Canalization and genetic assimilation: Reassessing the radicality of the Waddingtonian concept of inheritance of acquired characters

Laurent Loison

Version of Record: https://www.sciencedirect.com/science/article/pii/S1084952117302902
Manuscript_16eacfbff81a85522ad35b6901ccb0ce

Canalization and genetic assimilation: reassessing the radicality of the Waddingtonian concept of inheritance of acquired characters

Laurent Loison
CNRS, IHPST (UMR 8590, CNRS, Paris 1 Panthéon-Sorbonne, ENS) France

Abstract

Genetic assimilation is often mixed up with the Baldwin effect. For Waddington, genetic assimilation was both a phenomenon and a specific mechanism of adaptive evolution which was grounded in the concept of canalization. This theoretical link between canalization and genetic assimilation, which was pivotal in Waddington's view, has been weakened since the early 1960s. The aim of the present article is to emphasize the specificity and to reassess the possible radicality of Waddington's proposal. What he claimed to have elaborated was an actual and genuine mechanism of inheritance of acquired characters that did not rely on soft Lamarckian inheritance. Consequently his "theory" of genetic assimilation, unlike the Baldwin effect, might not be as easily integrated in the framework of the Modern Synthesis.

Keywords: canalization; genetic assimilation; Conrad H. Waddington; inheritance of acquired characters; Modern Synthesis

1. Introduction

After a long eclipse, canalization and its possible molecular mechanisms has become a topic of growing interest for developmental and evolutionary biologists over the last twenty years [1-3], especially since the work of Rutherford and Lindquist [4]. Quite the same timing applies to genetic assimilation and the Baldwin effect in evolutionary biology: first considered as almost insignificant processes in adaptive evolution [5,6], they have received a newfound attention in the wake of the debate regarding the (in)sufficiency of the Modern Synthesis [7]. But for the most part, these two parallel histories are not interrelated. Modern debates about genetic assimilation/accommodation primarily focus on the evolutionary significance of plasticity, not canalization [8].

In contrast, during the 1940s and 1950s, Conrad Hal Waddington (1905-1975) elaborated canalization as a property of evolved organisms that might be the basis of an adaptive evolutionary mechanism. To him, canalization was the cornerstone in the explanation of genetic assimilation. The aim of this article is to reconsider and clarify the way in which Waddington, in his attempt to create a bridge between development and evolution, closely *linked* these two concepts. The relationship between canalization and genetic assimilation was not conceived by Waddington after the fact. On the contrary, since the very beginning, genetic assimilation was seen as the direct and necessary evolutionary outcome of canalization.

The original Waddingtonian account, scattered in several publications, is rather complex, often elusive and sometimes even cryptic [9, p. 225]. Waddington was intuitive and liked to think in visual terms. Several of his more famous concepts were first envisioned in diagrammatic forms, like the concept of epigenetic landscape (see figures 1 and 2 below). He did not always translate his speculative intuitions into workable analytical terms. What Waddington offered was therefore more a "heuristic" [10] than a precise theory, an approach whose specificity and radicality have been to some extent smoothed out by biologists and historians.

Waddington's experiments with genetic assimilation are in contrast still very well known today and accordingly not discussed in detail here [11-13]. They are usually reduced to the status of empirical cases supporting only the reality of the phenomenon of genetic assimilation. For Waddington, they were much more than that: they were also evidence that canalization was an inescapable explanation in the mechanism of genetic assimilation (see section 4.3).

These concepts were part of Waddington's original "epigenetics" framework. In his effort to causally understand how the genotype brings the phenotype into being, canalization was indisputably supposed to play a central role (see section 4). However, I will not engage the history of epigenetics as such here because much confusion still surrounds both the content of this concept [14] and consequently its history. Arguably, over the past few years, excessive emphasis has been placed on Waddington as a "precursor" of modern epigenetics (see for example [15, p. 817]), causing confusion between the original Waddingtonian account and our modern understanding (for a clear-cut and convincing distinction, see [16]).

2. The Baldwin effect and genetic assimilation: two different explanations of the same Lamarckian phenomenology

In the scientific literature, genetic assimilation and the Baldwin effect are often described as more or less equivalent. Such an appreciation can be found both in textbooks (for example [17, pp. 268-269]) and in more specialized articles (for example [18, p. 2362]). Usually, a short survey of the history of the concept of genetic assimilation traces its roots back to the work of Baldwin, Morgan and Osborn, who independently formed the concepts of 'organic' and 'coincident' selection at the very end of the nineteenth century [19, p. 732]. The standard definition describes genetic assimilation and the Baldwin effect as processes "by which a phenotypic response to the environment becomes, through the process of selection, taken over by the genotype so that it becomes independent of the original environmental inducer" [19, p. 732].

This kind of narrative directly implies that the term "genetic assimilation", coined by Waddington in 1953, is thought to be mostly a new word for an already old explanation [20, p. 112, 21, p. 216]. Thus, Waddington should be valued only for his ability to reframe organic selection in the modern terms of genetics [18, p. 2362], i.e. to propose a somewhat "modified form of organic selection" [21, p. 216].

This identification of genetic assimilation with the Baldwin effect – which is strongly contested in the present article – can be explained by at least two complementary causes. The first reason is the undeniable similarity, on a *descriptive* level, between these two phenomena. The standard definition quoted above [19] is correct: both the Baldwin effect and genetic assimilation are the transformation of an induced phenotypic response into a robust genetic one. Both were formed in order to explain apparently Lamarckian cases of inheritance of acquired characters. But, as I will argue, the mechanism involved in Waddington's genetic assimilation is substantially different from the standard Baldwin effect.

Here the distinction between the *phenomenon* of genetic assimilation and the *mechanism* of genetic assimilation is a pivotal one. As Waddington himself eventually came to acknowledge in his 1961 review, "[t]he notion of genetic assimilation involves both a phenomenon, and a mechanism by which this phenomenon is brought about" [22, p. 259]. And while the phenomenon is quite the same as the Baldwin effect, the causal mechanism at work is different (see section 4).

The second reason that helps explaining why this identification became commonplace is the impact of Simpson's 1953 famous article entitled "The Baldwin effect", published in

Evolution. This article, which stands out by its clarity and scope, offered a model of the mechanism first put forth by J.M. Baldwin in 1896 in accessible modern terms. In Simpson's text, one first finds a descriptive definition of the phenomenon that is similar to the standard one quoted above [19]. As Simpson put it, "[c]haracters individually acquired by members of a group of organisms may eventually, under the influence of selection, be reinforced or replaced by similar hereditary characters. That is the essence of the evolutionary *phenomenon* here called 'the Baldwin effect'." [23, p. 110, my emphasis]. Simpson's aim was to clarify the *mechanism* proposed by Baldwin because he thought that Baldwin's explanation was in several ways obscure and insufficient [23, pp. 111-112, my emphasis]:

> "The term is in any case misleading. 'Organic selection' is no more organic than any other sort of selection. Moreover, the *phenomenon* discussed by Baldwin is not directly or solely selection anyway. It is a complex *process* in which selection, strictly speaking, is only one of several factors, or it is an effect that is postulated as a result of selection."

