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THE SHADOW OF A MECHANISM

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I stumbled across Conrad H. Waddington's 1942 paper a few years after my PhD while unwittingly retracing some of his thinking in the context of a narrow but illustrative toy-model of development, understood as a mapping from genotype to phenotype(s) (see Ancel and Fontana 2000; Fontana 2002). Digesting his paper and following its thread through his other writings made it clear that I hadn't said much that Waddington didn't already say fifty years prior. His prescience and subtle precision of thought at a time when far less was known than today are stunning. This is my brief take on it.

C. H. Waddington, "Canalization of Development and the Inheritance of Acquired Characters," *Nature* 150, 563–565 (1942).

The Darwinian framework of evolution through heritable variation and natural selection is the foundation for explaining adaptation, the functional integration of living systems and their environment. Consider, for example, the evolution of different shapes of bird beaks, such as long and pointed or short and stout, adapted to tapping distinct sources of food like fruits, seeds, or insects. A short and thick beak is not a useful tool for picking seeds from a cactus. As a consequence, there is a tendency for evolution to remodel the beak in a search process based on mutation and selection as posited by the Darwinian framework. Varying the timing of the action of "calmodulin," "bone morphogen protein 4," and other molecular players makes mechanistically intelligible how a blind evolutionary process can find a suitable beak (Wu *et al*. 2004; Abzhanov *et al*. 2004; Mallarino *et al*. 2011). Waddington did not know about any of these, but not knowing exactly which levers mutation and selection can play with is not an impediment to being, in principle, satisfied with the conceptual adequacy of the Darwinian foundation. Today, given the impressive tapestry of empirical evidence grounding Darwin's framework in mechanism, there is nothing implausible about the evolution of strong yet hollow bones in birds, even though we do not know in every detail how it happened.

The conceptual sufficiency of the Darwinian search process derives from a mechanism that does not prejudge what the search comes up with. It is a matter of theory to figure out what is contingent and what is necessary about evolutionary outcomes. The dearth of theory in regard does not affect the plausibility that any theory, once built, would be situated within the general framework. Human cognition, attuned to functional relations, might predict a long and pointed beak as a solution to the cactus problem, but this does not make it implausible that a search devoid of cognition comes up with that same solution. There is no final cause, only local guidance from gradients on a fitness landscape whose structure may be complex, shifting in time, and ill-understood. Darwin proposed a paradigm, not a theory.

Contrast this with situations that involve another kind of adaptation, one in which an individual organism adapts *during its lifetime* to environmental circumstances. Such real-time adjustment is a consequence of the varying degrees of plasticity that living systems are capable of. Today, we know that this flexibility arises from manifold interconnected processes of regulation in response to physical and chemical cues within and outside the organism. A so-adapted state is not hereditary, since it requires a persistent interaction with the environment to come about. Waddington notes that many cases exist in which evolution appears to have genetically "hardwired" an organismic state that was previously attainable only through experience, as it were. The problem now is that we are asked to believe in the blindness and rapidity of a search process arriving at the same solution that was successfully tried out in advance through real-time adaptation. This hinges on too much coincidence. It seems more plausible to assume that the suitability of an organismic reaction to the environment orchestrates the necessary genetic changes that make it heritable. Such an assumption, however, would shatter the Darwinian framework into Lamarckian pieces.

Waddington mentions by way of example the callosities of ostriches. These patches of thickened skin are situated on the sternum and near the tail, both of which rub against the ground when the ostrich is in a crouching position. Callouses like these arise plastically from continued friction, and since they are useful for the ostrich, it might be advantageous for them to be genetically hardwired. Indeed, these callosities have become

hereditary and form already in the embryo who has never been subject to friction on hard ground. Many cases of this sort exist in nature and many can be generated through breeding in the laboratory, as Waddington (1959) himself did. In sum, the Darwinian paradigm is plausible when its outcomes are *not directly* inducible by the environment and appears at risk when they are, because it raises the suspicion that "use and disuse" are *directly* complicit in causing genetic change rather than being jury of random trials.

This apparent Lamarckian phenomenon was debated by several evolutionists—among them J. M. Baldwin (1896), L. Morgan (1896) and H. F. Osborn (1896)—around 1896, forty-six years before Waddington's paper. It is instructive to follow Waddington's explanation by way of contrast to Baldwin's, which was laid out in a review by G. G. Simpson (1953). Simpson provided such a clear exposition of Baldwin's explanation that it henceforth became known as the Simpson–Baldwin effect, ironically despite Simpson suggesting that Baldwin's explanation is no explanation at all. Simpson summarizes Baldwin's reasoning as follows:

1. Individual organisms interact with the environment in such a way as systematically to produce in them non-hereditary adaptations that are advantageous to the individuals having them.

