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Hot Topic

Alice's living croquet theory



Lewis Carroll, the 19th century English author of fantasy novels, in his stories about the child Alice, such as 'Alice in Wonderland' and 'Through the Looking Glass', was a continuous source of theories alternative to reality. In the field of infectious diseases, Van Valen in 1973 proposed a new evolutionary law with his 'Red Queen hypothesis' [1], which has special relevance in the field of microbial resistance. 'The Red Queen hypothesis' proposes the concept that there is a constant 'arms race' between co-evolving species. In Carroll's novel, Alice runs with the Red Queen but, despite her best efforts, is unable to progress; the Red Queen says 'you have to run as fast as you can, just to stay in the same place'. Van Valen illustrated the evolutionary competition that is particularly applicable to micro-organisms and living beings [1]. Humans have developed various strategies to enable them to resist the invasion of pathogenic micro-organisms.

In the microbial field, as a means of combating vaccination *Bordetella pertussis* strains deleted the gene coding for the antigen targeted by vaccination [2], whilst *Chlamydia trachomatis* lost the plasmid harbouring sequences targeted for PCR diagnosis and thus escaped detection [3]. Although resistance mechanisms were present in micro-organisms before the advent of antibiotics, the extensive use of antibiotics by humans has resulted in the increase in bacterial resistance. 'The Red Queen hypothesis' is perfectly illustrated by our relationship with microbes. From these data, can one predict a future filled with bacteria resistant to all antibiotics? This prediction, which has been around for 40 years, has not been realised because, in complex ecosystems, the pressure from antibiotics used for human treatment plays a limited role, and resistance has a cost for the bacteria. Moreover, not all bacteria will remain resistant. For example, *Staphylococcus aureus* is now less resistant to oxacillin in Europe than it was 15 years ago [4]. Other bacteria are now resistant to imipenem; however, in our experience the total number of multiresistant bacteria has not increased. To try to illustrate this inability to predict the future here or elsewhere amongst living things, we should borrow from Lewis Carroll's game of 'living croquet'. In this game, which Alice plays with the Red Queen, the mallets used were pink flamingos and the balls were hedgehogs. Flamingos turn their heads from time to time, therefore it is impossible to predict when Alice will strike and in which direction.

As for hedgehogs, they roam wherever they want. The combination of the unpredictable behaviour of flamingos and hedgehogs makes it totally impossible to predict the outcome of a game. The

anthropologist Gregory Bateson raised this analogy [5] by saying that the future is unpredictable when living organisms are involved and predictive models always disappear [6]. I believe that this new living theory should inspire us to greater caution in predicting disasters such as we have seen develop in the crises of H1N1 influenza, avian influenza, SARS or MERS coronavirus outbreaks [7]. The disaster is a probability among many others. Finally, this unpredictability of outbreaks has been investigated in studies of human behaviour during outbreaks or epidemics; we note that human behaviour changes when faced with new epidemics as we learn from the previous ones. The future, when it includes interactions between two or more living beings, will remain completely unpredictable. Long live the 'living croquet theory'!

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