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Commentary

Why Physiology is now the key to understanding Evolution

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ABSTRACT
The standard Neo-Darwinist theory of evolution assumes that genetic change is random with respect to function. On this view physiology is relevant only as a way of explaining why some variations are selected over less successful ones. We now know there are other ways in which organisms can adapt functionally to the environment and pass this information on to their progeny. Evolution therefore can occur via more mechanisms than assumed by Neo-Darwinism. As the study of function, physiology has now become one of the keys to understanding evolution. The implications for healthcare are also highlighted.

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INTRODUCTION

In this article I will explain why one of the keys to further progress in understanding the evolution of life on earth now lies with research in the physiological sciences, and what the implications are for healthcare.
I will leave aside non-scientific explanations of the development of life on earth, such as creationism and the equivalent forms of intelligent design theories, which are metaphysical ideas, often proposed in a religious context, and that are most probably beyond the realm of scientific discovery. Many religions also interpret them as metaphors or myths rather than competing as scientific theories.
We are then left with two kinds of competing scientific explanations.

Blind chance and natural selection

The first is the idea that evolutionary variation is entirely the result of blind chance, i.e. changes in the genetic material arising from copying errors, radiation and other accidental (sometimes also called purely random) change. This is the theory that was developed during the first half of the 20th century to become what is usually called either the Modern Synthesis (Huxley, 1942), or Neo-Darwinism. The term ôNeo-Darwinismô was first coined by a physiologist, George Romanes (Romanes, 1883), who not only introduced the term, but did so to contrast the idea of Neo-Darwinism with Darwinôs own ideas. Interestingly Darwin was not a Neo-Darwinist.
Charles Darwin is justly praised for having formulated the theory of natural selection which he published in his famous book *The Origin of Species* in 1859 (Darwin, 1859). This theory could explain why some organisms would be selected to survive, reproduce and pass on their characteristics to their progeny. Alfred Russel Wallace also formulated the same idea at about the same time. But no-one at that time knew what might be the origin of the variation on which they supposed that natural selection acts, nor what was responsible for inheritance.
It was Wallace and August Weismann who were the originators of the late nineteenth century idea that led to Neo-Darwinism. The reason Darwin was not a Neo-Darwinist is because he had included the idea that acquired characteristics could be inherited, which had been championed by Lamarck 50 years earlier. Weismann argued that this was impossible since there was no way in which changes in the somatic cells could be transmitted to the germ cells. He assumed therefore that variation occurred in a random way. Neo-Darwinism was the synthesis of this idea with natural selection, to which Mendelian genetics was added

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when Mendelôs nineteenth century work was rediscovered at the beginning of the twentieth century.

This theory which, as the Modern Synthesis, became the dominant theory of evolution, essentially excludes physiology from any role other than to provide an explanation for why some variants function better than others and could therefore be more likely to be selected. This restricts physiology to a retrospective search for reasons why some variants work better than others. It tells us nothing about how those variants arose.

Earlier discoveries of Lamarckian mechanisms

The alternative to Neo-Darwinism says that physiology, as the study of function, *is* relevant to the origins of variation. This would require that functional adaption to environmental pressures in some way directs variation so that the changes are not entirely random. This kind of theory would require that at least *some* adaptations to environmental pressure can be inherited. This is the inheritance of acquired characteristics. Theories of this kind are usually called Lamarckian since this is the cause of variation favoured by Jean-Baptiste Lamarck in his great work *Zoologie Philosophique*, published in 1809 (Lamarck, 1994).

In Lamarckôs time this would have been the most likely scientific explanation, so much so that even fifty years later Darwin also assumed that it must occur: around 12 references to the inheritance of acquired characteristics occur in *The Origin of Species (Darwin, 1859)*. Darwin did not see this as incompatible with his theory of natural selection. After all, selection can work on any form of variation, whether random or directed.

Lamarckism however became discredited, as Neo-Darwinism came to be established as the orthodox view around the middle of the twentieth century. For many years any exceptions to this orthodoxy were explained away with Neo-Darwinist explanations, or simply dismissed as unimportant. They became the exceptions that - to use a common phrase - óprove the ruleô.

