What history tells us XVII. Conrad Waddington and *The nature of life*

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1. Introduction

Conrad Hal Waddington is probably one of the most frequently quoted biologists of the middle of the 20th century; not because, as Francis Crick, he was one of the founders of the new molecular vision of organisms, but because, on the contrary, he anticipated the difficulties that a too reductionist approach of organismic facts would generate, and proposed some of the solutions that are presently explored. He is considered to be the founder of epigenetics, and his representation of the epigenetic landscape is repeatedly reproduced in articles and books. His model of genetic assimilation is considered as one of those new mechanisms that might complete Darwin's theory (Kirschner and Gerhart 2005). Waddington is also credited to have been one of the first to try to bridge the gap between embryology, genetics and evolutionary biology. He was also a supporter during the last part of his life of theoretical biology, and of the place that modelling must have in future biological explanations.

So much has been written on Waddington that it is difficult to be original (*see*, for instance, Yoxen 1986; Gilbert 2000). After a brief description of his main scientific contributions made in Cambridge, and then in Edinburgh, I will focus on one of his last books, *The nature of life* (Waddington 1962a), not the most famous one. It was based on a series of lectures that he delivered at the University College of the West Indies in Kingston, Jamaica, in the spring of 1960. His introducing statement that science is the unique domain in which humans apply *all* their major faculties (Waddington 1962a, 15-16) may sound as an outdated remnant of scientism. But, despite this "weakness", this book is seductive an account of the quality of its style, and its simplicity, when compared for instance with the rather difficult contemporary *New patterns in genetics and development* (Waddington 1962b). In a few pages, the main ideas of Waddington are collected, and they display the coherence of the successive statements made during his career. The richness of its content casts some doubts on the true originality of many of the ideas that are currently fashionable! Waddington also devotes a large part of his book to evolutionary theory, and the way the new developments in genetics and molecular biology enriched it 100 years after Darwin's *On the origin of species*. His attempts can be compared with those that presently flourish, 50 years later, in 2009, this 'Darwin' year.

2. Waddington's main scientific contributions

His first brilliant contribution (Gilbert 1991) was the demonstration that the principles of embryological development discovered by Hans Spemann in amphibians were also valid in chicks and ducks: an organiser directs the future development of these organisms (Waddington 1930; 1932). With Joseph Needham and Jean Brachet, he initiated a series of experiments in order to determine the chemical nature of the substances produced by this organiser. The puzzling result that many simple chemical molecules were able to mimic induction led Waddington to propose the hypothesis of the 'masked evocator' (Waddington 1940). The effect of the induction was simply to abolish the action of an inhibitor present in the target cells which were already competent to differentiate: all the chemical treatments unmasked a preexisting evocator, essential for the differentiation process, whose nature remained to be discovered.

At the end of the 1930s, Waddington spent one year in T. H. Morgan's lab in Caltech. That triggered him to reorient his work towards *Drosophila* and the role that genes play in development. Waddington fully agreed with the model

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proposed by Morgan in his 1934 book *Embryology and genetics (*Morgan 1934). Development is the result of an ongoing dialogue between genes and the cytoplasm. The action of maternal genes creates a heterogeneity in the cytoplasm of the egg, that leads to a differential gene expression in the first cells originating from the division of the egg. This pattern of gene expression differentially affects the cytoplasm, leading to a subsequent change in gene expression, generating step by step the fully differentiated tissues of the adult organism. For Waddington, what he called "epigenetics" was no more than the description of this complex action of genes on development (Waddington 1942; van Speybroeck 2002); his view has little in common with the present use of the word "epigenetics" to designate the control of gene expression by DNA and chromatin modifications (Jablonka and Lamb 2002; Morange 2002). For Waddington, epigenetics was development (epigenesis) as clarified by the description of gene action.

Nevertheless, much more than Morgan, Waddington emphasised two characteristics of the developmental process. As he demonstrated by his own work on the genes involved in the development of the wings in *Drosophila*, many genes contribute to the development of one single tissue or organ (Waddington 1939). In addition, development is buffered against the variations in gene activities (and environment) which might affect it. Waddington invented a new word, "creode", to describe the geography of differentiation and development, with its succession of crises, times at which cells can abruptly shift from one differentiation pathway to another, and intermediate well-buffered steps. The representation of the epigenetic landscape supported by the genes was an image that helped to understand how development is canalised (Waddington 1940; Waddington 1957).

Genetic variations can alter the landscape. They can perturb the critical phases of development, as well as increase or decrease canalisation. Faced with changes in their environment, organisms have the capacity to physiologically adapt to these variations by modifying the epigenetic landscape. Genetic assimilation is the subsequent stabilisation by genetic variations of this initial physiological adaptation (Waddington 1941). Waddington tried to demonstrate the existence of this process by a complex series of experiments performed on *Drosophila* in the next twenty years (*see*, for instance, Waddington 1953).

