President's Lecture

Physiology is rocking the foundations of evolutionary biology

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New Findings

- **What is the topic of this review?**
  Have recent experimental findings in evolutionary biology concerning the transmission of inheritance opened the way to a reintegration of physiology with evolutionary biology?
- **What advances does it highlight?**
  The answer is yes, and that this requires a new synthesis between evolutionary theory and experimental physiology.

The 'Modern Synthesis' (Neo-Darwinism) is a mid-20th century gene-centric view of evolution, based on random mutations accumulating to produce gradual change through natural selection. Any role of physiological function in influencing genetic inheritance was excluded. The organism became a mere carrier of the real objects of selection, its genes. We now know that genetic change is far from random and often not gradual. Molecular genetics and genome sequencing have deconstructed this unnecessarily restrictive view of evolution in a way that reintroduces physiological function and interactions with the environment as factors influencing the speed and nature of inherited change. Acquired characteristics can be inherited, and in a few but growing number of cases that inheritance has now been shown to be robust for many generations. The 21st century can look forward to a new synthesis that will reintegrate physiology with evolutionary biology.

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Introduction

As 2012 came to a close, an article appeared in the *Proceedings of the National Academy of Sciences of the United States of America* with a title that would have been inconceivable in such a prestigious journal only 5–10 years ago. 'Rocking the foundations of molecular genetics' (Mattick, 2012) is a commentary on a ground-breaking original experimental article (Nelson *et al.* 2012) in the same issue of the journal showing epigenetic maternal inheritance over several generations. My title echoes that of Mattick, but it also goes further. It is not only the standard 20th century views of molecular genetics that are in question. Evolutionary theory itself is already in a state of flux (Jablonka & Lamb, 2005; Noble, 2006, 2011; Beurton *et al.* 2008; Pigliucci & Müller, 2010; Gissis & Jablonka, 2011; Shapiro, 2011). In this article, I will show that all the central assumptions of the Modern Synthesis (often also called Neo-Darwinism) have been disproved. Moreover, they have been disproved in ways that raise the tantalizing prospect of a totally new synthesis; one that would allow a reintegration of physiological science with evolutionary biology. It is hard to think of a more fundamental change for physiology and for the conceptual

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foundations of biology in general (Melham *et al.* 2013). The Modern Synthesis (Fisher, 1930; Huxley, 1942; Mayr, 1982) attributed genetic change solely to chance events, about which physiology could say very little. The germ line was thought to be isolated from any influence by the rest of the organism and its response to the environment, an idea that was encapsulated in the Weismann barrier (Weismann, 1893). Note that this was animal specific and did not apply to other life forms. But if acquired changes can be inherited through many generations, then physiology becomes relevant again, because it is precisely the study of function and functional changes. These are what determine epigenetic processes.

I start with some definitions. I will use the term 'Modern Synthesis' rather than 'Neo-Darwinism'. Darwin was far from being a Neo-Darwinist (Dover, 2000; Midgley, 2010), so I think it would be better to drop his name for that idea. As Mayr (1964) points out, there are as many as 12 references to the inheritance of acquired characteristics in *The Origin of Species* (Darwin, 1859) and in the first edition he explicitly states 'I am convinced that natural selection has been the main, but not the exclusive means of modification', a statement he reiterated with increased force in the 1872, 6th edition. In some respects, my article returns to a more nuanced, less dogmatic view of evolutionary theory (see also Müller, 2007; Mesoudi *et al.* 2013), which is much more in keeping with the spirit of Darwin's own ideas than is the Neo-Darwinist view.

Summary of the Modern Synthesis

The central assumptions of the Modern Synthesis that are relevant to this article are fourfold (see also the summary by Koonin, 2011).

First, genetic change is random. Interpreted in modern terms as referring to DNA, the changes can be thought of as restricted to single step changes in one (or a very few) bases brought about, for instance, by copying errors, radiation or any other random event. The concept of a purely random event is not easy to define. The physicochemical nature of biological molecules will, in any case, ensure that some changes are more likely to happen than others. Randomness cannot therefore be defined independently of asking 'random with respect to what'? I will use the definition that the changes are assumed to be random with respect to physiological function and could not therefore be influenced by such function or by functional changes in response to the environment. This is the assumption that excludes the phenotype from in any way influencing or guiding genetic change.