An example of a discovery that was explained away like this is the work of the brilliant developmental biologist, Conrad Waddington. In the 1940s he treated fruit fly embryos either with gentle heat shock or with ether. The result was to canalise development towards a different phenotype. He then selected those adults displaying the new phenotype to breed from them. In each generation the proportion of these increased. After around 14 generations he tested whether the new phenotype could be inherited without the treatment of the embryos. The experiment worked. He described this process as óassimilationô of the acquired characteristic, since the new phenotype could now be transmitted by standard genetic mechanisms. This was clearly an acquired characteristic that became inherited. By the usual definition of Lamarckism, it was an example showing how this could occur.

Waddingtonôs work was dismissed, perhaps because it was not certain that no mutations were involved, although this would have been very unlikely considering the time scale of his experiments. Any variation that was necessary was almost certainly already present in the gene pool. His work essentially consisted in selecting for certain combinations of existing DNA sequences in the population gene pool but not in any particular individuals. The assimilation process brought the relevant combinations together.

He was the first to call this mechanism ópigeneticsô (i.e. over and above genetics), but he did not mean the specific form of epigenetics that we now understand by that term, i.e. the marking of chromatin to change the patterns of expression. But he should be honoured for having been the first to demonstrate an inherited epigenetic effect.

Waddingtonôs experiments should not therefore have been dismissed, for example, as simply óa special case of the evolution of phenotypic plasticityô. The standard theory of evolution may 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 in response to the environment, because that is precisely what is meant by the modern use of the term Lamarckism.

The second example of earlier work is that of Sonneborn on the unicellular organism Paramecium (Sonneborn, 1970). His work demonstrated the inheritance of cellular change independent of DNA by changing the structure of the cell. The experiment consisted in cutting the apex of the cell and then reinserting it the wrong way round so that the cilia that enable the organism to move point the wrong way. This change was inherited across two further generations.

This example illustrates an important point about the Neo-Darwinian theory of evolution. Since it is based on the Weismann Barrier, it doesnôt apply to most organisms, since no unicellular organisms have a separate germ-line. The development of multicellular organisms with a separate germ-line occurred late in the evolution of life on earth. Moreover, many multicellular organisms with separate germ-lines, such as plants, can also reproduce asexually. The evolution of sexual reproduction is also an outstanding problem in evolutionary biology.

New epigenetic mechanisms

There is a variety of processes now known to exist that are not included in Neo-Darwinism. These include symbiogenesis, niche construction, various forms of transfer of DNA (mobile genetic elements) and modern forms of epigenetics. These have recently been reviewed in a special issue of *The Journal of Physiology* (Noble *et al.*, 2014).

The processes that are most immediately relevant to physiology are epigenetic. Although the idea of epigenetics was introduced by Waddington, the modern use of the term is rather different from his use. Waddingtonôs epigenetic mechanism is a recognition that new phenotypes can arise through the formation of new patterns of alleles from forms that are already present in a population. This is explicitly stated in his book *The Strategy of the Genes*: ñThere is no reason which would prevent us from imagining that all the genes which eventually make up the assimilated genotype were already present in the population before the selection began, and only required bringing together.ò (Waddington, 1957 p 176). Not only does he clearly see this possibility, he also tests it. He continues (p 178): ñAttempts to carry out genetic assimilation starting from inbred lines have remained quite unsuccessful. This provides further evidence that the process depends on the utilisation of genetic variability in the foundation stock with which the experiment begins.ò His words could not be clearer.

This is epigenetics in the sense of being óaboveô the level of *individual* genes since he was drawing attention to a characteristic of *whole* genomes and the consequences of recombination of existing DNA sequences. Moreover, the evidence from whole genome sequencing shows that this must also have happened during evolution since that evidence shows that in the evolution of at least two classes of proteins, transcription factors and chromatin binding proteins, whole domains of DNA sequences must have been moved around in the genome to produce new forms of proteins (Shapiro, 2011). This modern discovery shows that an idea related to Waddingtonôs idea also applies to large scale evolutionary change. New patterns in the genome need not be restricted to new patterns of existing genes, they can also arise through rearrangement of sections of genes.