Because Simpson was cautious about the mechanism involved, he favored the term "effect" which puts the emphasis on the end-result of a phenomenon that remained to be investigated and clarified. As a general basis for further research, he identified three main stages that could explain the so-called effect. Here again, his reasoning would have decades-long legacy (see for instance [5, p. 610]), and still represents the standard framework for discussing these topics [23, p. 112]:

> "(1) Individual organisms interact with the environment in such a way as systematically to produce in them behavioral, physiological, or structural modifications that are not hereditary as such but that are advantageous for survival, i.e., are adaptive for the individuals having them.
>
> (2) There occur in the population genetic factors producing hereditary characteristics similar to the individual modification referred to in (1), or having the same sorts of adaptive advantages.
>
> (3) The genetic factors of (2) are favored by natural selection and tend to spread in the population over the course of generations. The net result is that adaptation originally individual and non-hereditary becomes hereditary."

The three-step model proposed by Simpson is a tentative mechanism supposed to explain the effect at stake, i.e. how an "adaptation originally individual and non-hereditary becomes hereditary". Ironically, the next article in the same *Evolution* issue was Waddington's famous "Genetic Assimilation of an Acquired Character" where he presented the first experimental results supporting his own model (Waddington 1953a). Worth noting is that while Waddington did not go unmentioned in Simpson's review, his name came up only at the very end of the paper, in the discussion of the genetic basis of the ability to acquire a character [23, p. 116]. This treatment did much to reinforce the view that Waddington's genetic assimilation was a mere episode in the history of the Baldwin effect.

Waddington was worried about this kind of possible misunderstanding and quickly sent a response to *Evolution* that was added at the end of the same issue. His two-page comment's motivation was "to indicate the way in which the idea [he] was putting forward [genetic assimilation] differs from those which [Simpson] recapitulated" [24, p. 386]. Waddington disagreed with the idea that the mechanism of genetic assimilation could be reduced to the three-step model proposed by Simpson. In Simpson's account – and in most of the accounts that would follow until now (see for example [25, p. 1126]) – there is no direct

link between step (1) and step (2). This was because only two alternative configurations were thought possible. According to the Modern Synthesis approach, genetic mutations are random, i.e. they are not intrinsically adaptive: step (1) therefore cannot causally produce step (2), it can only, as already mentioned by Huxley in his 1942 seminal book "[hold] the strain in an environment where mutations tending in the same direction will be selected" [26, p. 304] (the same formulation can be found in the 2nd (1963) and 3rd (1974) editions). Whereas, according to classical Lamarckism, step (2) is the direct long-term consequence of step (1) because of the existence of a physiological mechanism of inheritance of acquired characters. Thus, because only two options were considered, Simpson and all the supporters of the Modern Synthesis after him dismissed any possible causal connection between the first two stages of the Baldwin effect on the grounds that it would reintroduce a Lamarckian component in modern biology.[1] The Baldwin effect is thus just classical selection acting on random mutations in plastic populations that are facing new environmental challenges. This is why Waddington insisted that the Baldwin effect, as a *mechanism*, "signifies very little" [24, p. 386, 27, p. 164].

Since the beginning, i.e. since the publication of his 1942 paper entitled "Canalization of development and the inheritance of acquired characters" [28], Waddington tried to elaborate an explanation that could escape the alternative between Lamarckism and the Modern Synthesis, between adaptive and blind variations. In his 1953 critical review, he remained cryptic and elusive as to how he envisioned this third way. He only suggested that "the initial non-hereditary response therefore does not merely allow the organism to persist in a new environment and become adapted to it [as in Huxley's and Simpson's account]; it enables natural selection to set the stage in such a way that the useful genetic effect is likely to occur." [24, p. 386].

But how could natural selection "set the stage"? Waddington, in his own words, was looking for a process of "conversion" [22, p. 257, 27, p. 168] of phenotypic variations into the genome that did *not* involve Lamarckian inheritance. The answer he progressively devised from the early 1940s to the 1960s was a very complex and subtle one (see section 4) but could nonetheless easily be summed up: mainly because of canalization. In Waddington's understanding of the mechanism of genetic assimilation, canalization was the key concept to explain how, in developmental systems, adaptive acquired characters could be eventually transferred to the genome.

3. The concept of canalization: from causal development to adaptive evolution

In contrast to genetic assimilation, the Waddingtonian concept of canalization was less often the object of serious misunderstandings, at least during Waddington's lifetime. Even if much more is now known about the mechanisms at work [2-4], standard definitions remain almost identical between them and very close to Waddington's original formulations (for instance, see [3, p. 290, 17, p. 263, 19, p. 731, 29, p. 116], for a review, see [30]). Canalization can thus be defined as the property to produce standard phenotypes despite genetic and environmental perturbations.

The aim of this section is not to offer a detailed reconstruction of the history of the concept of canalization, but to show that its final elaboration by Waddington during the 1940-

[1] Mayr was especially explicit [5, p. 610]: "Simpson points out correctly that this hypothesis is, of course, no reconciliation between Lamarckism and Darwinism, as is still believed by some French and Russian evolutionists. If the Baldwin effect occurs and if there were a direct effect on the phenotypic modification on the induction of the genetic factors reinforcing the favored phenotype, then we would have Lamarckism pure and simple. If there is no such induction, then we have simply natural selection, that is, the synthetic theory of evolution."

1942 period was deeply related to the search for an explanation of the mechanism of what would be termed genetic assimilation in 1953. The concept of canalization was thus at the same time the end result of Waddington's research program devoted to causal embryology (1930-1940) and the starting point of his work on genetic assimilation (1942-1961).

After starting a PhD in paleontology, Waddington soon moved to the field of causal embryology in the early 1930s in the wake of Spemann and Mangold's famous results about the "organizer" and induction [31]. Peterson's recent book shows how understanding Spemann's organizer "became something of a scientific gold rush in early 1930s European embryology and biochemistry" [32, p. 93]. This is the main reason why Joseph and Dorothy Needham, Waddington, and a few others[2], formed the "Theoretical Biology Club" in Cambridge (for a detailed study of the history of the TBC, see [32]). After almost ten years working on amphibian and avian embryos – most of the time in collaboration with others, especially the Needhams and Jean Brachet – Waddington's own thoughts on the way organizers proceed in development culminated in his 1940 book *Organisers and Genes*. At the time when the evolutionary Modern Synthesis was about to be completed, Waddington wanted to offer another kind of synthesis, a synthesis between embryology and genetics [33, p. vii, p. 2].

The concept of canalization emerged during the 1930s mostly as the result of the complete failure of the work done by Waddington and others to identify the chemical nature of the organizer. To the initial question of the mechanism by which the organizer was supposed to drive embryonic development, Waddington progressively answered by emphasizing the inadequacy of the question [34, p. 190]: the organizer, whatever its nature, cannot be the only – not even the main – "cause" of development. Development and differentiation must be seen as the end result of a "complex system of actions and interactions" [33, p. 4]. The *specificity* of developmental paths was thus transferred from the chemical substance secreted by the organizer to the system able to react to it, i.e. the developmental system [29, p. 117, 35, p. 140, 36, pp. 149-150].

Waddington coined the term "competence" to account for the faculty of response to an organizer. Competence was an evolved property of embryonic tissues and the main cause of the specificity of development. During the 1930s, Waddington progressively undermined the causal role of the organizer: the "evocator" it produced, he demonstrated, must only be seen as a mere stimulus able to push the tissue into one of the developmental paths already available. This is why he came to picture the whole process of development as an "epigenetic landscape" (Fig. 1) where developmental paths are well-defined discrete entities which pre-exist the running down of the ball [33, p. 45, pp. 92-93]. Moreover, for Waddington, these paths have to be sharp alternatives if development has to produce functional end-results [33, p. 47, 37, p. 109].

