PART I

SOURCES
INTRODUCTION

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With the discovery of antibiotics came the recognition of antibiotic resistance. With time, the concept emerged: wherever antibiotics exist, resistance determinants reside. Thus, the early emergence of antibiotic resistance clinically occurred among patients in hospitals where these new therapeutics were introduced. Resistance appeared initially to sulfa drugs (1930s) and then to penicillin (1940s) (Levy, 2002).

While the early warnings were largely disregarded, resistance increased, continuing to follow mounting antibiotic use. The true breadth of the problem appeared in the 1970s and 1980s, when many different multidrug-resistant (MDR) infectious organisms became evident. Hospitals were no longer the only source of drug resistance. Resistant organisms were appearing among both clinical and nonclinical strains stemming from antibiotic use in the community. The latter microorganisms carried genes for resistance that were shared with other bacteria in the environment.

Over the past several decades, recognition of the environmental load of resistant organisms has increased. Bacteria of little clinical consequence have become health threats because they harbor antibiotic resistance genes that can be transferred to organisms, causing disease in people. The phenomenon has arisen on the heels of increased antibiotic use in communities and among farm animals. Moreover, antibiotics from various sources are being discharged as active drugs into the environment through inadequate waste management. For example, a recent report links finding antibiotics and drug resistance in river sediments to discharge from an antibiotic-producing company in India (Kristiansson et al., 2011). Antibiotics are delivered to crops in manure from animals fed antibiotics for therapy and growth promotion. The presence of both the antibiotic and the resistance genes in the same environment selects for resistant bacteria that are then spread widely. Thus, if for no
other reason, it should come as no surprise why and how drug resistance has emerged outside the hospital and in the environment.

As this book presents, recognition of resistance is now broad but not necessarily connected with antibiotic use. Resistance may occur in the absence of an antibiotic substrate, particularly in soils where organisms may bear resistance traits to drugs not detected in that environment. Moreover, the environment aids in the spread of resistance through gene transfer.

Antibiotics affect not only the microbial flora of the treated individual or animal, but also the people (and animals) sharing the environment. Thus, the resistance phenomenon can extend well beyond the treated individual, person or animal. These findings illustrate why these therapeutics can be called “societal drugs” (Levy, 2002).

Studies performed by William Cunliffe and associates in London demonstrated that those taking antibiotics for acne selected skin bacteria resistant not only to the acne drug but also to other drugs as well. Importantly, resistant bacteria were found not just on the skin of the treated patients but also on the skin of those sharing the same household (Miller et al., 1996). This kind of “societal” sharing involved an ecologic selection of resistant organisms in the environment of the acne patient. A similar ecologic consequence has been noted on a farm where growth promotion use of oxytetracycline led to selection and spread of resistant fecal *Escherichia coli* among treated and nontreated animals and people (Levy et al., 1976). Chronic use of a single antibiotic led to multidrug resistance (Levy et al., 1976). This phenomenon of antibiotic use and emergence of resistance in nontreated people or animals sharing the same environment is described in other experimental studies as well (Levy, 2002).

In 1986, Dick Novick and I organized a Banbury meeting in Cold Spring Harbor on the epidemiology of antibiotic resistance (Levy and Novick, 1986). Little did we surmise then that in two-and-a-half decades, studies of soil would reveal large numbers of indigenous drug-resistant bacteria. In fact, these organisms can be regarded as “reservoirs” of resistance genes and they far out-number those we face clinically.

In 1989, Bob Miller and I edited a book entitled *Gene Transfer in the Environment* (Levy and Miller, 1989). This volume converged the knowledge of experts in the area of gene transfer with an emphasis on natural environments as locales for gene spread. As cited in the Preface, “gene transfers occur in all ecologic niches.” The thrust of both the conference and the book was to illustrate the potential spread of any organism and any resistance gene in the environment, with particular reference to genetically engineered microorganisms. The environment was not the focus of that book. It represented the backdrop for gene exchanges.

