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EDITORIAL

Darwin, Medicine and the Rise of Antibiotic Resistance

This year and the next mark two Darwin anniversaries. The first public unveiling of the ideas of natural selection and biological evolution happened at a meeting of the Linnean Society in London in 1858. It was at this meeting that Charles Lyell and Joseph Hooker presented to the Society the papers of Charles Darwin and Alfred Wallace, which had been produced independently. They noted that the papers 'relate to the same subject, viz. the Laws which affect the Production of Varieties, Races and Species'. The second and more celebrated event is the publication of Darwin's, *The Origin of Species*, which first appeared in November 1859. Coincidentally, 2009 also marks the 200th anniversary of Darwin's birth. Darwin's evolutionary synthesis has grown to be one of the three pillars on which modern biology rests; Gregor Mendel's work on inheritance and the recognition by Oswald Avery, James Watson and Francis Crick of the chemical basis of heredity are, arguably, the other two. In the century that has passed since the appearance of *Origins*, Darwin has attained scientific immortality; Wallace is much less known amongst those interested in science, although he occupies an important position in the pantheon of heroes in the field of evolutionary biology (Sarkar, S., *J. Biosci*., 1998, **23**, 3; Smith, C. H., *Nature*, 2006, **443**, 33). A review of a Wallace biography published in this journal begins on a note of regret: 'In the folklore of evolution, Alfred Russel Wallace probably is destined to be the Other Man' (Nanjundiah, V., *Curr. Sci*., 2002, **83**, 1151; reprinted in *Resonance*, 2008, **13**, 277). The impending Darwin anniversaries have triggered the writing of many scholarly retrospectives on his influence in biology and our understanding of life and its origins on earth. The final lines of *The Origin of Species* convey a sense of awe that Darwin must have felt and generations of readers must undoubtedly feel: 'Thus from the war of nature, from famine and death the most exalted object which we are capable of conceiving, namely the production of the higher animals directly follows. There is grandeur in this view of life, with its several powers having been breathed by the Creator into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved'. In the century and a half since Darwin wrote these lines, the chemistry of life has been unravelled to reveal a complexity that is most intimidating. There remains a great deal of work to be done on establishing the connections between chemical and biological evolution. Complexity and diversity of form and function appear to be attributes of both molecules and organisms.

A recent essay on Darwin's enduring legacy begins emphatically: 'Perhaps no individual has had such a sweeping influence on so many facets of social and intellectual life as Charles Darwin. . . ' (Pandian, K., *Nature*, 2008, **451**, 632). The author notes eloquently that Darwin, a 'child of the Enlightenment was well aware of more ancient world views, and humbled by what the new investigations of the cosmos revealed. Humans are animals, one species of many on the planet bound by common ancestry to all other species, part of an ages-old dance of reproduction, accommodation, survival and alteration. It is for this vision, one that liberates humans from the conceit of special creation', that we honour Darwin two centuries after his birth. Since this is also examination time, I wondered how much are our children taught about Darwin. I took a clandestine look at a X standard biology textbook and found a picture of Gregor Mendel, but no mention of Darwin. There were sections on cell structure, genetics, respiration, nervous and reproductive systems, population and health, but surprisingly not even a passing mention of the origins of biological diversity. On enquiry, the owner of the textbook was dismissive: 'Only you and the BBC are interested in Darwin'. I was left wondering about the curious fact that while no physics textbook can escape mentioning Newton, Darwin whose impact on science is surely no less, does not appear to merit the same importance.

In this frame of mind, I was instantly alert when the lead speaker at a seminar, while describing the problem of antimicrobial resistance, displayed a slide with a picture of Charles Darwin, unlegended but clearly recognizable. It was indeed reassuring to see that practitioners in the area of public health and those interested in pathogenic microorganisms and antibiotics were ready to acknowledge an intellectual debt to Darwin. A little over two years ago the journal *Science* recognized 'Evolution in action' as the 'Breakthrough of the Year' (Culotta, E. and Pennisi, E., *Science*, 2005, **310**, 1878). In the commentary justifying the choice, evolution was described 'as the foundation of biology, so basic and all pervasive