[2] According to Peterson [32], the main members of the TBC were: Joseph and Dorothy Needham, Dorothy Wrinch, John Desmond Bernal, Conrad Waddington and Joseph Henry Woodger.

Fig. 1. The first representation of an epigenetic landscape published by Waddington [33]. As a frontispiece of his book *Organisers and Genes*, Waddington reproduced this drawing of John Piper

In *Organisers and Genes*, Waddington already used the famous example of the embryonic formation of the callosities of the ostrich. This example was endowed with a precise function: to illustrate that the specificity of the phenotype, in nowadays highly evolved organisms, has become a consequence of the competence of the developmental system [33, p. 49]:

> "In fact, one would expect that in general the more highly developed the competence, that is to say the more sharply the alternatives are contrasted, the smaller the external stimulus which will be necessary to decide between them. The evolution of a really efficient competence may therefore be expected to reduce the importance of the evocator, which will probably tend to disappear; and we may expect to find cases in which the functions of the evocator are so slight that they are taken over by minor variations in conditions which are very difficult to identify. Phenomena of this kind may lead to the evolution of a mosaic type of development from a regulative; and they may also help to explain cases, such as that of the callosities of the ostrich, in which structures which are apparently adaptive responses to external stimuli actually develop before the stimuli can possibly be present."

To this general explanatory framework, Waddington eventually made two fundamental additions in his effort to link embryology and genetics. First, competence is necessarily under genetic control. This statement was grounded on a theoretical reasoning: competence being the cause of the specificity of developmental pathways, since the genes are responsible for the characters of an organism, it ensues that "it must in general be the genes which determine the properties of the competence" [33, p. 54]. Second, if genes are ultimately the cause of development, it does not follow that a precise phenotypic character is the

consequence of any individual allele. For Waddington, the whole genome is responsible for the formation of the entire embryo [33, p. 59] (see also section 4).

At the end of the 1930s, Waddington thus had all the tools in hand to elaborate the concept of canalization. This concept already shows through in *Organisers and Genes* (see for instance [33, pp. 43-44]). A few months later, he came even closer to the standard formulation of canalization in an article entitled "Evolution of developmental systems". Of pivotal significance for the argument supported here is the fact that, already in this text, Waddington closely connected the concept of canalization (without using the word) to a mechanism that would lead to the one of genetic assimilation [37, p. 110]:

> "A developmental path has to be equilibrated; natural selection must build up a genetic background which stabilizes each path at the optimum. If, by an early-acting gene, a whole set of paths are thrown out of their old equilibria, a very considerable modification of the genetic background will be called for. Once accomplished, this will not be easily reversed or copied; and the new form will be effectively isolated from the old."

The final step was made in his famous 1942 article. In the same short text published in *Nature*, Waddington unambiguously formulated the concept of canalization and that of genetic assimilation (the latter was not termed yet). He emphasized that canalization was the central tenet of his argument, and the most original one (a concept "new in such discussions"). He defined it as follows [28, p. 563, emphasis in the original]:

> "The main thesis is that developmental reactions, *as they occur in organisms submitted to natural selection*, are in general canalized.[3] That is to say, they are adjusted so as to bring about one definite end-result regardless of minor variations in conditions during the course of the reaction."

At this time, he was still hesitant about the terminology, admitting that the term "buffering" might be more appropriate [28, p. 563] (only in 1961 did he explain in detail why "canalization" is the best term available and should be preferred to others like "equilibrium" or "homeostasis" [22, pp. 276-278]). After World War II, when he became Professor of Animal Genetics at the University of Edinburgh (1947), Waddington was no longer interested in causal embryology and devoted most of his time to the experimental demonstration of the phenomenon of genetic assimilation.

The aim of this section has been to briefly sketch the historical path that led Waddington to conceptualize canalization and, consequently, genetic assimilation. But this does not mean that the link between canalization and genetic assimilation was only historical, i.e. a mere episode in Waddington's biography. On the contrary, Waddington always strongly insisted on the fact that this link was first and foremost conceptual: even after he gave up embryology, he remained focused on canalization because he was convinced that this concept was the key to designing a plausible and original mechanism for genetic assimilation.

4. Causal relationships between canalization and genetic assimilation

It bears repeating that for Waddington, canalization was the main *cause* of the process of genetic assimilation. In his 1961 review on genetic assimilation, one of the sections is

[3] The substantive "canalization" is used by Waddington a few lines after this first definition.

unambiguously entitled "Genetic Assimilation as a *Consequence* of Canalization" [22, p. 271, my emphasis]. This causal relationship from canalization to genetic assimilation is indeed a reliable criterion to draw a distinction between the Waddingtonian account and traditional loose accounts of both genetic assimilation and the Baldwin effect. It is commonly argued in the scientific literature that canalization is (only) the consequence of genetic assimilation [38, p. 360, 39, p. 770]. Even authors who are primarily concerned with identifying differences between the Baldwin effect and genetic assimilation reduce canalization to a by-product of genetic assimilation. For instance, West-Eberhard cannot be clearer when she writes that "[c]analization is the developmental consequence of genetic assimilation" [8, p. 25]. Crispo, despite her will to "provide clear, definitive interpretations of the meanings of the Baldwin effect and genetic assimilation" [40, p. 2469] also reduces canalization to a final outcome of genetic assimilation [40, p. 2472].

As a matter of fact, Waddington's conception of the causal relationship between canalization and genetic assimilation has often been misunderstood and, consequently, generally neglected (with, of course, exceptions, especially [10, 41] and [42] which, unfortunately, went completely unnoticed[4]). The specificity of Waddington's account of the mechanism of genetic assimilation is based on three causal roles he ascribed to canalization. These roles were not distinguished as follows by Waddington himself. The retrospective distinctions proposed here separate explanations that in Waddington's own conceptual framework and published texts are often closely interrelated. They nonetheless help us capture Waddington's core conception of the mechanism of genetic assimilation.

4.1 Canalization and the channeling of pre-existing developmental pathways

The first of these roles allowed Waddington to clearly distinguish between his mechanism and coincident selection in the form this concept was usually understood during the 1940s and 1950s. In the reconstruction of the views of Baldwin and others[5] put forth by the architects of the Modern Synthesis during the 1940s and 1950s (Huxley, Simpson and Mayr especially), as we have seen in section 2, there is a complete causal independence between the adaptive response of an organism to a new environmental challenge and the occurrence of a genetic mutation that would later mimic the induced and adaptive phenotype. Only an indirect selective causal connection does exist: individual plastic transformations allow time for appropriate mutation(s) to occur in the population and to be selected under the new environmental pressures (for a modern treatment, see [25]).