Second, genetic change is gradual. Since random events are best thought of as arising from microscopic stochasticity, it will generally be the case that many such events would have to accumulate to generate a major change in genome and phenotype. Of course, there are point mutations that can have a dramatic effect on the phenotype, but these are rare. The prediction would be that the evolution of gene sequences and the amino acid sequences of the proteins formed should not occur in ways that would require large domains to move around within and between genomes.

Third, following genetic change, natural selection leads to particular gene variants (alleles) increasing in frequency within the population. Those variants are said to confer an advantage in terms of fitness on the individuals concerned, which therefore increasingly dominate the population. By this process and other mechanisms, including genetic drift and geographic isolation, new species can arise.

Fourth, the inheritance of acquired characteristics is impossible. This is the main thrust of the synthesis and it is the means by which Darwin's ideas were represented as distinct from those of Lamarck (1994, originally published 1809). This assumption also excludes any notion of what Lamarck called 'le pouvoir de la vie', a life force that could in some way be seen as directing evolution through increasing complexity or through adaptation. Lamarckism was excluded not only by the experiments of Weismann (1893) but also by the central dogma of molecular biology (Crick, 1970). Both claim that the genetic material is isolated from the organism and its environment; 'sealed off from the outside world', to use *The Selfish Gene* popularization of the idea (Dawkins, 1976, 2006).

All these assumptions have been disproved in various ways and to varying degrees, and it is also important to note that a substantial proportion of the experimental work that has revealed these breaks has come from within molecular biology itself. Molecular biology can now be seen to have systematically deconstructed its own dogmas (Shapiro, 2009, 2011).

Are mutations random?

'It is difficult (if not impossible) to find a genome change operator that is truly random in its action within the DNA of the cell where it works. All careful studies of mutagenesis find statistically significant non-random patterns of change, and genome sequence studies confirm distinct biases in location of different mobile genetic elements' (Shapiro, 2011, p. 82). Shapiro gives large numbers of references on the non-random nature of mutations. As already noted, though, the key question is not so much whether changes are truly random (there can be no such thing independent of context) but whether they are chance events from the viewpoint of function. The evidence is that both the speed and the location of genome change can be influenced functionally. Changes in the speed of change are well known already from the way in which genome change occurs in immunological processes. The germ line has only a finite amount of DNA. In order to react to many different antigens, lymphocytes 'evolve' quickly

to generate extensive antigen-binding variability. There can be as many as 10^{12} different antibody specificities in the mammalian immune system, and the detailed mechanisms for achieving this have been known for many years. The mechanism is directed, because the binding of the antigen to the antibody itself activates the proliferation process. Antigen activation of B-cell proliferation acts as a selective force. The targeting of the genomic changes, which maintains the functional structure of the antibody while diversifying antigen recognition, occurs by protein–DNA binding specificity (VDJ joining; Shapiro, 2011, p. 173), coupling to transcription signals (somatic hypermutation) and lymphokine-directed transcription of heavy chain switch regions (class switch recombination; Shapiro, 2011, pp. 66–69).

