level, more than 60% of the *Enterobacteriaceae* isolates from the freshwater environment unaffected by human activity could be multidrug resistant (Lima-Bittencourt et al. 2007). Isolation of functional antibiotic resistance genes from the environments that have been isolated from any human influence (D'Costa et al. 2011; Bhullar et al. 2012) suggests that these genes have an ancient evolutionary history. These experimental observations are confirmatory to the phylogenetic analyses of antibiotic resistance genes performed by us and others (Ogawara 1993; Aminov et al. 2001, 2002; Hall and Barlow 2003; Aminov and Mackie 2007, Aminov 2009, 2013a; Koike et al. 2010) that suggested the ancient evolutionary history of these classes of genes. The question then is, what is the functional role of antibiotics and antibiotic resistance in microbial (and possibly not only microbial) ecosystems?

23.14 The Role of Antibiotics in Natural Ecosystems

The occurrence of antibiotics in the environment is usually associated with anthropogenic factors such as agricultural activities, human settlements of various size, hospitals, and pharmaceutical industry (Yang and Carlson 2003; Kim and Carlson 2006; Mackie et al. 2006; Pei et al. 2006; Baquero et al. 2008; Walraven and Laane 2009; Watkinson et al. 2009; Manzetti and Ghisi 2014; aus der Beek et al. 2016). The question, however, is: what are the natural concentrations of antibiotics generated by the antibiotic producers *in situ*? In some soils, for example, in Jordan's red soils, the *in situ* concentration of antibiotics may reach therapeutic levels, so the soil applications have been used in the past and used presently as well (as an inexpensive alternative to present-day pharmaceutical products) for treating skin infections (Falkinham et al. 2009). This type of red soil in another geographical location also seems harbor a high diversity of actinomycetes that are producing a large number of secondary metabolites, including macrolides, polyethers, diketopiperazines, and siderophores (Guo et al. 2015). Interestingly, compared with the less affected recreational environments, residential environments seem to drive the changes in the composition of soil microbiota toward the increase of antibiotic-producing microorganisms (Woappi et al. 2013). The authors hypothesize that this may indicate a coevolutionary biosynthesis of novel antibiotics driven by the increase of bioactive microbiota in residential environments.

While antibiotic resistance genes can be encountered in the environments apparently unaffected by human activities, the concentrations of antibiotics in these environments are very low, usually below the detection limit. In fact, this type of environments served as controls for measuring the impact of human activity on natural ecosystems (Yang and Carlson 2003; Kim and Carlson 2006; Pei et al. 2006). These concentrations are not lethal but may be involved into the signaling, sensing, and regulatory processes in the microbial world (Davies