3. The limits of the reductionist approach

One recurrent theme in the last writings of Waddington, frequently raised to a pinnacle by present biologists, was his reluctance to adopt a purely reductionist approach such as that developed by molecular biologists. This idea initially came from his attachment to dialectical materialism. It led him in *The nature of life* to express some doubts on the value of the most recent results of this discipline, such as the structural characterisation of DNA, and the determination of its function (Waddington 1962a, 43–44). For Waddington, science had always progressed by a combination of atomistic and continuum explanations. It was high time to balance molecular biology with what Waddington called 'objective vitalism' (Waddington 1962a, 17).

In *New patterns in genetics and development* (Waddington 1962b), Waddington emphasised the continuity in his scientific attitude from the 1930s to the 1960s. He had always played the devil's advocate, underlining the limits of present descriptions in order to press biologists not to follow the dominant lines of research, but to engage with what would be future breakthroughs. Embryology was a dominant science in the 1930s, and Waddington argued that it might no longer progress without recognising the importance of genes in development and characterising their action. Similarly, the molecular biology of the 1960s had to be complemented by an organismic thinking.

The fact that molecular biology had to be complemented to be able to explain development was obvious. There is a range of phenomena specific to development: the existence of a transient phase of competence for cells, during which they can differentiate; the fact that cells are determined to differentiate far before the differentiation process initiates. It would be absurd to explain them with models, such as the operon model (Jacob and Monod 1961), derived from the study of microorganisms in which these phenomena do not exist.

What exactly is this "organismic thinking" is less clear. Waddington appeals to three different traditions to add flesh to the newly sketched organismic, continuum approach. The first is simply to pay attention to the spatial organisation of the different components within cells, a tradition well anchored in biochemistry since the contributions of Frederick Gowland Hopkins at the Department of Biochemistry of Cambridge. The differences between the reactions in the organism and those in the test tube originate from the existence of this intracellular organisation. It explains the efforts made by Waddington to elucidate, with the help of the electron microscope, the complex organisation of cells. The existence of ergatoplasm – now called endoplasmic reticulum –, cast, according to him, new light on the phenomenon of protein synthesis; and the position of genes on chromosomes, as well as the existence of different forms of chromatin, were fundamental to understand gene action. It explains why the Britten-Davidson model (Britten and Davidson 1969) emphasising the importance of gene organisation for development (and evolution) was enthusiastically received by Waddington (Waddington 1970).

The second tradition, well represented by D'Arcy Thompson (1917) and Alan Turing (1952), considered that physical forces and more generally physico-chemical factors, mould shape and pattern in cells and organisms. For Waddington, the way cells organise to form, during embryogenesis, structures such as the notochord might be the result of physical forces acting at the supramolecular level.

But Waddington paid much more attention to the recent developments of cybernetics, to a third tradition the existence of a complex network of relations between macromolecules. He praised the efforts made by Brian Goodwin to apply the equations of Volterra – initially used to account for the relations between prey and predator in ecology – to the behaviour of these macromolecular networks. In the 1960s, both through the *Journal of Theoretical Biology* and the numerous meetings he organised, Waddington urged the development of a theoretical biology.

The form of the 'objective vitalism' that Waddington thought necessary to complement molecular biology remains therefore fuzzy and heterogeneous. Is the situation more clear 50 years later?

4. Waddington and the Darwinian theory of evolution

The fourth chapter of *The nature of life* was devoted to evolution. It is the longest chapter of the book. Although he recognises the important historical contribution of Lamarck to the idea of evolution, Waddington is not a lamarckian: he rejects the idea that organisms' will might be playing a role in their adaptation, as well as the existence of a heredity of acquired characteristics *stricto sensu*. But he emphasises the role of the organism in its adaptation to the environment. Not only because it is able to physiologically adapt its functioning and behaviour to this environment – and therefore makes the action of natural selection subtle, but also because the organism is able to modify the environment to which it adapts – an anticipation of the notion of niche construction. In fact, Waddington regretted that ecological science was not more developed.

He considered that population geneticists had over-emphasised the role of chance in evolution (Waddington 1962a, 87). The complexity of the regulations, of the cybernetic control of the living systems, make their behaviour and evolution 'quasi-finalistic' (Waddington 1962a, 88).

All the previous considerations led Waddington to believe in the existence of progress. As a joke, he said that we have the right to consider that humans are superior to worms, as long as the latter do not come and present the claim that they are our equals. More seriously, although he recognised that adaptation is always local, he considered that one objective criterion of progress was the progressive independence of the organisms from their environment, their capacity to be less at its mercy: a conclusion which fitted well with the importance he gave to genetic canalisation in the development of organisms.

The last chapter was devoted to human beings. Waddington insisted on the role of culture in human societies, a form of Lamarckian heredity. Without developing an evolutionary theory of ethics, he nevertheless positions ethics in the context of human evolution. Although admitting that human faculties are perhaps limited, he considers that the faculties we have to interact with our environment and which constitute the basis of science have probably a considerable degree of effectiveness.

Finally – it demonstrates the remarkable contemporary relevance of this small book – one finds an excellent argument against Intelligent Design (Waddington 1962a, 26–27). Either the 'Designer' is outside the Universe, and his purposes are clearly not open to our understanding, or the Creator's purposes are expressed in the world, and the best thing to do is to examine scientifically what they are, since we cannot interrogate the Creator as we interrogate an engineer about his projects.

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