Secrets of life from beyond the grave

"The story of how humans and all living things came into existence is told in two widely believed versions: the Book of Genesis and Darwin's Origin of Species. It was the philosopher Karl Popper who presented us with a third story, no less important." (Niemann, 2014)

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The title of the special issue of *The Journal of Physiology* on 1 June 2014 reflected the theme of the opening of the 2013 IUPS Congress: *physiology moves back onto centre stage* (Noble *et al.* 2014). The articles focus on ways in which new and often controversial developments in evolutionary biology have opened the door to the discovery of physiological functions, which play a role in determining the variations in inherited characteristics on which natural selection may act. This is known as Lamarckian heresy, which the founders of Modern Synthesis (neo-Darwinism or Synthetic Theory of Evolution) sought to exclude. But did we really have to wait until 2014 for all that to happen?

A recent book by Niemann (2014) shows that if history had taken a slightly different turn three decades ago the answer might well have been 'no'. On 12 June 1986, the great logician and philosopher of science, Karl Popper, gave the first Medawar Lecture in honour of the Nobel laureate Peter Medawar. Popper was well known for his magisterial *Logic of Scientific Discovery* and *The Open Society and its Enemies*. Very few people know that he was also deeply involved with a group of scientists, including JBS Haldane, Joseph Needham and Conrad Waddington, with discussions dating from 1936 on the then 'new' subject of molecular biology, its implications for evolutionary theory and the formulation of the Modern Synthesis. Connoisseurs of history will not be surprised by the fact that the title of Popper's lecture was 'A new interpretation of Darwinism'. It was given in the presence of Sir Peter Medawar, Max Perutz and other key figures; it must have shocked his audience.

He proposed a radical interpretation of Darwinism, essentially rejecting the Modern Synthesis, by proposing that organisms themselves are the source of the creative processes in evolution, not random mutations in DNA. Popper suggested Darwinism was not so much wrong, but seriously incomplete. He also stated that biochemistry (and so *a fortiori* physiology) could not be reduced to physics and chemistry.

Many of the points made in the recent special issue of *J Physiol* were therefore made nearly 30 years ago. So why did I and the other 35 authors in the special issue not know this? The answer is that, despite 8 years of patient waiting, the written manuscript was not submitted to the Royal Society before Popper's death in 1994. Worse still, his documents remain archived and closed until 2029.

Hans-Joachim Niemann has, however, worked with the executors to repeal the classification and obtained a copy of Popper's lecture article, which is now published for the first time in English (Nieman, 2014). It should be required reading for anyone interested in the fundamental rethinking of evolutionary biology. Niemann is a lucid and enthusiastic expositor of Popper's lecture and of the ideas

[1] In the 1986 lecture Popper writes: 'My problem is exactly the same as that of my forerunners, such as Baldwin, who felt that the activities ... of individual organisms have played a far more important role in the history of evolution than Darwinists have as a rule admitted.' I suspect he meant 'neo-Darwinists' rather than 'Darwinists'. Darwin admitted the role of organisms and their emotions, and he accepted Lamarckian inheritance.

[2] In a 1973 text reproduced by Niemann, Popper writes, 'There is however a mechanism [he then describes transcription of RNA into DNA]. If this is taken as established it means that it is possible that enzymes exist in all cells which can re-translate RNA into DNA.' Later in the same text he writes, 'It would constitute a break with current dogma.'

[3] Barbara McClintock (1902–1992) was an American geneticist who won the 1983 Nobel Prize in Physiology or Medicine for her discovery of genetic transposition, or the ability of genes to change position on the chromosome (http://profiles.nlm.nih.gov/LL/).

that led to it. He shows that these ideas follow on naturally from Popper's conjectures and refutations approach to scientific discovery.

I think that many of the 'new' ideas can already be found in Popper's lecture. He was heard by a large and distinguished audience, so why was he ignored? One possible answer to that question is that Max Perutz was in the audience and he published a serious criticism of the lecture, arguing that Darwin was right (Perutz, 1986). Actually, Popper did not so much argue that Darwin was wrong, as that his theory was incomplete. The central problem for Perutz was the claim that biochemistry could not be reduced to physics and chemistry. He strongly opposed Popper on this point and said so in discussion after the lecture. The reason why Popper did not immediately reply by sending his article to the Royal Society for publication was that he entered into extensive correspondence with Perutz and wanted to conclude the discussion before finally submitting. By then Popper was in the ninth decade of his life. We should not be too surprised that, despite repeated requests from the Royal Society, the lecture was never published.