This, for Waddington, is just ignoring that nowadays organisms are evolved systems, which have been subjected to natural selection for many generations in various environmental conditions. Because they are highly evolved systems, organisms (and, for Waddington, especially animals) are endowed with plastic abilities that are grounded in their genetic repertoire, i.e. that are themselves evolutionary constructions. Therefore, most of the plastic (adaptive) accommodations an organism might perform in its lifetime are instantiations of genetic potentialities that were already there and that are only "evoked" by the new

[4] In 1998, Paul Dominic Lewin defended a very interesting and original PhD entitled *Embryology and the Evolutionary Synthesis: Waddington, Development and Genetics* (Leeds University). According to Google Scholar (09/29/2017), this work – which was never published – has been quoted only twice (which includes a reference by historian Peter Bowler, who was one of the two examiners). The dissertation is available here: http://etheses.whiterose.ac.uk/1455/

[5] These reconstructions, especially Simpson's (1953), might to some extent be unfaithful to Baldwin's own writings [8, pp. 152-153]. But this is a problem that the present article is not interested in: only the standard interpretation of the Baldwin effect that prevailed when Waddington conceptualized genetic assimilation is relevant for the purposes of my argument here.

environmental configuration [28, p. 564]; whereas in the Baldwin effect, "nongenetic mechanisms" are involved [22, p. 287]. Plasticity was mostly an evolved feature for Waddington, and not an inherent attribute of living systems.

It must be noted that this means of distinction between initial formulations of the Baldwin effect and Waddington's understanding of genetic assimilation progressively became inoperative in the 1960s when standard definitions of the Baldwin effect derived from Simpson's three-step model came to include the fact that reaction norms of organisms are themselves "genetically determined" [5, p. 610].

But to Waddington, the most important point was not so much that plastic potentialities are genetic – and as such liable to be the target of selection – but that they were specifically conceived as channeling more or less already defined pathways in a multidimensional epigenetic landscape. Altogether, these pathways represent the complete set of developmental responses an organism is capable of [28, p. 564] (see Fig. 2). The standard developmental pathway that usually leads to the wild-type phenotype is the most canalized. Yet the other ones are already at least rough sketches, susceptible to being remodeled in new environmental conditions. This was another significant property of plastic variations for Waddington: these already existing paths in the epigenetic landscape can be further transformed and eventually "converted" into automatic developmental sequences regardless of any environmental stimulus. In some cases, alternative pathways are even already significantly canalized themselves; they are just *less* canalized than the standard one in typical environmental conditions. And whereas the almost complete *de novo* deepening of a new path requires some time, the existence of such "pre-canalized" paths explains why genetic assimilation could sometimes be so fast [22, p. 172, 28, p. 565].

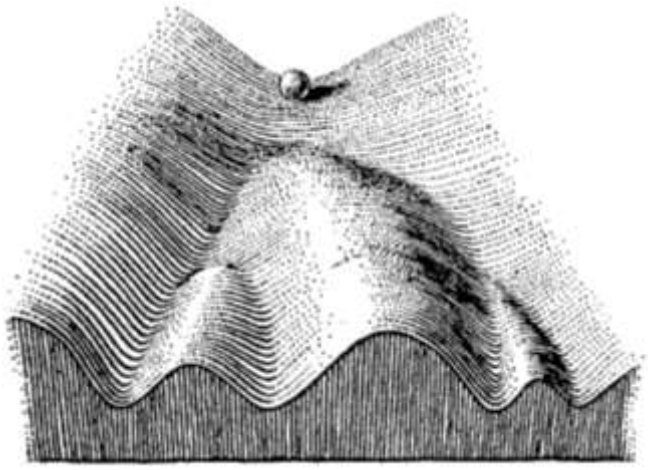

Fig. 2. The typical Waddingtonian representation of a genetic landscape [27]. This diagram shows multiple, more or less canalized pathways that preexist the ball's downhill journey.

Thus, for Waddington, the developmental path that first led to an individual eco-physiological adjustment is the *same* that later might have become the highly canalized channel that produces the standard genetically-determined character. The phenotypic effect is in both cases the consequence of the same sequence of developmental events, whereas in the traditional Baldwin effect this is not necessarily the case (it could happen that the way *coincident* mutations eventually produce the adaptive phenotype significantly differs from the developmental path of the original plastic response). This is precisely the non-Lamarckian "connection" [24, p. 386] that, according to Waddington, was missing in the standard

explanation of the Baldwin effect between the first two steps of Simpson's model (cf. section 2).

4.2 Canalization and the storage of cryptic genetic variation

Canalization was also seen by Waddington as responsible for the storage of cryptic genetic variation in a population. By definition, when canalization becomes strong enough, it decouples the end-result of embryological development from standard genetic mutations: mutations can therefore accumulate in the genome without disturbing development because they remain unexpressed. This cryptic genetic polymorphism is only revealed when a strong perturbation occurs (genetic or environmental), i.e. when development escapes the standard pathway in the epigenetic landscape (decanalization[6]). Decanalization offers significant material to natural selection, serving as the starting point of a genetic assimilation event.

Waddington unambiguously formulated this notion of disruption of canalization in at least two occasions in his publications. In *The Strategy of the Genes* (1957), he first mostly focused on the fact that this evolutionary role of canalization is itself susceptible to being the target of selection (at the population level and in the context of what is now called evolvability). According to Waddington, the ability to store cryptic genetic variation helps to understand how and why canalization itself might have evolved [27, p. 122, my emphasis]:

> "It is advantageous to a population to contain some genic variability to cope with environmental changes and to give the potentiality for evolutionary advance. The more strongly the epigenetic system is buffered against genic variation, the more *reserve* of such variability the population will be able to contain without endangering the attainment of the optimum in the normal environment. There will thus be a selective pressure in favour of epigenetic systems which can absorb some genic variation without this producing any phenotypic effects, although, as we have seen, this lack of response to variation of genes cannot be pushed too far."

Four years later, in his 1961 review, Waddington devoted a short section to the "disruption of canalization". This time, he was more interested in the potential evolutionary impact of this function of canalization than in the way it had previously evolved [22, p. 280]:

> "When a wild type phenotype is strongly canalized very little of the genetic variation present in a normal population will come to expression and thus be available for selection. A greater amount of the variation can be revealed if some way is found to push the processes of development away from the canalized phenotype, so that they follow a path which is more susceptible to the influence of minor genetic variation."

This aspect of Waddington's own theory of genetic assimilation is by far the least forgotten [43, pp. 350-360]. Especially since the pioneering work of Rutherford and Lindquist on Hsp90 (1998), "capacitors" for evolution have become an attractive topic [44, see also 45 in the present special issue]. Rutherford and Lindquist provided for the first time a specific molecular device able to explain how, in concrete real organisms such as *Drosophila*, the buffering of development could be weakened, thereby revealing a significant amount of

[6] As far as I know, the term "decanalization" cannot be found in Waddington's published writings.

genetic variation that was kept silent before, like Waddington's model predicted. At least in some occasions [22, p. 273], Waddington, surprisingly, explicitly made the hypothesis that there must be genes responsible for the canalization of development exactly in the same way Rutherford and Lindquist did more than thirty years later. It is surprising – and, to some extent, inconsistent in the original Waddingtionian framework – because Waddington constantly opposed the idea that a specific function could be ascribed to a particular gene (see 4.3). One would thus have expected that, to him, canalization would have been more a systemic and emergent property of the whole developmental system than the consequence of a few specific genes [46]. It must be noted that this holistic account of canalization is nowadays promoted on the basis of network modeling [2, see also 47 in the present special issue].