Similar targeted genomic changes occur outside the context of the immune system. The reader is referred to table II.7 (Shapiro, 2011, pp. 70–74; http://shapiro.bsd.uchicago.edu/TableII.7.shtml) for many examples of the stimuli that have been shown to activate this kind of 'natural' genetic engineering, while table II.11 from the same book (pp. 84–86; http://shapiro.bsd.uchicago.edu/TableII.11.shtml) documents the regions of the genomes targeted. Thirty-two examples are given. One example will suffice to illustrate this. P element homing in fruit flies involves DNA transposons that insert into the genome in a functionally significant way, according to the added DNA. There is up to 50% greater insertion into regions of the genome that are related functionally to DNA segments included within the P element. Thus, 'Insertion of a binding sequence for the transcriptional regulator Engrailed targets a large fraction of insertions to chromosomal regions where Engrailed is known to function.' (Shapiro, 2011, p. 83). A possible explanation is that the donor element and the target site may be brought close together in the nucleus, i.e. organization of the genome is important. This kind of information is also therefore 'genetic'. We should not limit the concept of a 'gene' and the description 'genetic' to protein-template regions of the genome, particularly as we now know that 80% of the non-protein regions are transcribed, although it is uncertain how much is functional (http://www.genome.gov/10005107; http://genome.ucsc.edu/ENCODE/). It was clearly premature to label this DNA as 'junk'. Structural organization also represents information that is transmitted down the generations. DNA is not merely a one-dimensional sequence. It is a highly complex physiological system that is regulated by the cells, tissues and organs of the body. This will become even clearer in the next section.

Is genetic change gradual?

It was the Nobel Prize-winner Barbara McClintock who introduced the idea that the genome is 'an organ of the cell' (McClintock, 1984). She won her prize for physiology or medicine in 1983 over 40 years after she had made the ground-breaking discovery of chromosome transposition (now called mobile genetic elements). She worked on maize, and early reactions to her work were so sceptical that she stopped publishing her research in 1953 (Keller, 1983). The consequences for evolutionary theory were also ignored, because the phenomenon was not thought to occur in animals. We now know that animal genomes are full of transposons. About 3500 of the estimated 26,000 human protein-template regions contain exons originating from mobile elements (Shapiro, 2011, p. 109). This contrasts with a much lower number, 1200, in mice, even though the number of protein template regions is similar in both genomes. This suggests that transposons may have played a major role in primate and human evolution. Over two-thirds of the human genome is derived from mobile elements (de Koning *et al.* 2011), and there have been well over 3 million transposition events in its evolution.

McClintock could not have anticipated the evidence that would later emerge from whole-genome sequencing studies in various species, but it fully vindicates the general and widespread significance of her discovery. The *Nature* 2001 report (International Human Genome Mapping Consortium, 2001) compared protein-template regions for several classes of proteins from yeast, nematode worms, *Drosophila*, mice and humans. In the case of transcription factors (Figure 45 of the *Nature* report) and chromatin-binding proteins (Figure 42 of the *Nature* report) the evidence shows that whole domains up to hundreds of amino acids in length have been amplified and shifted around among different genetic loci in the genome. Of course, the sequencings were done on the contemporary species. We do not therefore know precisely when in the evolutionary process the transpositions may have occurred. However, a number of the domains and combinations are restricted to certain lineages. And of course, gradual changes also occurred within the sequences. The experimental evidence on genome sequencing shows multiple ways in which evolutionary change has occurred. Note also that domain shuffling and the polyphyletic origins of genomes were established facts well before the full sequencing of genomes (Gordon, 1999; Shapiro, 2011).

The mechanisms of transposable elements illustrate one of the important breaks with the central dogma of molecular biology. Retrotransposons are DNA sequences that are first copied as RNA sequences, which are then inserted back into a different part of the genome using reverse transcriptase. DNA transposons may use a cut-and-paste mechanism that does not require an RNA intermediate. As Beurton *et al.* (2008) comment, 'it seems that a cell's enzymes are capable of actively manipulating DNA to do this or that. A genome consists largely of

semi-stable genetic elements that may be rearranged or even moved around in the genome thus modifying the information content of DNA.' The central dogma of the 1950s, as a general principle of biology, has therefore been progressively undermined until it has become useless as support for the Modern Synthesis (Werner, 2005; Mattick, 2007; Shapiro, 2009) or indeed as an accurate description of what happens in cells. As Mattick (2012) says, 'the belief that the soma and germ line do not communicate is patently incorrect.'

An important point to note is the functionally significant way in which this communication can occur. In bacteria, starvation can increase the targeted transposon-mediated reorganizations by five orders of magnitude, i.e. by a factor of over 100,000 (Shapiro, 2011, p. 74).