Scientists like James Shapiro who have studied these mechanisms of natural genetic engineering for many years no longer use the concept of an individual gene. As Beurton et al (Beurton *et al.*, 2008) comment ñit seems that a cellôs 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.ò The genes-eye view favoured by Neo-Darwinists is therefore partially blind. We need to view the genome as a system in interaction with the rest of the organism and its physiological functions. The Australian specialist on RNAs and plasticity, John Mattick, expressed a similar sentiment when he wrote ñthe belief that the soma and germ line do not communicate is patently incorrect.ò (Mattick, 2012).

To the concept of rearranging patterns of DNA sequences in the genome modern epigenetics has added the various forms by which gene expression levels can be modified by control from the organism. Some of these mechanisms have been known for a long time, ever since it was shown that expression patterns are controlled by transcription factor proteins that bind to regulatory parts of the genome. We now know that expression levels can also be controlled by methylation of one of the nucleic acid bases, cytosines, and by binding to the tails of histones. These are all epigenetic mechanisms in the sense of being forms of control of existing genome sequences.

New forms of Lamarckism

The main reason why all of these new developments are relevant to physiology is that they are the means by which physiological adaptation to environmental change in the life time of an organism can be transmitted to subsequent generations, which is the essence of what we mean by Lamarckism.

The orthodox reply to the challenge posed by inherited epigenetic patterns is that they necessarily die out after a generation or two. That may often be correct. But it is now clear that this is not always true. In this article I will highlight four examples that illustrate different ways in which epigenetic changes can transmit across many generations and so be a factor in evolutionary change.

The tiny planarian worm, *C elegans*, is a favourite organism for genetic and molecular biological studies. Infected with a particular virus, organisms that possess the correct DNA can react to this environmental stimulus by making an RNA that silences the virus, preventing it from using the host mechanisms for reproduction. By breeding these worms with others that do not have the relevant DNA Oded Rechavi and his colleagues (Rechavi *et al.*, 2011) obtained worms in subsequent generations that did not have this DNA. Yet they still inherited the acquired resistance to the virus, through small quantities of the viral-silencing RNA