Waddington's emphasis on the alternation of decanalization and recanalization events is also pivotal in that it helps distinguishing between two related but nonetheless different causal interpretations of genetic assimilation: Waddington's and the one preferred by Stern [48, 49] and Bateman [50], which became the standard "threshold" account [51, p. 223]. Bateman and Stern promoted an interpretation that was to some extent already part of Waddington's own framework but that does not seem, in its standard formulation, to need the concept of canalization[7] [52, pp. 68-69]. When genetic assimilation and the Baldwin effect are not completely mixed up, genetic assimilation is almost systematically explained in terms of a threshold model [53, pp. 309-310]:

> "In such a situation [genetic assimilation] there are two thresholds, one spontaneous and the other induced […]. The spontaneous threshold is at first outside the range of variation of the population, so that there is no variation of phenotype and no selection can be applied […]. The induced threshold, however, is within the range of liability covered by the population, and it allows individuals toward one end of the distribution to be picked out by selection. In this way the mean genotypic value of the population is changed. If this change goes far enough, some individuals will eventually cross the spontaneous threshold and appear as spontaneous variants […]. When the spontaneous incidence becomes high enough, selection may be continued without the aid of the environmental stimulus, and the spontaneous incidence may be further increased […]."

[7] In contrast to what is usually believed and written, the threshold model first put forth by Bateman, although it does not use the *term* "canalization" in its standard formulation, nevertheless makes some room for the *concept*. As Bateman initially acknowledged, the shift of the threshold at the population level corresponds, at the level of the individual organism, to the "cutting-away of a ridge separating two valleys" [50, p. 470]. This means that the threshold model, while it does not need a recanalization phase, nonetheless requires, like Waddington's account of genetic assimilation, a decanalization event.

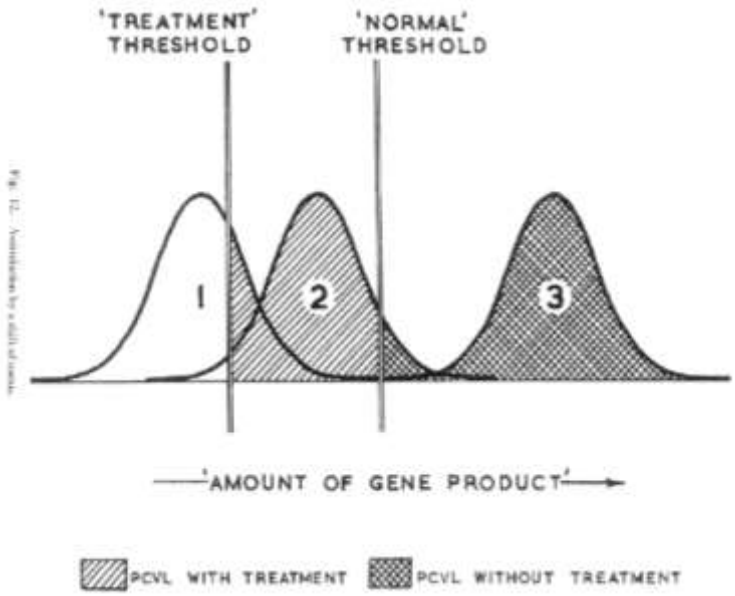

Fig. 3. The first representation of the "threshold" model published by Bateman [48]. This diagram (reproduced in [51]) shows no change in population variance, only a shift in mean.

In such a model, only the mean of the distribution is changed, not its variance (Fig. 3). In other words, because the variance is constant, there is no subsequent modification of the degree of canalization applied to the developmental pathway that produces the character. Waddington himself included threshold selection in his account [54, p. 58]. This is precisely why he made a distinction between "normalizing selection" (i.e. threshold selection) and "canalizing selection". But only the latter tends to stabilize the optimal phenotype. This final "increase in the canalisation of the abnormal phenotype" [50, p. 470] lowers the variance of the trait and allows it to be produced even in the absence of the previous environmental stimulus.

This last stage of recanalization – i.e. the deepening of the valley in the epigenetic landscape (Fig. 4) – was pivotal for Waddington because it explains both the phenotypic stability of a recently acquired character in various environments [11, p. 118] and the reason why phenotypic characters develop nearly always to "*exactly* the optimum degree" [27, p. 120, my emphasis]. Waddington called this specific step the "tuning of adaptive phenotype" [27, p. 172].

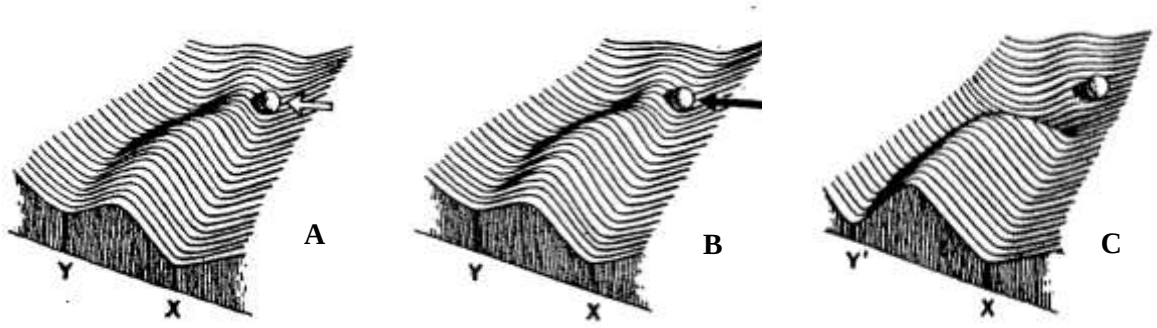

Fig. 4. These three diagrams display the Waddingtonian distinction between the Baldwin effect and genetic assimilation [27]. In the initial situation (A), an environmental stimulus (hollow arrow) pushes the ball over the threshold: the development will end in Y instead of X. In the Baldwin effect (B), the topography of the epigenetic landscape is not modified; a mutant allele (dark arrow) has simply replaced the environmental stimulus. In genetic assimilation, the epigenetic landscape is modified twice: there is a disappearance of the threshold and a deepening of the Y valley, from Y to Y'. Waddington insisted that "the genotype as a whole" was responsible for the modification of the epigenetic landscape.

This significant part of Waddington's account (see 4.3) simply does not exist in the standard threshold model. In 1963, in his highly influential *Animal Species and Evolution*, Mayr took a strong stance in favor of this interpretation when he wrote that "[what] we really have here is threshold selection" [5, p. 190]. It follows that because genetic assimilation was nothing more than "the normal process of selection of a polygenic character", it "requires no special terminology" [5, p. 612]. Genetic assimilation was reduced only to an "interpretation" [5, p. 612] of the Baldwin effect [55], fully compatible with the Modern Synthesis.

4.3 Canalization and the blindness of genetic mutations

The tuning of canalization, because it determines the "*direction* taken by a canalized pathway" [22, p. 286, my emphasis], is at the basis of the last aspect of the causal role ascribed to canalization in genetic assimilation. This one is by far the most heterodox from the Modern Synthesis perspective, which might explain why it has been almost completely forgotten.

A central claim of the Modern Synthesis is the blindness of genetic mutations: these do not arise because of their adaptive value. Therefore, the *direction* of evolutionary change is determined only by natural selection. This claim is not threatened by the Baldwin effect. On the one hand, coincident selection is only classical selection acting on random mutations occurring in plastic populations that are facing new environmental challenges. On the other hand, the threshold model of genetic assimilation is no more than "selection of polygenic threshold shifts", i.e. "one of the normal aspects of natural selection" [5, p. 612]. Waddington's account implies something more that has remained largely undiscussed: a claim about the direction of the evolutionary change in evolved organisms which is highly constrained by the global canalization of developmental systems [9].