Mobile transposable elements that have been involved in evolution come in more forms than only retrotransposons and DNA transposons. They include the movement and/or fusion of whole genomes between species. Symbiogenesis is the mechanism by which eukaryotes developed from prokaryotes, with mitochondria and chloroplasts being the most well-known examples, having originated as bacteria that invaded (or were engulfed by) the 'parent' cell (Margulis, 1981; Brown & Doolittle, 1997; Margulis & Sagan, 2003). During evolution, some of the acquired DNA transferred to the nucleus. Horizontal transfer of DNA is ubiquitous in the prokaryote world, but also far from absent amongst eukaryotes (Shapiro, 2011). Other forms of mobile DNA include plasmids, viruses and group II introns, which are all prokaryotic elements. To these we can add group I introns and inteins (Raghavan & Minnick, 2009), multiple classes of transposons (Curcio & Derbyshire, 2003), multiple classes of retrotransposons (Volff & Brosius, 2007) and various forms of genomic DNA derived from reverse transcription (Baertsch *et al.* 2008). One of the major developments of Darwin's concept of a 'tree of life' is that the analogy should be more that of a 'network of life' (Doolittle, 1999; Woese & Goldenfeld, 2009). As with other breaks from the Modern Synthesis, that synthesis emerges as only part of the evolutionary story.

The inheritance of acquired characteristics

In 1998, the great contributor to the development of the Modern Synthesis, John Maynard Smith, made a very significant and even prophetic admission when he wrote 'it [Lamarckism] is not so obviously false as is sometimes made out' (Maynard Smith, 1998), a statement that is all the more important from being made by someone working within the Modern Synthesis framework. The time was long overdue for such an acknowledgement. Nearly 50 years before, Waddington had written 'Lamarck is the only major figure in the history of biology whose name has become to all extents and purposes, a term of abuse. Most scientists' contributions are fated to be outgrown, but very few authors have written works which, two centuries later, are still rejected with an indignation so intense that the skeptic may suspect something akin to an uneasy conscience. In point of fact, Lamarck has, I think, been somewhat unfairly judged.' (Waddington, 1954).

So why, given his extraordinary (but completely correct) admission, did Maynard Smith not revise his view of the mechanisms of evolution? The reason he gave in 1999 was that 'it is hard to conceive of a mechanism whereby it could occur; this is a problem' (Maynard Smith, 1999). At that time, the examples of the inheritance of acquired characteristics could be counted on the fingers of one hand. They included Waddington's work on genetic assimilation (Waddington, 1959) and Sonneborn's work on the inheritance of non-genetic changes in *Paramecium* membrane–cilia orientation (Sonneborn, 1970). The flow of papers during the last 5 years showing non-Mendelian inheritance is, however, now becoming a flood of evidence. Sadly, Maynard Smith is no longer with us to comment on this important development. Let us try, though, to look at the evidence through his eyes, because although he saw a problem, he also added that it was 'not I think insuperable' (Maynard Smith, 1999).

The examples he had in 1998 were not only few and relatively old, they were also fairly easy to assimilate into the Modern Synthesis or ignore as special cases. Waddington's work could be dismissed, because it was not certain that no mutations were involved, although this would be very unlikely on the time scale of his experiments. Any variation that was necessary was almost certainly already present in the gene pool. His work on fruit flies essentially consisted in selecting for certain combinations of existing DNA sequences in the population gene pool by selective breeding from flies with unusual phenotypes induced by treating embryos with heat or ether (Bard, 2008). He was the first to call this mechanism 'epigenetics' (i.e. over and above genetics), but he did not mean the specific form that we now understand by that term, i.e. the marking of chromatin to change the patterns of expression.

The Modern Synthesists should not have dismissed Waddington's experiments, for example, as simply 'a special case of the evolution of phenotypic plasticity' (Arthur, 2010). Of course, the Modern Synthesis can account for the inheritance of the potential for plasticity, but what it cannot allow is the inheritance of a specific acquired form of that plasticity. Waddington's experiments demonstrate precisely inheritance of specific forms of acquired characteristics, as he claimed himself in the title of his paper (Waddington, 1942). After all, the pattern of the genome is as much inherited as its individual components, and those patterns can be determined by the environment.