What was not defined then but is now more directly addressed in this book is the occurrence of drug resistance within the environment flora. This phenomenon results from production of antimicrobials by the soil organisms themselves, as well as the dispersion of drugs and resistance genes through wastewater from treated animals and people.

Investigations have identified the natural soil environment as a source for both antibiotics and resistance genes. This volume extends that knowledge to many different environments that serve as a source and repository of antibiotic-resistant organisms. Studies detailed in this book stem from findings of a plethora of resistance determinants among soil *Streptomyces* (D’Costa et al., 2006). Other prior studies show evidence that naturally occurring resistance determinants in soil bacteria
degrade the antibiotic, producing nutrients for the growth of these bacteria (Dantas et al., 2008). The presence of resistance genes in the environment has recently been reviewed, addressing the many routes by which resistance genes emerge and spread in the natural environments (Allen et al., 2010).

The concept of intrinsic or naturally occurring resistance among soil organisms, now called the antibiotic resistome, is expanded upon by authors in this volume. Some resistances may be naturally occurring, but others are a result of “pollution.” The many avenues/means by which manure and wastewaters, antibiotics, and antibiotic-resistant bacteria are spread into the environment are well documented throughout this volume. The work under discussion includes not only food animals but also the use of antibiotics in fish farms, as reviewed here and elsewhere (Levy, 2002).

This book’s strong message is that there exists a broad, general environmental presence of antibiotics and drug-resistant bacteria. They may be concentrated in areas such as hospitals or farms, or spread more widely in the environment in association with people and animals, or found naturally, as demonstrated by the ubiquitous nature of antibiotic resistance genes in the soils. The findings raise a number of interesting questions. What purpose are the naturally present resistance determinants providing? What do they mean to the future discovery and use of antibiotics? Clearly, one can expect resistance emergence no matter how novel the new antimicrobial may be.

Ironically, the relatively high levels of resistance genes in the natural soil environment suggest a reason for our difficulty in finding new antibiotics in soils. Quite clearly, antimicrobials produced in the soil will be subject to inactivation by degrading enzymes that are present there. To salvage the antibiotic, the enzymes would need to be deactivated, for example, by heating, before attempting to find and extract an antimicrobial. Thus, a consequence of finding degradative enzymes among soil microbes is important to the origins of resistance as well as our ability to find new antibiotics (Levy, 2006).

Can we discern a relationship between the environmental reservoir of antibiotic resistance and the potential prediction of resistance emergence in human pathogens? Moreover, what is the level of antibiotics in these environments and does their presence wholly account for the emergence of resistant bacteria? These are naturally occurring microbes for which resistance offers some advantage, not just for survival against other microbes but in defense against discharged waste products, or as signal molecules in microbial community activities.

A Reservoirs of Antibiotic Resistance (ROAR) project, spear-headed by the Alliance for Prudent Use of Antibiotics (www.apua.org), involved experimental systems that demonstrated the transfer of resistance genes among environmental flora. This has led to the development of an online database that includes descriptions of these organisms and their resistance determinants.

A follow-up study, currently undertaken by APUA, examines the kinds of resistance traits genetically and phenotypically among nonclinical bacterial isolates: *E. coli*, *Streptococcus/Enterococcus*, *Staphylococcus*, *Aeromonas*, *Salmonella*, *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas* in environments in different areas of the world, including Bangladesh, Georgia, India, Turkey, Uganda, South Africa, South Korea, and Vietnam. The findings so far display large differences in the presence of drug resistances among the same species, but isolated from varied geographic sites.
This book is unique in bringing together a cadre of basic scientists and epidemiologists interested in the presence of antibiotics and resistant bacteria in the environment. It does not focus on organisms affecting disease in people but on the reservoir in nonclinical strains. This is a powerful and comprehensive illustration of change in thought, particularly as we compare what was considered several decades ago and how that has changed over time—from the interest in the environment as a place for gene transfer, to the evaluation of the environment as a reservoir of antibiotics, antibiotic-resistant bacteria, and transferrable resistance genes.

REFERENCES