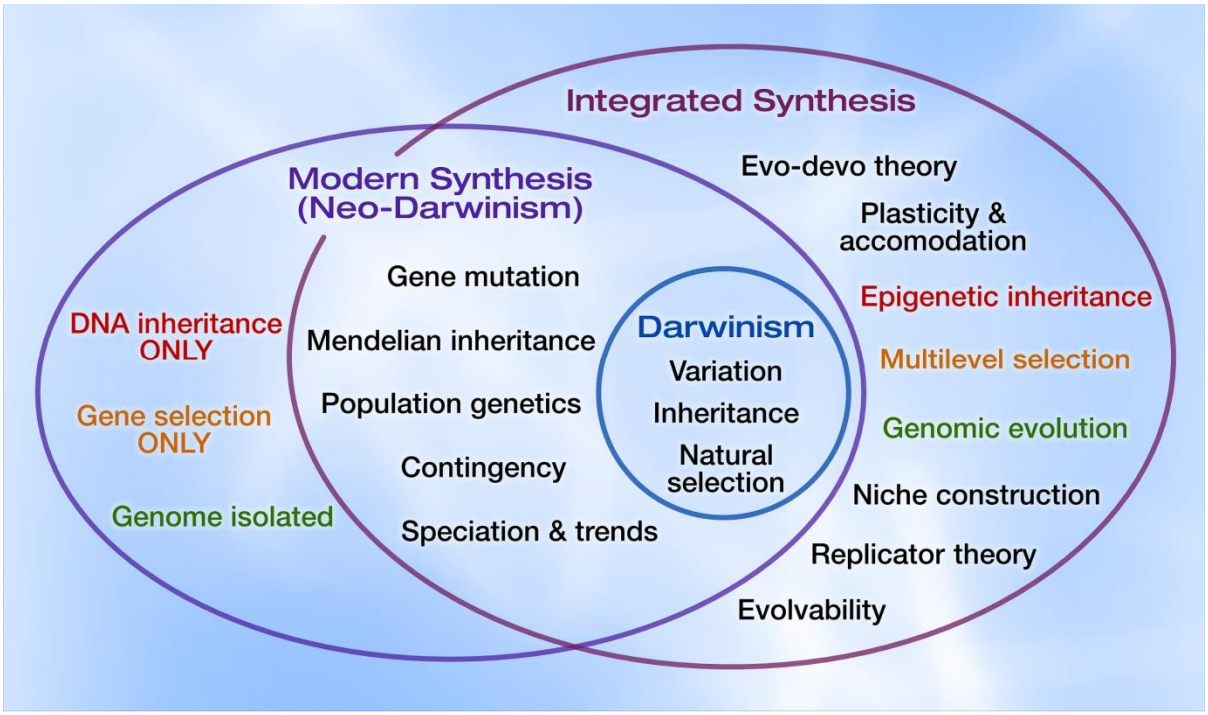

Fig. 1.
Diagram illustrating definitions of Darwinism, Modern Synthesis (Neo-Darwinism) and Integrated Synthesis. The diagram is derived from Pigliucci and Müllerôs (Pigliucci *et al.*, 2010) presentation of an Extended Synthesis. All the elements are also present in their diagram. The differences are: (1) the elements that are incompatible with the MS are shown coloured on the right; (2) the reasons for the incompatibility are shown in the three corresponding coloured elements on the left. These three assumptions of the MS lie beyond the range of what needs to extend or replace the MS; (3) in consequence, the MS is shown as an oval extending outside the range of the extended synthesis, which therefore becomes a replacement rather than an extension (from (Noble, 2015)).

passing through the male germ line and being amplified in each generation by an enzyme called RNA polymerase. The acquired characteristic is transmitted in this way through at least 100 generations. This example shows that the idea that an acquired characteristic will necessarily die out after a few generations is not correct. It also reveals that RNAs can also be transmitted through the germ line. DNA is therefore not the only inherited material.

Robust inheritance of an acquired epigenetic characteristic has been demonstrated in mice by Joe Nadeauôs group (Nelson *et al.*, 2012; Nelson *et al.*, 2010a; Nelson *et al.*, 2010b). They worked on a family of proteins that can insert mutations in DNA and RNA to show inheritance of epigenetic marking. When such marking was first discovered it was thought that the genome was always wiped clean of the marks in the germ line. This is clearly not true: on the contrary, Nadeauôs work shows that epigenetic inheritance can be just as robust as standard genetic inheritance and can persist for many generations.

Epigenetic mechanisms seem to be able to transmit memories of unpleasant experiences. Kerry Ressler and Brian Dias (Callaway, 2013; Dias *et al.*, 2014) at Emory University in the USA have shown that mice can be trained to fear a particular chemical smell through association of the smell with an electric shock: the progeny display the same fear of the smell even though they were not trained to do so. The precise epigenetic mechanism in this case remains to be discovered.

Another mechanism by which evolution can use epigenetics to by-pass the Weismann Barrier is to transmit the epigenetic marks through behaviour. This process has been demonstrated by Michael Meanyôs group in Canada (Weaver, 2009; Weaver *et al.*, 2004). Rodents, like many other animals, groom their young by licking and stroking them. This behaviour enhances the health and longevity of the progeny. It also

influences epigenetic marking in the region of the brain called the hippocampus which, amongst other roles, plays a part in emotional behaviour. The epigenetic effects can therefore predispose the progeny to show the same behaviour towards their young. This form of epigenetic inheritance doesnôt even require transmission through the germ line. It is a behavioural way of by-passing the Weismann Barrier.