2. Mutations ("genetic factors") producing similar traits as in 1 occur in the population.

3. These mutations are favored by natural selection (as they don't require the machinery for dynamically generating the adaptation) and tend to spread in the population.

The net result is that adaptation, originally individual and nonhereditary, has become hereditary. The crux, according to Simpson, is the *absence* of any logical connection between 1 and 2, for if there is one it could only be Lamarckian.

To fix what we are talking about, consider a simple hypothetical example at the molecular scale. Suppose an animal finds better food at high altitude. In response to lower oxygen levels the animal adapts by producing 2,3-diphosphoglycerate (DPG), which is a molecule that binds hemoglobin, altering its conformation, thereby lowering its oxygen affinity and causing

it to unload oxygen more thoroughly. This non-primary but advantageous behavior of hemoglobin, induced by an environmental condition via DPG, permits the population to linger in a hostile environment that provides a benefit. Following Baldwin's argument, eventually a random mutation occurs as a result of which hemoglobin achieves on its own what it previously required DPG for. Because of the continued exposure to the hostile environment, selection kicks in and spreads the mutant to fixation in the population. This process hardwires genetically a previously acquired characteristic (of hemoglobin) in a fashion wholly compatible with the Darwinian framework. Baldwin and everyone else at the time emphasized the independence of 2 (the origination of appropriate mutations) from 1 (plasticity). In particular, the random mutation would have eventually occurred regardless of plasticity and exposure to high altitude—it just would not have been selected; the only contribution from plasticity is that it permits continued exposure to a specific selection pressure. This, however, makes Baldwin's solution nearly vacuous, since we are being asked again to suspend disbelief that somehow the right mutation (or, more likely, several required mutations) show up whose effect happens to be precisely the previously plastically induced property.

Simpson could be read as dismissing the significance of the whole phenomenon alongside Baldwin's explanation, whereas Waddington must have felt that the phenomenon of a plastic adaptation becoming heritable tells us something important about evolution. Waddington (1953) thus wrote a reply to Simpson's paper, in which he objects that Simpson has overlooked a possible logical connection between 1 and 2 that is neither Lamarckian nor Baldwinian: Genotypes with "the ability to produce an adaptive phenotype would [. . .] encourage the appearance of genetically controlled variants mimicking the adaptive type." This is classic Waddingtonian and needs some decryption. "The ability to produce an adaptive phenotype" refers to plasticity and "the appearance of genetically controlled variants" refers to mutations. The operative word here is "encourage," as in "making more probable." Back to the hemoglobin story.

A protein, such as hemoglobin, is a sequence of amino acids folding into a native three-dimensional structure by virtue of a complex network of interactions between the side chains. This structure conveys chemical and

biological function. Given a protein, we can think of a conformation as a point on a landscape that assigns to every three-dimensional conformation a free energy. This landscape is high-dimensional, in indication of the many possible physical displacements that lead from a given conformation to neighboring ones—an Alpine terrain but with high-dimensional versions of passes, plateaus, saddle points, troughs, peaks, ridges, and valleys. The folding process traces a path guided by energy gradients on that landscape and ends up in a particular trough: the native configuration. It is easy to imagine the existence of nearby troughs, albeit separated by barriers. Our sequence could fold into one of the nearby troughs, but to do so would require a kick, such as an interaction with DPG. In the case of DPG, the interaction occurs between its negatively charged phosphate groups and specific positively charged lysine and histidine residues in hemoglobin. Thus, alternative shapes reveal themselves in response to exogenous triggers. However, chemical interactions, such as hydrogen bonds or electrostatic bonds, are completely *fungible*: nothing rides on the binding partner being specifically DPG; it could be any other molecule as long as it provides chemical groups with electrostatic charges in the proper positions. In fact, it could be a chemical group within hemoglobin itself, such as a suitable amino acid residue! It is, therefore, highly *likely* that some amino acid substitution can coax the network of extant interactions to switch into the conformation they were already capable of adopting in the presence of DPG. Conversely, it seems highly *unlikely* for such a substitution to achieve the same outcome in the context of an interaction network that cannot switch into the advantageous conformation even in the presence of DPG. This is Waddington's explanation. It obviates the need to suspend disbelief in the magical appearance of the right mutation(s) that would hardwire a plastically attained adaptation, because these mutations are bound to be readily accessible due to the mechanism enabling plasticity in the first place. The proverbial monkey being tasked with writing a meaningful sentence is vastly more likely to do so if given a typewriter than a pen. Waddington's insight could not be more different than Baldwin's.

