

## CLASSICS

## Conrad Waddington and the origin of epigenetics



Denis Noble discusses Conrad Waddington's classic paper, 'The genetic assimilation of the bithorax phenotype', published in *Evolution* in 1956.

In 1956, the British developmental biologist, Conrad Waddington, published a paper in the journal *Evolution* (Waddington, 1956) in which he succeeded in demonstrating the inheritance of a characteristic acquired in a population in response to an environmental stimulus. Much earlier, in 1890, August Weismann had tried and failed to achieve this. He amputated the tails of five successive generations of mice and showed absolutely no evidence for an effect on subsequent generations. Weismann's discovery that the effects of an environmental stimulus (tail amputation) cannot be transmitted to subsequent generations, together with his assumption that genetic change is random, formed the foundations of the Modern Synthesis (Neo-Darwinism) of our understanding of genetic inheritance.

Waddington's approach, however, was much more subtle and more likely to be successful because he realised that the way to test for the inheritance of acquired characteristics is first to discover what forms of developmental plasticity already exist in a population, or that the population could be persuaded to demonstrate with a little nudging from the environment. By exploiting plasticity that already existed he was much more likely to mimic a path that evolution itself could have taken.

He used the word 'canalised' for this kind of persuasion since he represented the developmental process as a series of

'decisions' that could be represented as 'valleys' and 'forks' in a developmental landscape (Fig. 1). He knew from his developmental studies that embryo fruit flies could be persuaded to show different thorax and wing structures, simply by changing the environmental temperature or by a chemical stimulus. In his landscape diagram, this could be represented as a small manipulation in slope that would lead to one channel in the landscape being favoured over another, so that the adult could show a different phenotype starting from the same genotype.

The next step in his experiment was to select for and breed from the animals that displayed the new characteristic. Exposed to the same environmental stimulus, these gave rise to progeny with an even higher proportion of adults displaying the new character. After a relatively small number of generations, he found that he could then breed from the animals and obtain robust inheritance of the new character even without applying the environmental stimulus. The characteristic had therefore become locked into the genetics of the animal. He called this process genetic assimilation. What he had succeeded in showing was that an acquired characteristic could first be inherited as what we would now call 'soft' inheritance, and that it could then be assimilated into becoming standard 'hard' genetic inheritance. Today, we call 'soft' inheritance epigenetic inheritance, and of course, we know many more mechanisms by which the same genome can be controlled to produce different epigenetic effects.

What was happening at the gene level in Waddington's experiments? A standard Neo-Darwinist explanation might be that some mutations occurred. That is possible, but extremely unlikely on the time scale of the experiment, which was only a few generations. Moreover, random mutations would occur in individuals, not in a whole group. Single small mutations would have taken very many generations to spread through whole populations, and many such mutations would have been required.

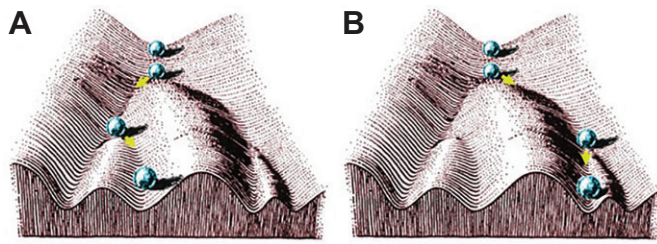
But I think there is a much simpler explanation. Recall that the experiment

exploited plasticity that is already present in the population. That strongly suggests that all the alleles (gene variants) necessary for the inheritance of the characteristic were already present in the population, but not initially in any particular individuals in the correct combination. The experiment simply brings them together. This is a modification of the pattern of the genome in response to the environmental change, but not in a way that requires any new mutations. I came to this conclusion before reading Waddington's (1957) book, *The Strategy of the Genes*. But it is in fact one of Waddington's own ideas! He writes 'There 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' (p. 176). Not only does he clearly see this possibility, he also tests it. He continues (p. 178) 'Attempts 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'. His text could not be clearer.

Orthodox Neo-Darwinists dismissed Waddington's findings as merely an example of the evolution of phenotype plasticity. That is what you will find in many of the biology textbooks even today (e.g. Arthur, 2010). I think that Waddington showed more than that. Of course, plasticity can evolve, and that itself could be by a Neo-Darwinist or any other mechanism. But Waddington was not simply showing the evolution of plasticity in general; he was showing how it could be exploited to enable a particular acquired characteristic in response to an environmental change to be inherited and be assimilated into the genome. Moreover, he departed from the strict Neo-Darwinist view by showing that this could happen even if no new mutations occur (Fig. 2).

Epigenetics means 'above genetics' and it was originally conceived by

Classics is an occasional column, featuring historic publications from the literature. These articles, written by modern experts in the field, discuss each classic paper's impact on the field of biology and their own work.