These four examples suffice to show what is happening in modern epigenetic research. Can these and many other examples be dismissed as simply rare exceptions that óprove the ruleö? Could the Neo-Darwinist synthesis live with that? After all, Newtonian physics lives on despite the exceptions at the micro scale of quantum mechanics and the mega scale of general relativity. Those exceptions really are negligible for the spatial and time scales at which the physics of everyday life operates. We continue to use Newtonôs equations successfully. In the case of the exceptions to standard inheritance in evolutionary theory, this option is not open to us precisely because those exceptions operate at the same spatial scales and over the same time periods as the evolutionary process itself. Inheritance is inheritance, whether it is genetic, epigenetic, RNA-based, culturally-based, or whatever. All the inheritance processes end up doing the same thing, which is to modify the organism. Selection would not be able to distinguish between them.

But arenôt the non-standard mechanisms rare? That is a good question and the best answer at this early stage in research on epigenetic inheritance is that we donôt know how rare it may be compared to mutations in DNA. But rarity is not really the issue. After all, speciation is also rare. Rare events could have been responsible. Thousands of years of selection of dogs, cats, and fish have not resulted in new species by the standard definitions, such as whether or not the variants can interbreed.

Figure 1 illustrates the definitions and relationships between the various features of Darwinism, the MS, and a proposed new integrative synthesis (IS). The diagram is based on an extension of the diagram used by Pigliucci *et al.* (2010) in explaining the idea of an extended MS.

The shift to a new synthesis in evolutionary biology can also be seen to be part of a more general shift of viewpoint within biology towards systems approaches. The reductionist approach (which inspired the MS as a gene-centred theory of evolution) has been very productive, but it needs, and has always needed, to be complemented by an integrative approach, including a new theory of causation in biology (Noble, 2008), which I have called the theory of Biological Relativity (Noble, 2012).

Implications for healthcare

There are many implications of epigenetic inter-generational transmission for healthcare, recently reviewed by Gluckman et al (Gluckman *et al.*, 2014). These include many chronic non-communicable diseases, such as obesity, metabolic and cardiovascular diseases, stress and mental illness, cancer and inflammatory diseases. Some of these effects are produced by maternal effects, through the influence of factors from the mother transmitted to the embryo. Others can be transmitted through the male line via RNAs in sperm. Gluckman et al conclude ñThe relevance of molecular epigenetics to human disease is only now emerging. The role of somatic epimutations in the etiology of many cancers is now well established, and parental imprinting disorders, while rare, are well-recognisedé .it seems probable that epigenetic mechanisms play a significant role in influencing disease riské ..understanding these processes may lead to interventions based on manipulation of the epigenetic state.ò

It is important though to recognise that the epigenetic state is a multifactorial one: epigenetic control is exercised on many genes simultaneously to generate patterns of gene expression. This was one of the significant insights of Waddingtonôs work: that it is *patterns* of gene combinations and gene expressions that matter. This leads to what we may call a systems view of medication. Multi-factorial diseases require treatment with multi-action remedies, designed to counter the multiple disturbances of normal physiological function. Modern medicine is discovering that in treating the diseases of aging populations in developed countries. Drugs that may work for one problem can produce long-term side effects, that ultimately require treatment with yet more drugs. The end result is multi-component, multi-action medications, even if they were not originally designed that way. Furthermore, these medications may be expensive, and beyond the ability of governments, health organizations and individuals in developing countries to afford them.

It is possible therefore that more attention should be paid to the use of natural products in medication. There is a long tradition of such remedies in African traditional medicine. A valuable contribution that African medical science could contribute is to employ the systems approach to study these remedies and bring those that prove effective and can be clinically

validated into the domain of modern science. It should be remembered that a large proportion of existing medical drugs developed by pharmaceutical companies originated from herbal remedies.

There is also a justification for this approach in the context of evolution. After billions of years of evolution the natural chemical control of organisms occurs through hormonal and other chemicals that have been selected for their efficacy in combination. We should copy nature and find the combinations of medication that work most effectively in multi-factorial diseases. With modern multi-screening technologies it has become possible to screen potential medications using tests for multiple receptors, and computational physiology has been successful in identifying synergistic and non-synergistic combinations in some fields (Mirams *et al.*, 2011). What is missing is scientific understanding at a systems level of the relevant interactions when multiple receptors are activated or inhibited. That is a task that physiology can undertake in the twenty-first century.

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