Waddington develops his explanation in a different, necessarily far less mechanistic language and against the more complex background of developmental processes. The stylized hemoglobin example provided us with discrete (coarse-grained) conformational states, so we could speak of a "switch" at the level of a single molecule by virtue of its interaction with DPG. For Waddington's argument to work, development of an organism must have likewise acquired some quasi-discrete structure that allows one to speak of developmental trajectories that are meaningfully distinguishable from one another in the face of noise or perturbation. Waddington (1940, p.91) uses the term "epigenetic landscape" for what mathematicians call the *phase space* of a dynamical system. The landscape of conformations in the hemoglobin example plays the role of the epigenetic landscape. Waddington spends most of his paper arguing that natural selection has sculpted the epigenetic landscape into identifiable valleys separated by barriers. This structure creates developmental trajectories and enables them to reliably reach defined endpoints. He refers to such a phase space as "canalized" and the action of selection leading to this structure as "canalizing." (See Wagner, Booth, and Bagheri-Chaichian 1997; Ancel and Fontana 2000; Siegal and Bergman 2002 for computational models that have contributed to elucidating the circumstances under which canalization occurs.) Waddington dwells on canalization, because it allows him to cast the effects of mutations in semi-discrete terms such as the switching of states by crossing or shifting thresholds and sculpting the epigenetic landscape (Waddington 1957) to internalize external signals.

While all this is sensible, I felt that the quote from his reply to Simpson was the closest he came to succinctly stating a principle. *Waddington is asserting what even today is all too often forgotten: that a mutation at the genetic level may be random, but its consequences at the phenotypic level are not, because a mechanism necessarily biases in specific ways the effects of its modification.* This is true in particular for mechanisms with a prior evolutionary history, since they are canalized. A mechanism that implements plasticity by enabling input signals to switch among a repertoire of behaviors is vastly more likely to be modified by a genetic mutation in such a way as to make any of these behaviors independent of the trigger signal. I refer to these preferred directions of change as the "shadow" of a mechanism.

As a final thought I would like to draw attention to an unspoken assumption. Waddington's theory implicitly posits an alignment of sorts between possibilities whose realization is dependent on agents external to the organism, such as signals, and possibilities whose realization is entirely dependent on agents internal to the organism, such as genes. In the hemoglobin story, for example, this alignment is built into the physics of folding (where the "genes" are the amino acids along the sequence). As if by revenge, contemplating the limits of the alignment between plastic and genetic realizability leads us back to Baldwin. Baldwin was an evolutionary psychologist and his paradigmatic case of plasticity was *learning*. Even if the capacity to learn is entirely genetically determined, what we learn is certainly not. Depending on the specific mechanism, learning can open up vast ranges of plasticity. It stands to reason that many ranges of plastic possibility are *not* aligned, and perhaps even impossible to align, with genetic realizability. If someone has learned how to solve Rubik's cube in a few seconds, it does not follow that mutations are readily at hand whose effect is to hardwire this skill genetically. Some mechanisms may cast no shadow. It is tempting to speculate that the elaboration of learning mechanisms eventually opened the floodgates to the infinitely plastic and genetically non-alignable, morphing biology into something alien to the Darwinian framework that gave rise to it.

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REFERENCES

Abzhanov, A., M. Protas, B. R. Grant, P. R. Grant, and C. J. Tabin. 2004. "*Bmp4* and Morphological Variation of Beaks in Darwin's Finches." *Science* 305 (5689): 1462–1465. https://doi.org/10.1126/science.1098095.

Ancel, L., and W. Fontana. 2000. "Plasticity, Evolvability, and Modularity in RNA." *Journal of Experimental Zoology,* https://doi.org/10.1002/1097-010X(20001015)288:3<242::AID-JEZ5>3.0.CO;2-O.

Baldwin, J. M. 1896. "A New Factor in Evolution." *The American Naturalist* 30 (354): 441–451. https://doi.org/10.1086/276408.

Fontana, W. 2002. "Modelling 'Evo–Devo' with RNA." *BioEssays* 24 (12): 1164–1177. https://doi.org/10.1002/bies.10190.

Mallarino, R., P. R. Grant, B. R. Grant, A. Herrel, W. P. Kuo, and A. Abzhanov. 2011. "Two Developmental Modules Establish 3D Beak-Shape Variation in Darwin's Finches." *Proceedings of the National Academy of Sciences USA* 108 (10): 4057–4062. https://doi.org/10.1073/pnas.1011480108.

Morgan, C. L. 1896. *Habit and Instinct.* London, UK: Arnold.

