

Foreword

Could a bright outlook for antibiotics usage emerge from the colossal health issue?

Ada Yonath

The Helen and Milton A. Kimmelman Center for Biomolecular Structure and Assembly, Weizmann Institute, Rehovot, Israel

One of the major problems in modern medicine is the increasing resistance of pathogenic bacteria to antibiotics. Since the production of the first pharmaceutically active antibiotics around the mid twentieth century, which revolutionized the treatment of infectious diseases and led to an unforeseen decrease in mortality and an increase in life expectancy, the clinical usage of the currently available antibiotics has suffered from a number of severe problems. These fallouts include (i) the development of resistance to one or several antibiotics (namely, multidrug resistance), caused by pathogens capability of undergoing modifications and mutations that minimize or remove the contacts between the antibiotics and their targets, (ii) the unintentional damage of the microbiome owing to the preference for using broad-spectrum antibiotics alongside the structural similarities of the antibiotics' binding sites among diverse bacteria, and (iii) the contamination of the environment caused by significant amounts of antibiotic metabolites that enter it. This crucial environmental issue results from the chemical nature of the molecular scaffolds of most currently used antibiotics, which are composed of organic metabolites that cannot be fully digested by humans or animals. These nondigestible, rather toxic compounds are also nonbiodegradable and contaminate the environment. Furthermore, following release into agricultural irrigation systems, these compounds are increasingly being consumed by humans and animals and thereby spreading antibiotic resistance.

Currently, almost all clinically useful antibiotic therapeutics are derived from natural compounds produced by microorganisms for inhibiting the growth of competing bacteria so they can defend themselves. Many of the natural antibiotics that are medically useful have undergone subsequent chemical modifications to improve their effectiveness. In addition to the natural and semisynthetic substances, very few fully synthetic drugs are in use.

Similarly, the various resistance mechanisms are basic natural processes for the survival of microorganisms, regardless of their exposure to modern clinical treatment and/or nutrition, thus suggesting that microbes have long evolved the capability to fight toxins, including antibiotics. Resistance to antibiotics is generally acquired by molecular

mechanisms, some of which, such as activation of cellular efflux pumps, are common to almost all antibiotics. In conjunction, many bacteria have developed specific molecular pathways that cause resistance. The prominent frequently used mechanisms of acquiring resistance to a single or several antibiotics (called multidrug resistance) include modifications of the antibiotic binding pockets by mutations; activation of key enzymatic processes, such as methylation; enzymatic inactivation of the antibiotic; removal of the antibiotic drug from its target by cellular components; or disruption of the interactions between cellular components that play key roles in key life processes. **Indeed, it seems that combating resistance to antibiotics is unlikely, since bacteria “want” to live and because bacteria are extremely “clever” in terms of survival!**

The increasing development of multidrug-resistant bacterial strains, together with the minimal (negligible) number of new antibiotic drugs that are presently undergoing development and/or clinical trials by the major pharmaceutical companies, is becoming a colossal health threat. Thus, the World Health Organization stated that it seems that we will soon revert back to the pre-antibiotic era, during which diseases caused by parasites or by simple (*e.g.* pneumonia, wounds) or severe infections (such as tuberculosis), were almost untreatable and resulted in frequent deaths. The World Bank estimated that up to 3.8% of the global economy will be lost by 2050 because of resistance to antibiotics and several funding agencies, such as the National Institutes of Health, European Research Council, and the Group of Eight, came up with grants for researching antibiotics resistance. On the other hand, most pharmaceutical companies have stopped developing new antibiotics, owing to the expected development of resistance and to the huge mismatch between the investment needed and the low profit anticipated.

Is there a way out from this depressing and frightening situation? Will longevity decrease to the pre-mid-twentieth century level soon?

Not necessarily. An encouraging initial outcome that may indicate partial winning was recently obtained from investigating the process of protein biosynthesis, which plays a key role in life and is performed by ribosomes in all living cells. In fact, owing to its key role in life, about half of the existing antimicrobial drugs hamper this process. The clinical use of antibiotics is facilitated by the minute differences between the prokaryotic and eukaryotic (human and animal) ribosomes that enable their selectivity toward prokaryotic ribosomes.

Analyses of high resolution molecular structures and sequences of ribosomes from nonpathogenic and multidrug resistant pathogenic bacteria showed that the clinically used antibiotics bind exclusively to ribosomal active sites, mostly located at the ribosome's core. These analyses also revealed unique structural motifs crucial to protein biosynthesis and specific to each pathogen, which are located mostly on the ribosome periphery and are not involved in the primary ribosomal activity hence, currently no pathogen contains genes for their modification.

Promising preliminary results in designing inhibitors exploiting these unique motifs indicated that these sites may provide specific novel antibiotic binding sites with the potential for minimized resistance alongside preserving the microbiome that is occasionally unintentionally damaged by the broad-spectrum antibiotics used clinically. Applying a multifaceted approach could lead to optimization of the novel antibiotics for maximum potency, minimal toxicity (namely high selectivity, obtained by the location of the potential binding sites on the ribosomal periphery, which is the maximal evolving region), and

appropriated degradability. Thus, in addition to the medical advantages, these new antibiotics should reduce the ecological burden caused by the non-degradable cores of many of the currently available antibiotics.

Although there will clearly be resistance to the next-generation of novel antibiotics, a much slower resistance development is predicted as principles for the design of further antibiotics have been identified. This approach represents a revolution in the future arsenal of antibiotics as it combines conventional and nonconventional critical aspects that may relieve, to some extent, the current problematic medical situation.