that scientists sometimes take its importance for granted'. Here the authors seem to be echoing Theodosius Dobzhansky who many years ago stated simply that 'nothing in biology makes sense, except in the light of evolution'. Considering the accepted importance of evolutionary concepts in biology, the cavalier treatment meted out to Darwin in the high school textbook puzzled me. But, I quickly discovered that 'evolution' is a word that is avoided elsewhere too. An essay in the journal *PLoS Biology* (Antonovics, J. *et al*., 2007, **5**, e30), entitled 'Evolution by Any Other Name: Antibiotic Resistance and Avoidance of the E-word', points out that authors studying the rise of antibiotic resistant microbes generally eschew the word 'evolution' in their papers. They appear to prefer the words 'emerge', 'arise' and 'spread' rather than 'evolve'. The major biomedical journals, *The Lancet*, *The New England Journal of Medicine* and *The Journal of Antimicrobial Chemotherapy* overwhelmingly prefer the word 'emergence' to 'evolution', when describing the appearance of microbial strains resistant to antibiotics. In their opening paragraph Antonovics *et al*. note that: 'The increase in resistance of human pathogens to antimicrobial agents is one of the best-documented examples of evolution in action at the present time, and because it has direct life-and-death consequences, it provides the strongest rationale for teaching evolutionary biology as a rigorous science in high school biology curricula, universities and medical schools'.

The connection between microorganisms and infectious disease was established by the heroic work of Louis Pasteur and Robert Koch in the 19th century, not long after Darwin's insights. The control of infection by chemotherapy made a dramatic advance following the introduction of penicillin, which marks the beginning of the antibiotic era. Penicillin's impact was spectacular, coming as it did towards the end of the Second World War. The presentation speech in December 1945 on the occasion of the Nobel award to Fleming, Florey and Chain recognize the double-edged nature of inventive genius: 'In a time when annihilation and destruction through the inventions of man have been greater than ever before in history, the introduction of penicillin is a brilliant demonstration that human genius is just as well able to save life and combat disease'. Alexander Fleming was prescient in his Nobel lecture, an instinctive Darwinian, when he sounded a note of warning: 'Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose and poisoning the patient. There may be a danger though in underdosage. . . . The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant'. Fleming concluded with a moral: 'If you use penicillin, use enough'.

For over a decade now the spectre of microbial resistance has begun to look increasingly more threatening. Public health authorities in the advanced countries have begun to react with concern to every case of infection by resistant microbes. Common pathogens like *Staphylococcus aureus* and *Mycobacterium tuberculosis* are now emerging (evolving in a Darwinian sense under the selective pressures of antibiotic use) as drug-resistant strains. Hospital environments are a fertile ground for accelerating the evolution of resilient bacteria, with the result that hospitalization can always entail a risk of acquiring a troublesome infection. An overview of the antibiotic resistance problem published a few years ago noted that 'bacteria are wily warriors but even so, we have given them – and continue to give them – exactly what they need for their stunning success. By misusing and overusing antibiotics we have encouraged super-races of bacteria to evolve. We don't finish a course of antibiotics. Or we use them for viral and other inappropriate infections – in fact, researchers estimate that one-third to one half of all antibiotic prescriptions are unnecessary' (Nicolaou, K. C. and Boddy, C. N. C., *Sci. Am*., 2001, pp. 56–61). The microbial world is so adaptable that it is not only bacteria, but viruses, fungi and parasites which have all learnt the tricks of mutation and survival, despite attack from the enormous weaponry of the pharmaceutical industry. Faced with an environmental challenge the power of Darwinian 'natural selection' is best illustrated by the rise and spread of resistant microbes.

Since biology textbooks in school may pass lightly over Darwin and evolution, we might well ask if medical education fills this gap at a later stage. An editorial in *Science* notes that evolution's 'full potential for use in medicine has yet to be realized. Some insights have immediate clinical application, but most are fundamental, as is the case in other basic sciences. . . . Although anatomy, physiology, biochemistry and embryology are recognized as basic sciences for medicine, evolutionary biology is not (Nesse, R. M. *et al*., *Science*, 2006, **311**, 1071)'. The authors go on to add that while 'the evolution of antibiotic resistance is widely recognized' very few in the biomedical community appreciate that 'competition among bacteria has shaped chemical weapons and resistance factors in an arms race that has been going on for hundreds of millions of years. The incorrect idea that selection reliably shapes a happy coexistence of hosts and pathogens persists, despite evidence for the evolution of increased virulence when disease transmission occurs through vector such as insects, needles or clinicians' hands'. The spread of resistance to drugs is a problem that transcends the area of bacterial resilience to antibiotics. The evolution of ever more virulent strains of pathogens is a problem that will remain with us; an inevitable consequence of the evolutionary forces that shape biology. In marking the 150th anniversary of the Darwin–Wallace papers, we recognize profoundly powerful insights that have transformed the modern view of biology.

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