But I can see why Modern Synthesists thought the way they did. Giving up such a central tenet of the Synthesis

would have been difficult anyway, not least because of the extraordinary distinction of the 20th century biologists who developed it. We are talking, after all, of Julian Huxley, Sewell Wright, J. B. S. Haldane, R. A. Fisher, George Price and Bill Hamilton, to name but a few. Waddington's genetic assimilation process was discounted as a break with the Modern Synthesis precisely because it did not involve gradual accumulations of mutations and was not viewed as a challenge to that process. But that is to put the question the wrong way round. It is precisely whether gradual mutations form the only mechanism that is in question. Waddington's work was a proven alternative additional mechanism. Even 70 years ago, the Modern Synthesis could have been admitted to be incomplete.

In a different way, Sonneborn's work was brushed aside as being on a unicellular organism, with no separate germ line. The Modern Synthesis has always had a strongly zoological basis, tending to ignore prokaryotes, unicellular organisms and plants, even though these cover more than 80% of the whole duration of the evolutionary process long before 'zoology' could even have a meaning in evolutionary history.

But the evidence for the inheritance of acquired characteristics has now moved right into the zoological domain. All the remaining examples I shall quote here are on multicellular organisms, including mammals, and they refer to pioneering work done in the last 7 years.

Anway *et al.* (2006*a*,*b*) demonstrated that an endocrine disruptor, vinclozolin (an anti-androgenic compound), can induce transgenerational disease states or abnormalities that are inherited for at least four generations in rats. The transmission is via epigenetic modifications carried by the male germ line and may involve either marking of the genome or transmission of RNAs. More recent work from the same laboratory has shown that the third generation granulosa cells carry a transgenerational effect on the transcriptome and epigenome through differential DNA methylation (Nilsson *et al.* 2012). The sperm nucleus contains much more than the genome (Johnson *et al.* 2011).

An alternative approach to determining how the organism as a whole may influence the genome and whether such influences can be transmitted transgenerationally is to study cross-species clones, e.g. by inserting the nucleus of one species into the fertilized but enucleated egg cell of another species. Following the gene-centric view of the Modern Synthesis, the result should be an organism determined by the species from which the genome was taken. In the great majority of cases, this does not happen. Incompatibility between the egg cytoplasm and the transferred nuclear genome usually results in development freezing or completely failing at an early stage. That fact already tells us how important the egg cell expression patterns are. The genome does not succeed in completely dictating development regardless of the cytoplasmic state. Moreover, in the only case where this process has resulted in a full adult, the results also do not support the prediction. Sun *et al.* (2005) performed this experiment using the nucleus of a carp inserted into the fertilized but enucleated egg cell of a goldfish. The adult has some of the characteristics of the goldfish. In particular, the number of vertebrae is closer to that of the goldfish than to that of a carp. This result echoes a much earlier experiment of McLaren and Michie, who showed an influence of the maternal uterine environment on the number of tail vertebrae in transplanted mice embryos (McLaren & Michie, 1958). Many maternal effects have subsequently been observed, and non-genomic transmission of disease risk has been firmly established (Gluckman & Hanson, 2004; Gluckman *et al.* 2007). A study done in Scandinavia clearly shows the transgenerational effect of food availability to human grandparents influencing the longevity of grandchildren (Pembrey *et al.* 2006; Kaati *et al.* 2007).

Epigenetic effects can even be transmitted independently of the germ line. Weaver and co-workers showed this phenomenon in rat colonies, where stroking and licking behaviour by adults towards their young results in epigenetic marking of the relevant genes in the hippocampus that predispose the young to showing the same behaviour when they become adults (Weaver *et al.* 2004; Weaver, 2009). (This field is growing so rapidly that there is not space in this review to cover it. A more extensive bibliography can be found at http://shapiro.bsd.uchicago.edu/Transgenerational_Epigenetic_Effects.html.)