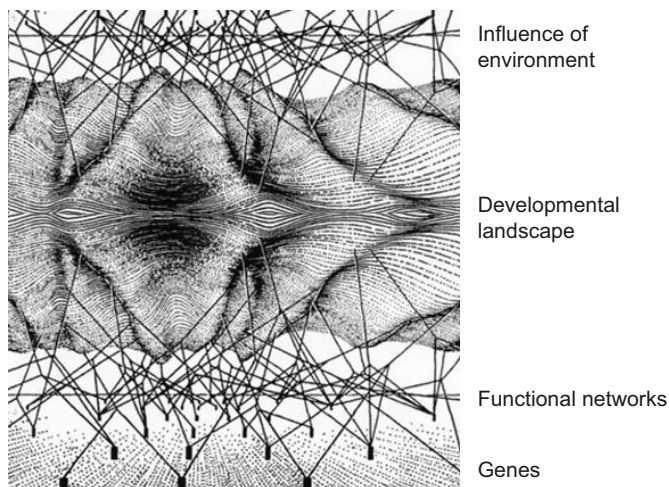


**Fig. 1. Waddington's developmental landscape diagram.** The landscape itself and the ball at the top are from his original diagram. The subsequent positions of the ball have been added to illustrate his point that development can be canalised to follow different routes (A and B). The plasticity to enable this to happen already exists in the wild population of organisms (modified diagram by K. Mitchell).

Waddington himself to describe the existence of mechanisms of inheritance in addition to (over and above) standard genetics (Bard, 2008). Waddington regarded himself as a Darwinist since Darwin also, in *The Origin of Species*, included the inheritance of acquired characteristics. But significantly, Waddington was not a Neo-Darwinist since Neo-Darwinism, following Weismann, specifically excludes such inheritance. Waddington was a profound thinker about biology, and much else too. *The Strategy of the Genes* is a masterly account of the many reasons why he dissented from Neo-Darwinism, and it has stood the test of time. It was reprinted over half a century later, in 2014. He did not describe himself as a Lamarckian, but by revealing mechanisms of inheritance of acquired characteristics, I think he should be regarded as such. The reason he did not do so is that Lamarck could not have conceived of the processes that Waddington revealed. Incidentally, it is

also true to say that Lamarck did not invent the idea of the inheritance of acquired characteristics. But, whether historically correct or not, we are stuck today with the term 'Lamarckian' for inheritance of a characteristic acquired through an environmental influence.

Waddington's concepts of plasticity and epigenetics have been very influential in my own thinking about experiments on cardiac rhythm. We found that the heart's pacemaker is very robust, so much so that protein mechanisms normally responsible for a large part of the rhythm could be completely blocked or deleted (Noble et al., 1992). Only very small changes in rhythm occur, because other mechanisms come into play to ensure that pacemaker activity continues. The relation between individual genes and the phenotype is therefore mediated through networks of interactions that can buffer individual gene variation, just as Waddington envisaged in his diagrams of epigenetic effects and canalisation. This is one of the



**Fig. 2. Waddington's diagram to show how the developmental landscape relates to individual genes (bottom pegs) through networks of interactions in the organism.** Since he also showed the influence of the external environment on canalisation of development, I have extended the diagram by adding the top part to represent the environmental influences. It is the combination of these influences that can lead to an evolutionary change without mutations (modified from Waddington, 1957).

reasons why I became interested in evolutionary biology many years ago, and why I have also explored ways in which evolutionary theory can be integrated with recent discoveries in molecular and physiological biology (Noble et al., 2014).

Waddington's concepts are also highly relevant to biologists interested in the ways in which organisms adapt to their environment, and to comparative biologists interested in how this varies between species. Many of the ways in which modern epigenetics plays an essential role in these fields have been described in a special issue of this journal (see overview by Knight, 2015). The discovery of epigenetic marking of DNA and its associated chromatin proteins has opened up new vistas for experimental biology.

I conclude this article with a warning: if you are inspired to try to repeat Waddington's 1956 experiment, do remember that you will fail if you try to do it on a cloned laboratory population. The mechanism depends on using a wild population with natural genetic diversity. In this respect it resembles a phenomenon first noted by James Baldwin (1896). This is that individuals in a population with the 'correct' allele combinations could choose a new environment and so permanently change the evolutionary development in that environment. It resembles Waddington's idea, as he himself recognised, because it does not require new mutations. More recently, Karl Popper, the great logician of science, also noted the possible importance of genetic assimilation without mutations in evolutionary theory (Niemann, 2014; Noble, 2014). Popper and Waddington had both taken part in discussions on evolutionary biology during the 1930s and 1940s when the field of molecular biology was still developing (Niemann, 2014).

While celebrating the recent rapid rise in epigenetics research (see Hoppeler, 2015; Knight, 2015), let's also celebrate the father of epigenetics, Conrad Waddington, who opened our eyes to the rich opportunities of adaptation through epigenetic regulation.

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