How did Popper arrive at his radical position? His way in was his clear understanding of a phenomenon known as the Baldwin effect[1]. Organisms can choose new niches for themselves and their descendants. Moving to a new niche can change the course of evolution even with no mutations whatsoever. That choice is a physiological characteristic of the phenotype, not a change in DNA. So how can it change the course of evolution? The answer is surprisingly simple. In a wild population, in which individual genomes are not identical to the combination of alleles in the adventurous organisms, discovering new niches will be favoured. This is an evolution of the genome by combinatorial selection, not selection of new random mutations. It is not surprising that a logician like Popper should have immediately understood the immense significance of this fact. To illustrate his hypothesis, he even invented an imaginary world, in which there was no competition for survival, no 'selfish genes'. The organisms would still evolve. Of course, the world in which such evolution could occur would have to be effectively infinite in size to accommodate all the organisms that have ever lived. However, this was just a thought experiment, which found agreement with the British developmental biologist and geneticist, Conrad Waddington. Why then do selfish gene theorists ignore it? They do so by taking an atomistic gene-centred view. As Popper saw, it is the insistence on just one atomistic approach that is the problem. Physiologists today will readily see Popper's point. It is combinations of genes, or rather combinatorial interactions between large numbers of their products, RNAs and proteins, that are important functionally. Most single genes contribute very little to complex functions, which is why the correlations between genes and complex diseases have been found to be a matter of large numbers of very small effects, still summing up to a small overall fraction of causation. The atomistic view was never going to be of much use in physiology and pathology.

The second way 'in' for Popper was his appreciation of the significance of the discovery of reverse transcription of RNA into DNA[2]. He saw that this drives a cart and horses through the Central Dogma of molecular biology and was deeply suspicious of sophisticated manoeuvrings and redefinitions to protect the dogma from falsification. In his conjectures and refutations view of science, it is better to acknowledge when a strong version of a theory has been refuted. The strong, original version of the Central Dogma was refuted. But he went further than this. He saw that this could be one of the routes through which Lamarckian processes and wholesale reorganisation of genomes could occur. Again, the philosopher in him wanted to see this recognised, not hidden behind a web of clever re-interpretations. He has been completely vindicated. Wholesale genome reorganisation, what Shapiro, in *Evolution: A View from the 21st Century* (Shapiro, 2011), calls natural genetic engineering, has occurred many times in evolutionary history. Like Shapiro, Popper appreciated the significance of the work of Barbara McClintock[3].

With two such fundamental breaks with the standard theory under his belt, what – if anything – was missing in his 1986 lecture?

Actually, quite a lot. As John Maynard Smith also recognised in *Evolutionary Genetics* (1998), where he wrote 'it [Lamarckism] is not so obviously false as is sometimes made out'. The mechanisms known to twentieth century biologists were very few and could be regarded as the rare exceptions that any theory might cope with, by claiming that such processes were not of any great consequence. Popper's strength was his logical foresight. He could, philosophically speaking, smell a consequence from miles away. He took his own refutation theory very seriously indeed, but not in a pernickety way. Reverse transcription, however one looks at it, was a fissure that could grow into a chasm, as it has. The Baldwin effect should be rampant. All organisms, even bacteria, have what he called 'real activity', meaning goal-directed behaviour that distinguishes them from purely physical and chemical processes in nature. This was his fundamental disagreement with Perutz. No wonder he wished to refine his lecture before it was published. Think of a 90-year-old man, each year flashing by, focusing on what he saw as a discovery of great significance. He knew also that the great majority of the scientific establishment was against him. Lamarck had been rubbished, Waddington side-lined, McClintock ignored until the surprise Nobel Prize rescued her great contribution. I believe he was determined to make his lecture unanswerable.

Had he been alive today, just 20 years after his death at the age of 92, he would surely have been delighted with the discoveries that have shown just how wide that fissure has grown. His views are now seen as not simply gene-centred, but that all levels can be the object of natural selection (Okasha, 2006). The rivers of experimental evidence from epigenetics, natural genetic engineering, niche theory, symbiogenesis, and much more have totally changed the landscape of biological theory. The mighty scientific establishment that Popper faced is now a much smaller conservative group of those who still wish to defend the standard story against all comers. My belief is that they can do so only by rearranging goalposts, by redefining the boundaries of what the Modern Synthesis can contain.

Remember too that this is the Popper who wrote *The Open Society and its Enemies*, opposing closed society dogmatism; the Popper who narrowly escaped the holocaust (he included racism as one of the disastrous social consequences of the language of neo-Darwinism, which he realised was largely colourful metaphorical veneer); the Popper who advised us not to hide clear refutations of scientific theory in over-sophisticated manipulations of the goalposts through endless redefinitions. Dogmatism in all its forms, and most particularly in science, was his enemy.

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