Molecular mechanisms

The results I have described so far establish the existence of transgenerational non-Mendelian inheritance. This section describes recent studies that demonstrate the molecular biological mechanisms and that the transmission can be robust for many generations.

Rechavi *et al.* (2011) worked on *Caenorhabditis elegans* and the non-Mendelian inheritance of the worm's response to viral infection. This is achieved by the infection inducing the formation of an RNA silencer. They crossed worms with this response with worms that do not have it and followed the generations until they obtained worms that did not have the DNA required to produce the silencing RNA but which nevertheless had inherited the acquired resistance. The mechanism is that transmission of RNA occurs through the germ line and is then amplified by using RNA polymerase. The inheritance of the acquired characteristic is robust for over 100 generations.

The work of Nelson *et al.* (2012) that stimulated Mattick's article in *Proceedings of the National Academy of Sciences of the United States of America*, with which I began this review, is from the laboratory of Joe Nadeau

at the Institute of Systems Biology in Seattle. Their article begins by noting that many environmental agents and genetic variants can induce heritable epigenetic changes that affect phenotypic variation and disease risk in many species. Moreover, these effects persist for many generations and are as strong as conventional genetic inheritance (Richards, 2006; Jirtle & Skinner, 2007; Youngson & Whitelaw, 2008; Cuzin & Rassoulzadegan, 2010; Nelson & Nadeau, 2010; Guerrero-Bosagna & Skinner, 2012). The challenge now is to understand their molecular basis. The experiments of Nelson and co-workers were on the Deadend1 (*Dnd1*) gene, which enhances susceptibility to testicular germ cell tumours in mice, in part by interacting epigenetically with other testicular germ cell tumour modifier genes in previous generations. They showed that genetically engineered deficiency of Apobec1 modifies susceptibility, either alone or in combination with *Dnd1*, and either in a conventional or a transgenerational manner. The heritable epigenetic changes persisted for multiple generations and were fully reversed after consecutive crosses through the alternative germ lineage. The Apobec family is an unusual protein family of cytidine deaminases that can insert mutations in DNA and RNA (Conticello, 2008).

A further example of a molecular mechanism is that of paramutation, which consists in the interaction between two alleles at a single locus. This can induce permanent epigenetic changes in organisms from maize to mice (Chandler, 2007, 2010; Cuzin *et al.* 2008; Sidorenko *et al.* 2009; Arteaga-Vazquez *et al.* 2010; Erhard & Hollick, 2011).

These examples of robust inheritance of acquired characteristics reveal a wide array of mechanisms by which such inheritance can be achieved. Nature seems to work through the cracks, as it were, of the gene-centric view. Those cracks have now been discovered to be great fissures, through which functionally significant inherited changes occur. Such mechanisms could not have been foreseen at the time when the Modern Synthesis was formulated, or even a decade ago. To Maynard Smith's (1999) comment ('it is hard to conceive of a mechanism whereby it could occur'), the reply must be that some of those mechanisms have now been found and they are robust.

In addition to establishing the molecular mechanisms, these experiments help to explain an otherwise puzzling finding. Conventional genetic inheritance often accounts for $<10\%$ of observed inherited risk. Similar conclusions have been drawn from genome-wide association studies and from studies on identical twins (Roberts *et al.* 2012). This observation, in itself, creates problems for the gene-centric view, and it is now clear that non-Mendelian inheritance may provide a large part of the explanation (Slatkin, 2009).

What went wrong in the mid-20th century that led us astray for so long? The answer is that all the way from the Weismann barrier experiments in 1893 (which were very crude experiments indeed) through to the formulation of the central dogma of molecular biology in 1970, too much was claimed for the relevant experimental results, and it was claimed too dogmatically. Demonstrating, as Weismann did, that cutting the tails off many generations of mice does not result in tail-less mice shows, indeed, that this particular induced characteristic is not inherited, but it obviously could not exclude other mechanisms. The mechanisms found recently are far more subtle. Likewise, the demonstration that protein sequences do not form a template for DNA sequences should never have been interpreted to mean that information cannot pass from the organism to its genome. Barbara McClintock deservedly gets the last laugh; the genome is indeed an 'organ of the cell'.

