP hydrolysis to move solutes against a gradient, and the major facilitator superfamily, small multidrug resistance family, resistance–nodulation–cell division superfamily, and multiple antibiotic and toxin extrusion protein family, all of which use ion gradients as energy sources.

Among the various classes of bacterial efflux pumps the resistance–nodulation–division (RND) family is widely considered as the most important to the broad phenomenon of bacterial resistance, and we have focused on this group here. Nikaido and co-workers performed some of the earliest work toward discovering the role of this group of proteins in bacterial resistance and in elucidating their mechanism of action. In a review of the RND family of efflux pumps, he provides both a unique

historical perspective on the discovery of the family, and a review of biochemical, biophysical, and genetic studies on both the activity and inhibition of this extraordinarily important group of proteins. The activity of bacterial efflux pumps operates under extraordinary multilevel control, and Amaral and co-workers report on the nature and mechanism of that control, inducers of RND efflux pump activation, and inhibitors of bacterial efflux pumps. Finally, Yu and co-workers review the extensive body of knowledge that has accumulated on the structure of tripartite RND transporters vital to the pathogenicity of several important human pathogens, including *Escherichia coli*, *Campylobacter*, and *Neisseria*, and describe the use of this structural information for the elucidation of mechanism and the development of inhibitors.

The largest and structurally most diverse group of secondary membrane transport proteins is the major facilitator superfamily (MFS) group. Despite the group's size—some 15,000 members, representing 25% of all known prokaryotic membrane transporters—relatively little is known about the fundamental biochemistry and structural biology of the group. This lack of knowledge is largely the result of the composition of MFS proteins; as transmembrane proteins they are hydrophobic, poorly behaved in solution, and difficult to purify. In the fourth chapter, Henderson and co-workers review the strategies relevant to the expression and purification of members of the MFS class of efflux pumps.

The quinolone antibiotics occupy a special place in the history of medicinal chemistry, as being among the first antibiotics developed against malaria. Later, quinolone antibiotics were widely used for the treatment of urinary tract infections, and several later-generation drugs, including ciprofloxacin, remain in use today for the treatment of a variety of bacterial infections. The utility of almost all quinolone antibiotics is greatly limited by the phenomenon of multidrug resistance, due in large part to the activity of efflux pumps. In the fifth chapter, Vila and co-workers consider the role of various efflux pumps in quinolone resistance in important human pathogens, including gram-positive and gram-negative bacteria, in Enterobacteriaceae and in other species of clinical relevance, including *Haemophilus influenzae*, *Campylobacter*, and *Mycobacterium*.

Most transporter proteins do not function to expel drugs, but rather, work to import various vital solutes into cells. Indeed, nearly 650 families of transporter proteins have been identified and catalogued, grouped roughly into 10 or so superfamilies. In addition to the massive complexity afforded by the sheer number of transporters, the study of transmembrane

transporters is further hampered by the structural complexity of multimeric transmembrane proteins and the difficulties associated with culturing many pathogens. As a result of this complexity, much of our knowledge of efflux-pump-attributable multidrug resistance arises from genomic studies of pathogens and pathogenic flora. In the sixth chapter, San Francisco and co-workers report on the genomics of efflux pumps in both bacteria and fungi, and how such approaches offer novel avenues for the development of new therapeutic agents.

A final contribution to Volume 77 comes from Cooper and co-workers. This final review is unrelated to bacterial efflux pumps and multidrug resistance, but rather, considers the mechanism of paracatalytic reactions involving various electrophiles, including oxygen, induced by carbanion-generating enzymes. In such reactions a carbanionic reductant is intercepted by an electrophilic species, leading to off-pathway products and, in many instances, to modification of enzyme side chains. The ubiquitous presence of oxygen as an electrophilic species renders this process of special importance in many biological settings, and the deleterious effect of various enzyme-bound reactive oxygen species contribute to various pathophysiological conditions. Cooper and co-workers consider the enzymes susceptible to such paracatalytic reactions and consider the role of the intermediates and lesions in cancer and in neurodegenerative disease.

ERIC J. TOONE