The blindness of genetic mutations has been challenged in several ways since Luria and Delbrück's fluctuation test (1943). In various experimental and theoretical contexts, it has been proposed that mutations – especially in bacterial systems – might be preferentially oriented towards an increase in adaptation (see for example [56]; for a global treatment, see [57]). This possibility was explicitly considered by Waddington. At least twice, he briefly explained that the phenomenon of enzymatic adaptation made the possibility of directed

mutations not completely unlikely and that we shouldn't be "too much astonished if it should be found that some metabolic 'opportunity' available in the cell might tend to induce a gene mutation to an allele which in some way fitted it" [27, p. 180, 51, p. 55]. Nonetheless, such a speculative hypothesis was never examined in more detail and this was not how Waddington's mechanism of genetic assimilation challenged the Modern Synthesis approach to the blindness of variation.

As far as I know, the epilogue of *The Strategy of the Genes* contains Waddington's clearest formulation of why his account might explain that genetic mutations, despite being random, nonetheless produce specific and oriented phenotypic effects. The key to this apparent paradox is again to be found in the concept of canalized developmental pathways [27, p. 188, my emphasis]:

> "We have been led to conclude that natural selection for the ability to develop adaptively in relation to the environment will build up an epigenetic landscape which in its turn *guides the phenotypic effects of the mutations available*. In the light of this, the conventional statement that the raw materials of evolution are provided by random mutation appears hollow. The changes which occur in the nucleoproteins of the chromosomes may well be indeterminate, but the *phenotypic effects* of the alleles which have not yet been utilized in evolution cannot adequately be characterized as 'random': *they are conditioned by the modelling of the epigenetic landscape into a form which favours those paths of development which lead to end-states adapted to the environment.*"

In a few sentences, this paragraph remarkably summarizes the essence of the most challenging component of Waddington's mechanism of genetic assimilation. Once again, Waddington's understanding is rooted in the idea that living organisms are evolved developmental systems that have been selected over a long period within a specific environment. As such, their developmental repertoires have been built to produce only a few pathways in response to various environmental stimuli (cf. 4.1 above, see also [41, p. 585]). As Lewin perfectly expressed, "development has become canalized, and the phenotypic effects of subsequent minor genetic mutations will thus not be random at all, but will be guided along preexisting canalized pathways" [42, p. 111].

In his first response to Simpson's 1953 article, Waddington already emphasized the fact that the randomness of genetic mutations is true only "at the level of the gene as a protein-DNA complex", but that "the [phenotypic] effect of a mutation, as far as natural selection is concerned, is conditioned by the way it modifies the reaction with the environment of a genotype which has already been selected on the basis of its response to that environment" [24, p. 386].

Waddington's claim was not only a theoretical one. Some of the experiments he and his collaborators performed during the 1950s in Edinburgh were unambiguously designed to test this aspect of his account of the mechanism of genetic assimilation. If his hypothesis was correct, then it meant that the specificity of a phenotype in a given environment does not depend on the presence of specific alleles in the genome. Different stocks might thus evolve, through genetic assimilation, towards the same adaptive phenotype despite their initial genetic differences [11, p. 124].

Most of the work on *Drosophila* by Waddington's post-doc K.G. Bateman (1956-1959) was an attempt to test this extreme prediction. Bateman explicitly formulated the alternative her results were supposed to decide [50, p. 451]:

> "The purpose of the genetic analysis was to determine to what extent potential directions of assimilation are limited by the gene contents of a population: how specific is the genetic basis of assimilated characters? At one end of the scale of specificity would be a situation in which the presence of a particular gene is obligatory for the process; at the other, one in which control is due to a large number of genes, the individual effects of which are small. Various tests were designed to determine which of these alternatives is more nearly approached by the assimilated stocks."

To decide between these two alternatives, Bateman repeated and extended the original experiments on the selection of the four venation phenocopies in *Drosophila* (namely *pcvl*, *acvl*, *fpcv* and *smcv*). As Waddington did, she selected each of the four phenotypes in two consecutive stages, first with treatment (incubation at 40°C during four hours) and then without [50]. In accordance with Waddington's previous results, she conclusively established the occurrence of the phenomenon of genetic assimilation. But in contradiction with Waddington's account, some of her results seemed to support the fact that the influence of a few "major" genes was considerable in the phenotype that was finally assimilated: "what appears to be certain is that the assimilated characters are not controlled merely by an indefinite number of genes of individually small effect, i.e. are not 'polygenic'" [50, p. 461]. Waddington later tried to minimize the significance of this aspect of his student's interpretations. He did not deny that in some cases of genetic assimilation (such as the "dumpy" phenotype in *Drosophila*), the presence of a specific allele (here dp^{TP}) was obligatory [58]. But he strongly opposed the idea that this would be the general case. For him, as he insisted once again in 1961, when complete assimilation is achieved, such a process must "ha[ve] involved changes at many loci throughout the whole genotype" [22, p. 267].

Waddington always conceived the genome as an integrated whole where genes effects on the phenotype could hardly be individualized. His early studies on the morphology of *Drosophila* wings greatly reinforced his conviction [52, p. 66, 58]. This "coordination" of genes in "a network of interacting components" [19, p. 731] was the reason why he famously represented the modelling of the epigenetic landscape as a multidimensional surface anchored to the genome [27, p. 36] (see Fig. 5).

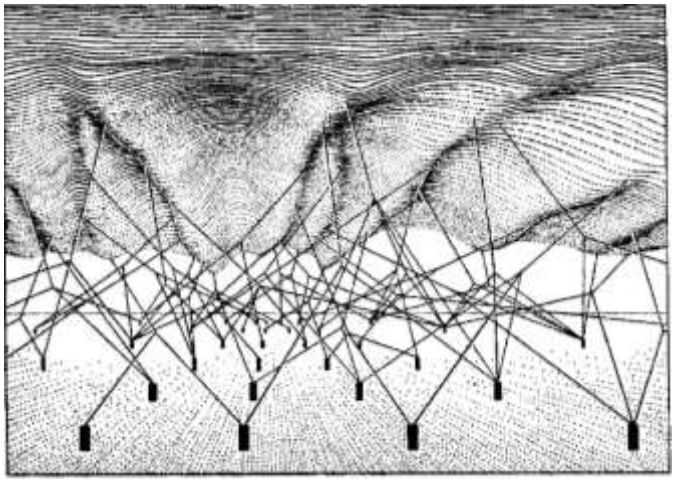

Fig. 5. This diagram shows "the complex system of interactions underlying the epigenetic landscape" [27]. Each peg represents a gene and each string its contribution to the network that causally produces the epigenetic landscape.

He also always vigorously contested the validity of attaching selective coefficients to the alleles present in a given population because only phenotypes are the target of natural

selection [9, pp. 226-227, 27, p. 65]. Taken together, these two claims imply that what is submitted to the operation of selection is a responsive and canalized genome in a given environment. A specific allele has no necessary phenotypic translation: its effect is dependent on the developmental system in which it is integrated. The more evolved is this system, the more canalized are its developmental pathways, up to a point where new genetic standard variations, whatever their molecular "blindness", are necessarily recruited for the building of these paths.

5. Conclusion: towards a challenging concept of the inheritance of acquired characters?

It is an understatement to say that the radicality of Waddington's account of the mechanism of genetic assimilation has been usually overlooked during half a century, even by some of the main critics of the Modern Synthesis [60, Chapter 2]. His "theory" of genetic assimilation – as he sometimes used to call it[8] – entirely relies on the concept of canalization, to such an extent that it can be seen as only the extrapolation of his understanding of developmental processes in an evolutionary perspective. Thus, with a few exceptions, what has been called the "canalization heuristic" of Waddington's model still remains to be fully engaged [10].

