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FOREWORD

Antibiotic resistance and the golden age of microbiology

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The ability of micro-organisms to develop resistance to the action of inhibitors has been known since the discovery of antimicrobial agents. The first reports were concerned with agents such as Salvarsan and Prontosil in the early 1900s; the phenomenon of 'fastness' to these agents was observed frequently during treatment with the drugs. Following the development of the sulfonamides in the 1940s and discovery of the 'true' antibiotics, those produced by fermentation such as penicillin, streptomycin, tetracycline, etc. in the 1950s, the study of antibiotic resistance and its mechanisms paralleled those concerned with mode of action. In the first place, the genetic characterization of a specific resistance mechanism was a critical step in defining antibiotic mode of action. The identification of a binding site or the accumulation of a biosynthetic intermediate provided important clues to the ways by which the antibiotics acted on microbes. To cite a specific case, mutants resistant to the aminoglycosides were early identified as alterations in ribosome structure, and these provided critical information about the structure of ribosomes and their functions in the translation process. The identification of these key components led to the characterization of antibiotic target sites within the ribosome structure: these have been confirmed by X-ray crystallographic studies (1). Similar analyses have revealed detailed molecular information on the targets for most classes of antibiotics. Interestingly, one phenotype that has never been adequately described is that of mutants that are dependent on the presence of antibiotics (such as streptomycin) for ribosome function in translation.

Antibiotic resistance (AR) has become a field of research in its own right, and deciphering the widespread biochemical mechanisms involved have revealed significant information about the biology of microbes (2). Resistance has compromised the use of every therapeutic agent ever discovered. At the end of the Second World War, extensive use of antibiotics was accompanied by drastic increases in susceptibility of hospital pathogens and led to clinical failures in many hospitals (3). As antibiotic use increased on a worldwide scale, it was discovered that antibiotic resistance developed not only by mutation but by an alternative mechanism, that of horizontal gene transfer. Initial reports of transferable multidrug resistance by R factors in Japan in 1959 were greeted by scepticism in other countries, but soon the phenomenon was confirmed worldwide. It is now accepted as the principal, clinically significant route to antibiotic resistance in microbes. There are notable exceptions; for example, no transferable antibiotic resistance has been reported in the mycobacteria.

There is a missing link in the evolution of R factors: they were first identified in Japan and subsequently in Europe and the US. Were R factors formed in the first years of extensive antibiotic use? Examination of bacterial pathogens isolated and stored from the 1930s showed no evidence for transferable antibiotic resistance at this time (4); however, the strains did contain plasmids. How and where did R factors evolve? Their discovery was the genesis of much exciting research, and, some 30 years later, horizontal gene transfer provided the foundation for practical genetic engineering and the creation of the biotechnology industry.

Gene transfer between bacteria is considered to be ancient and universal and is an important element in theories of cellular evolution and in the formation and maintenance of microbial communities. Mutation is one thing, but where do resistance genes come from?

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The answer is surprising: everywhere! Putative antibiotic resistance genes have been detected in isolated human populations never exposed to antibiotics (5), and similar gene families are present in microbial communities from all sources that have been examined including human, animal, and plant microbiomes, and even ancient environments (6). Nothing escapes the power of next-generation sequencing! AR was obviously present in the microbial world long before the introduction of antibiotics in the 1950s. What are the natural functions of antibiotic resistance genes? It is generally assumed that environmental AR is the origin of clinical resistance mechanisms and that the presence of antibiotics and AR genes in the environment implies conflict and competition within microbial communities. Are all microbial communities in humans, animals, birds, reptiles, soil, marine environments, and prehistoric caves in a state of perpetual warfare? Is it possible that the putative resistance genes play other roles in microbial communities in nature?