Table 1. Comparison between the Modern Synthesis and the proposed Integrative Synthesis

Before: Modern Synthesis	Now: towards an Integrative Synthesis
Gene-centred view of natural selection	Selection is multilevel
Impossibility of inheritance of acquired characteristics	Acquired characters can be inherited
Distinction between replicator (genes) and vehicle (phenotype)	The genome is an 'organ of the cell', not its dictator. Control is distributed
The central dogma of molecular biology	Genomes are not isolated from organism and environment

Towards a new synthesis between physiology and evolutionary biology?

This review has been written for a primarily physiological audience, but its implications are profound for biological science in general. It shows that, through recent discoveries on the inheritance of acquired characteristics, the analysis of physiological function can be important to the mechanisms of evolutionary change. The full extent of this feedback from function to inheritance remains to be assessed, but it cannot be doubted that it runs counter to the spirit of the Modern Synthesis. The challenge now is how to construct a new Synthesis to take account of this development. In Table 1, I call this the Integrative Synthesis. I believe that in the future, the Modern Synthesis and the elegant mathematics that it gave rise to, for example in the various forms and developments of the Price equation, will be seen as only one of the processes involved, a special case in certain circumstances, just as Newtonian mechanics remains as a special case in the theory of relativity. The mathematics of evolutionary theory is developing to take additional processes into account (e.g. Bonduriansky & Day, 2009; Slatkin, 2009;

Nowak *et al.* 2010). In many cases, that is already implicit, for example where the 'gene' is really an inherited phenotype regardless of the mechanism of inheritance. Where the mechanism matters, for instance in allowing blending rather than discrete inheritance, the mathematics will be interestingly different. There are also important implications for the rate of evolutionary change, because an adaptive characteristic may be acquired by many individuals simultaneously, thus avoiding the slow process of a chance mutation in an individual spreading through the population.

A central feature of the Integrative Synthesis is a radical revision of the concept of causality in biology. *A priori* there is no privileged level of causation. This is the principle that I have called the theory of biological relativity (Noble, 2008, 2012). As Werner puts it, 'all levels have an equal contributing value' (Werner, 2003). Control is therefore distributed, some of which is inherited independently of DNA sequences. The revision of the concept will also recognize the different forms of causality. DNA sequences are best viewed as passive causes, because they are used only when the relevant sequences are activated. DNA on its own does nothing. The active causes lie within the control networks of the cells, tissues and organs of the body.

Conclusions

We are privileged to live at a time of a major change in the conceptual foundations of biology. That change is set to bring the physiological study of function right back into centre stage. It is worth quoting the relevant paragraph from Mattick's commentary on the work of Nelson *et al.* (2012):

> The available evidence not only suggests an intimate interplay between genetic and epigenetic inheritance, but also that this interplay may involve communication between the soma and the germline. This idea contravenes the so-called Weismann barrier, sometimes referred to as Biology's Second Law, which is based on flimsy evidence and a desire to distance Darwinian evolution from Lamarckian inheritance at the time of the Modern Evolutionary Synthesis. However, the belief that the soma and germline do not communicate is patently incorrect.

The only parts of this statement that I would change are, first, to remind readers, as I noted earlier in this article, that Darwin himself did not exclude the inheritance of acquired characteristics and, second, to remind us that Lamarck himself did not invent 'Lamarckism' (Noble, 2010). As we move on beyond the unnecessary restrictions of the Modern Synthesis we move back towards a more genuinely 'Darwinian' viewpoint and we also move towards a long-overdue rehabilitation of Lamarck. Of course, neither Darwinism nor Lamarckism remains unchanged. Neither could have anticipated the work of the 21st century. But we can now see the Modern Synthesis as too restrictive and that it dominated biological science for far too long. Perhaps the elegant mathematics and the extraordinary reputation of the scientists involved blinded us to what now seems obvious; the organism should never have been relegated to the role of mere carrier of its genes.

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Additional information

Competing interests

None declared.

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