Since his first publication in 1942, Waddington clearly expressed his findings in the Lamarckian terminology of the inheritance of acquired characters. This also helps to understand why his ideas were marginalized by the founders of the Modern Synthesis and why he was sometimes depicted as a "frustrated neo-Lamarckian" [42, p. 272]. But why was he so insistent in his use of Lamarckian terms? The answer, rightly emphasized by Lewin [42], is that Waddington was convinced that genetic assimilation is a genuine mechanism of inheritance of acquired characters, but in a sense that does not fulfil the traditional Weismannian criterion, implying a physiological retroaction of the phenotype on the germplasm.

The nascent Modern Synthesis contrasted only two alternative explanations of adaptation: natural selection of blind genetic mutations and Lamarckian inheritance (i.e. the existence of a physiological process liable to transfer phenotypic variation to the next generation). All along, Waddington disputed the validity of this alternative [27, pp. 150-151, p. 164, 28, p. 563, 54, pp. 54-55, 61, p. 278]. Based entirely on classical genetic knowledge [22, p. 290], he thought of genetic assimilation as an actual mechanism of inheritance of acquired characters [27, p. 176] liable to explain at least some cases of adaptations. But canalization, not soft inheritance, was to him the conceptual key to understand how individual variations, although not hereditary transmitted, could be the starting point of microevolutionary processes. Since Lamarck, each Lamarckian theory had to face a problematic paradox that was explicitly formulated only at the very end of the nineteenth century [62, pp. 192-196]: the mechanism of inheritance of acquired characters requires organisms to be plastic enough to acquire a new character, and, at the same time, not to be too plastic for this new character to become hereditary. Even if Waddington did not believe in the possibility of soft inheritance, his claim that genetic assimilation must be seen as a genuine mechanism of inheritance of acquired character forced him to face the problematic issue of the balance between plasticity and robustness. Not only did he face it, but he finally came to *define* the concept of canalization in order to overcome this theoretical difficulty [22, pp. 269-270, my emphasis]:

[8] Waddington did not use the term "theory" lightly. It implies that he considered genetic assimilation to be a sufficiently elaborated explanation to deserve to be called that, which was obviously not the case of the Baldwin effect.

> "Genetic assimilation obviously involves the somewhat paradoxical character of phenotypes to be, on the one hand, to some extent susceptible and, on the other, to some extent resistant, to alteration by environmental agencies. It is only because development can be modified by the environment that an acquired character can appear in the first place, when a population is transferred from environment E to environment E'; but when this character becomes assimilated, that implies that the development of the phenotype is now resistant to the effects of changing the environment back from E' to E. *The property of a developmental process, of being to some extent modifiable, but to some extent resistant to modification, has been referred to as its "canalization"* (Waddington, 1940a)."

No doubt Waddington was a Darwinian, i.e, he was convinced that biological teleonomy was *ultimately* produced by natural selection of random variations. What he contested was the framework of population genetics that was at the basis of the Modern Synthesis. This framework equates the regulatory principle of variation/selection with the concrete processes currently at work in modern populations of organisms. In other words, population genetics ignored the fact that an organism – and for Waddington, crucially, especially an animal – is not a collection of alleles that could each be ascribed a selective coefficient, but a highly-evolved and constrained system whose epigenetic landscape is already a set of more or less canalized pathways [27, p. 189]. Consequently, nowadays evolutionary dynamics are also driven by genetic assimilation.

To be sure, Waddington's own synthesis was only sketchy and incomplete and as such marred by several limitations. The most central might be the one already emphasized by Williams in 1966 – namely, that the evolutionary building of an epigenetic landscape must be explained in the first place. According to Williams, this creates a paradoxical asymmetry because Waddington "finds the theory of natural selection entirely adequate to explain facultative adaptations, but feels that this theory has a "major gap" in its application to fixed adaptations" [6, p. 82] (for a critique of Williams' critique, see [63, pp.199-203]). Wilkins made a variation on the same point, remarking recently that Waddington "never seems to have asked himself how these alternative capacities might themselves have arisen" [9, p. 230]. Yet, despite all these gasps and weaknesses, Waddington's critique of the atomistic perspective of Neo-Darwinian population genetics seems to retain some accuracy today [9]. It might therefore still be the case that the synthesis between genetics, development and evolution that Waddington tried to elaborate cannot be easily integrated into the standard Modern Synthesis framework. For genetic assimilation to become a (small) part of it, it had to be weakened to become something closer to the Baldwin effect – which is exactly what happened.

Acknowledgements

I would like to thank Vincent Debat and Arnaud Le Rouzic for inviting me to contribute to this special issue on canalization and for their helpful comments throughout the elaboration of this paper. I would like also to thank the two anonymous reviewers for their insightful remarks and suggestions. The ideas presented here were first discussed in Montpellier, Roma and Paris in 2017, and of course benefited from the exchanges that followed each presentation. I am especially grateful to my colleague Guillaume Achaz, who, as a population geneticist, was able to see things that are difficult to grasp for a historian of science. Last but not least, the final version was edited by Jean-Yves Bart.

References

[1] A.S. Wilkins, Canalisation: A molecular genetic perspective, BioEssays 19 (1997) 257-262.
[2] M.L. Siegal, A. Bergman, Waddington's canalization revisited: Developmental stability and evolution, PNAS 99 (16) (2002) 10528-10532.
[3] T. Flatt, The evolutionary genetics of canalization, The Quarterly Review of Biology 80 (2005) 287-316.
[4] S. Rutherford, S. Lindquist, Hsp90 as capacitor for morphological evolution, Nature 396 (1998) 336-342.
[5] E. Mayr, Animal Species and Evolution, Cambridge, Belknap Press of Harvard University Press, 1963.
[6] G.C. Williams, Adaptation and natural selection, Princeton, Princeton University Press.
[7] M. Pigliucci, G.B. Müller (eds.), Evolution – the Extended Synthesis, Cambridge, London, The MIT Press, 2010.
[8] M.J. West-Eberhard, Developmental Plasticity and Evolution, Oxford, Oxford University Press, 2003.
[9] A.S. Wilkins, Waddington's Unfinished Critique of Neo-Darwinian Genetics: Then and Now, Biological Theory 3 (3) (2008) 224-232.
[10] J. Masel, Genetic assimilation can occur in the absence of selection for the assimilating phenotype, suggesting a role for the canalization heuristic, Journal of Evolutionary Biology 17 (2004) 1106-1110.
[11] C.H. Waddington, Genetic assimilation of an acquired character, Evolution 7 (1953) 118-126.
[12] C.H. Waddington, Genetic assimilation of the bithorax phenotype, Evolution 10 (1956) 1-13.
[13] C.H. Waddington, Canalization of development and genetic assimilation of acquired characters, Nature 183 (1959) 1654-1655.
[14] C. Deans, K. Maggert, What Do You Mean, "Epigenetic"?, Genetics 199 (2015) 887-896.
[15] D. Noble, Conrad Waddington and the origin of epigenetics, Journal of Experimental Biology 218 (2015) 816-818.
[16] D. Haig, The (Dual) Origin of Epigenetics, Cold Spring Harbor Symposia on Quantitative Biology 69 (2004) 67-70.
[17] J.B. Losos (ed.), The Princeton Guide to Evolution, Princeton and Oxford, Princeton University Press, 2017.
[18] M. Pigliucci, C.J. Murren, C.D. Schlichting, Phenotypic plasticity and evolution by genetic assimilation, The Journal of Experimental Biology 209 (2006) 2362-2367.
[19] S.F. Gilbert, Diachronic Biology Meets Evo-Devo: C.H. Waddington's Approcah to Evolutionary Developmental Biology, American Zoologist 40 (2000) 729-737.
[20] A. Pocheville, E. Danchin, Genetic assimilation and the paradox of blind variation, in P. Huneman, D. Walsh (eds.), Challenges to the Modern Synthesis, Oxford, Oxford University Press, 111-136.
[21] B.K. Hall, Organic Selection: Proximate Environmental Effects on the Evolution of Morphology and Behaviour, Biology and Philosophy 16 (2001) 215-237.
[22] C.H. Waddington, Genetic assimilation, Advances in Genetics 10 (1961) 257-290.
[23] G.G. Simpson, The Baldwin effect, Evolution 7 (1953) 110-117.
[24] C.H. Waddington, The 'Baldwin effect,' 'genetic assimilation,' and 'homeostasis', Evolution 7 (1953) 386-387.