Antibiotics can be isolated from many different microbial sources. However, it must be pointed out that the compounds referred to as antibiotics are generally present at undetectably low concentrations in the environment and that very few convincing demonstrations of *in situ* antibiotic activity have been reported (7). There is, however, increasing evidence for their roles in promoting morphological and other changes in bacterial populations at sub-inhibitory levels (8). The explanation for these seemingly contrasting results has a ready answer in history. Paracelsus (1493–1541) postulated that: 'Everything is a poison. the dose differentiates a poison from a remedy'. All molecules (potions) have concentration-dependent activities. It is probable that antibiotics (poisons at high concentration) perform 'other' functions in nature. Do the putative resistance genes also have 'split personalities'? The complexity of natural microbial communities is humongous, and precious little is known of the intracellular and intercellular interactions involved in their establishment and maintenance. Nonetheless a reservoir of potential resistance functions exists and, in principle, could be recruited and transferred to different hosts and so interfere with cell–cell interactions.

What is the connection between the AR genes in pathogens and their putative (precursor) relatives in nature? They encompass a large range of biochemical mechanisms and are widely distributed in the biosphere. Interestingly, many of the AR genes are enzymes involved in hydrolytic (cleavage) or modification (acylation, phosphorylation, methylation) of small molecules or proteins. The aminoglycoside kinases are closely related to eukaryotic protein kinases. Do the putative resistance genes modify other molecules and proteins by similar mechanisms? Continuing studies of the sources and types of antibiotic biosynthesis and putative resistance genes in nature (including those in animals and in man) must focus on their natural functions. This should shed light on the routes by which they may be recruited to form resistance plasmids in pathogens. Multifunctionalism is common in nature, for example ribosomal proteins exhibit extra-ribosomal functions (9,10). Do resistance genes influence the activities of low-molecular-weight bioactive compounds produced by microbes and so modulate inter- or intra-cell signalling? Do modified molecules play other roles in microbial growth and behaviour?

The universal distribution of putative resistance genes implies that they are capable of facile movement and expression within microbial environments. AR genes can be mobilized by plasmids or phage, but other mechanisms for the enhancement of natural gene transfer have been identified, including natural electroporation and nanoparticle-assisted processes (11).

Learning more about the nature and sources of putative antibiotic resistance genes (including those present in animal and plant microbiomes) should provide clues as to the roles of AR genes in nature and the selection pressures in operation when they are recruited to form AR plasmids in pathogens. We have a situation in which 'antibiotics that are not really antibiotics' are in apposition with 'resistance genes that are not really resistance genes'. The question is how we can use this information to reduce or eliminate all impediments to the successful treatment of infectious diseases! Countless conferences of learned scientists and physicians and other groups have enumerated proposals and recommendations to control/eliminate antibiotic resistance development with very little impact (12). It is highly likely that a better understanding of the natural roles of bioactive small molecules and the evolution of AR will provide more practical and workable solutions to current-day clinical problems (13).

There is one bright spot on the horizon. There are billions of bioactive small molecules in the environment (Einstein defined the environment as 'anything that is not him')! Most of these compounds will probably exhibit antibiotic activity at elevated concentrations 'à la Paracelsus' yet play different cellular roles at their natural concentrations. This suggests that there should be no shortage of potential antibiotics (and other drugs) to be discovered using modern sequencing, cloning, and expression methodology (14). But how can new drugs be kept active without stringent controls on their clinical use?

I wish Professor Otto Cars a productive retirement and hope that he will continue with a successful search for solutions to problems such as those described here.

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Julian E. Davies is since 1997 professor emeritus at the Department of Microbiology & Immunology, University of British Columbia, Vancouver, Canada. Dr. Davies has for over 50 years been involved in ground-breaking research in the areas of antibiotics and antibiotic resistance. Of particular interest is his recent work on antibiotics and their potential role as signalling molecules involved in intercellular communication. Dr. Davies is a member of several distinguished academies and societies, honorary doctor at six different universities and receiver of many awards, including the Hoechst-Roussel Award, American Society for Microbiology 1986, Microbial Chemistry Medal, Kitasato Institute 1991, Scheele Award, Swedish Academy of Pharmaceutical Sciences 1997, Bristol-Myers Squibb Distinguished Achievement Award in Infectious Disease Research 1999 and American Society for Microbiology Lifetime Achievement Award 2013.