[25] A.V. Badyaev, Evolutionary significance of phenotypic accommodation in novel environments: an empirical test of the Baldwin effect, Philosophical transactions of the Royal Society B 364 (2009) 1125-1141.
[26] J. Huxley, Evolution, The Modern Synthesis, London, George Allen & Unwin Ltd, 1942.
[27] C.H. Waddington, The Strategy of the Genes, London, Allen and Unwin, 1957.
[28] C.H. Waddington, Canalization of development and the inheritance of acquired characters, Nature 150 (1942) 563-565.
[29] B.K. Hall, Waddington's Legacy in Development and Evolution, American Zoologist 32 (1992) 113-122.
[30] V. Debat, P. David, Mapping phenotypes: canalization, plasticity and developmental stability, Trends in Ecology and Evolution 16 (10) (2001) 555-561.
[31] J.M.W. Slack, Conrad Hal Waddington: the last Renaissance biologist?, Nature Reviews Genetics 3 (2002) 889-895.
[32] E.L. Peterson, The life organic, The theoretical biology club and the roots of epigenetics, Pittsburgh, University of Pittsburgh Press, 2016.
[33] C.H. Waddington, Organizers and Genes, Cambridge, Cambridge University Press, 1940.
[34] J.B.L. Bard, Waddington's Legacy to Developmental and Theoretical Biology, Biological Theory 3 (3) (2008) 188-197.
[35] S.F. Gilbert, Epigenetic Landscaping: Waddington's Use of Cell Fate Bifurcation Diagrams, Biology and Philosophy 6 (1991) 135-154.
[36] S.F. Gilbert, Dobzhansky, Waddington and Schmalhausen: Embryology and the Modern Synthesis, in M.B. Adams (ed.), The Evolution of Theodosius Dobzhanky: Essays on His Life and Thought in Russia and America, Princeton, Princeton University Press, 1994, 143-154.
[37] C.H. Waddington, Evolution of developmental systems, Nature 147 (1941) 108-110.
[38] M. Pigliucci, Phenotypic plasticity, in M. Pigliucci, G.B. Müller (eds.), Evolution – the Extended Synthesis, Cambridge, London, The MIT Press, 355-378.
[39] I.M. Ehrenreich, S.W. Pfennig, Genetic assimilation: a review of its potential proximate causes and evolutionary consequences, Annals of Botany 117 (2016) 769-779.
[40] E. Crispo, The Baldwin Effect and Genetic Assimilation: Revisiting Two Mechanisms of Evolutionary Change Mediated by Phenotypic Plasticity, Evolution 61 (2007) 2469-2479.
[41] M.W. Ho, P.T. Saunders, Beyond neo-Darwinism – An Epigenetic Approach to Evolution, Journal of Theoretical Biology 78 (1979) 573-591.
[42] P.D. Lewin, Embryology and the Evolutionary Synthesis: Waddington, Development and Genetics, PhD in Philosophy, University of Leeds, Department of Philosophy, 1998.
[43] A.S. Wilkins, The Evolution of Developmental Pathways, Sinauer, 2002.
[44] D.M. Ruden, M.D. Garfinkel, V.E. Sollars, X. Lu, Waddington widget: Hsp90 and the inheritance of acquired characters, Seminars in Cell & Developmental Biology 14 (2003) 301-310.
[45] R.A. Zabinsky, G.A. Mason, C. Queitsch, D.F. Jarosz, It's not magic – Hsp90 and its effects on genetic and epigenetic variation, Seminars in Cell and Developmental Biology (2018), in press.
[46] B. Hallgrimsson, R.M. Green, D. Katz, J.L. Fish, F.P.J. Bernier, C.C. Roseman, N.M. Young, J.M. Cheverud, R.S. Marcucio, The Developmental-Genetics of Canalization, Seminars in Cell and Developmental Biology (2018), in press.
[47] K. Geiler-Samerotte, F.M.O. Sartori, M.L. Siegal, Decanalizing thinking on genetic canalization, Seminars in Cell and Developmental Biology (2018), in press.
[48] C. Stern, Selection for sub-threshold differences and the origin of pseudo-exogenous adaptations, American Naturalist 92 (1958) 313-316.

[49] C. Stern, Variation and hereditary transmission, Proceedings of the American Philosophical Society 103 (1959) 183-189.
[50] K.G. Bateman, Genetic assimilation of four venation phenocopies, Journal of Genetics, 56 (1959) 443-474.
[51] I. Dworkin, Towards a genetic architecture of cryptic variation and genetic assimilation: the contribution of K.G. Bateman, Journal of Genetics 84 (3) (2005) 223-226.
[52] W. Scharloo, Canalization – genetic and developmental aspects, Annual Review of Ecology and Systematics 22 (1991) 65-93.
[53] D.S. Falconer, T.F.C. Mackay, Introduction to Quantitative Genetics, Essex, Longman, 1996.
[54] C.H. Waddington, Inheritance of acquired characters, Proceedings of the Linnean Society, London 169 (1958) 54-61.
[55] E. Mayr, Where Are We?, Cold Spring Harbor Symposia on Quantitative Biology 24 (1959) 1-14.
[56] J. Cairns, J. Overbaugh, S. Miller, The origin of mutants, Nature 355 (1988) 142-145.
[57] F. Merlin, Mutations et aléas, le hasard dans la théorie de l'évolution, Paris, Hermann, 2013.
[58] K.G. Bateman, Genetic assimilation of the dumpy phenocopy, Journal of Genetics 56 (1959) 341-352.
[59] C.H. Waddington, The genetic control of wing development in Drosophila, Journal of Genetics 39 (1940) 75-139.
[60] E. Jablonka, M.J. Lamb, Epigenetic Inheritance and Evolution, The Lamarckian Dimension, Oxford, Oxford University Press, 1995.
[61] C.H. Waddington, Selection of the genetic basis for an acquired character, Nature 169 (1952) 278.
[62] L. Loison, Qu'est-ce que le néolamarckisme ? Les biologistes français et la question de l'évolution des espèces, 1870-1940, Paris, Vuibert, 2010.
[63] E. Sobber, The Nature of Selection, Evolutionary Theory in Philosophical Focus, Chicago and London, The University of Chicago Press, 1993.