Osborn, H. F. 1896. "Ontogenic and Phylogenic Variation." *Science* 4 (100): 786–789. https://doi.org/10.1126/science.4.100.786.

Siegal, M. L., and A. Bergman. 2002. "Waddington's Canalization Revisited: Developmental Stability and Evolution." *Proceedings of the National Academy of Sciences USA* 99 (16): 10528–10532. https://doi.org/10.1073/pnas.102303999.

Simpson, G. G. 1953. "The Baldwin Effect." *Evolution* 7 (2): 110–117. https://doi.org/10.1111/j.1558-5646.1953.tb00069.x.

Waddington, C. H. 1940. *Organisers & Genes.* 182. Cambridge, UK: Cambridge University Press.

———. 1942. "Canalization of Development and the Inheritance of Acquired Characters." *Nature* 150 (3811): 563–565. https://doi.org/10.1038/150563a0.

———. 1953. "The 'Baldwin Effect,' 'Genetic Assimilation' and 'Homeostasis'." *Evolution* 7 (4): 386–387. https://doi.org/10.1111/j.1558-5646.1953.tb00099.x.

———. 1957. *The Strategy of the Genes.* London, UK: George Allen & Unwin.

———. 1959. "Canalization of Development and Genetic Assimilation of Acquired Characters." *Nature* 183 (4676): 1654–1655. https://doi.org/10.1038/1831654a0.

Wagner, G. P., G. Booth, and H. Bagheri-Chaichian. 1997. "A Population Genetic Theory of Canalization." *Evolution* 51 (2): 329–347. https://doi.org/10.1111/j.1558-5646.1997.tb02420.x.

Wu, P., T.-X. Jiang, S. Suksaweang, R. B. Widelitz, and C.-M. Chuong. 2004. "Molecular Shaping of the Beak." *Science* 305 (5689): 1465–1466. https://doi.org/10.1126/science.1098109.

CANALIZATION OF DEVELOPMENT AND THE INHERITANCE OF ACQUIRED CHARACTERS

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The battle, which raged for so long between the theories of evolution supported by geneticists on one hand and by naturalists on the other, has in recent years gone strongly in favour of the former. Few biologists now doubt that genetical investigation has revealed at any rate the most important categories of hereditary variation; and the classical 'naturalist' theory—the inheritance of acquired characters—has been very generally relegated to the background because, in the forms in which it has been put forward, it has required a type of hereditary variation for the existence of which there was no adequate evidence. The long popularity of the theory was based, not on any positive evidence for it, but on its usefulness in accounting for some of the most striking of the results of evolution. Naturalists cannot fail to be continually and deeply impressed by the adaptation of an organism to its surroundings and of the parts of the organism to each other. These adaptive characters are inherited and some explanation of this must be provided. If we are deprived of the hypothesis of the inheritance of the effects of use and disuse, we seem thrown back on an exclusive reliance on the natural selection of merely chance mutations. It is doubtful, however, whether even the most statistically minded geneticists are entirely satisfied that nothing more is involved than the sorting out of random mutations by the natural selective filter. It is the purpose of this short communication to suggest that recent views on the nature of the developmental process make it easier to understand how the genotypes of evolving organisms can respond to the environment in a more co-ordinated fashion.

It will be convenient to have in mind an actual example of the kind of difficulties in evolutionary theory with which we wish to deal.

We may quote from C. and Richards (1936): "A single case will make the difficulty clear. Duerden (1920) has shown that the sternal, alar, etc., callosities of the ostrich, which are undoubtedly related to the crouching position of the bird, appear in the embryo. The case is analogous to the thickening of the soles of the feet of the human embryo attributed by Darwin (1901) 'to the inherited effects of pressure.' As Detlefsen (1925) points out, this would have to be explained on selectionist grounds by the assumption that it was of advantage to have the callosities, as it were, preformed at the place at which they are required in the adult. But it is a large assumption that variations would arise at this place and nowhere else."

In this case we have an adaptive character (the callosities) of a kind which it is known can be provoked by an environmental stimulus during a single lifetime (since skin very generally becomes calloused by continued friction) but which is in this case certainly inherited. The standard hypotheses which come in question are the two considered by Robson and Richards: the Lamarckian explanation in terms of the inheritance of the effects of use, which they cannot bring themselves to support at all strongly, and the 'selectionist' explanation, which, in the form in which they understand it, leaves entirely out of account the fact that callosities may be produced by an environmental stimulus and postulates the occurrence of a gene with the required developmental effect. A third possible type of explanation is to suppose that in earlier members of the evolutionary chain, the callosities were formed as responses to external friction, but that during the course of evolution the environmental stimulus has been superseded by an internal genetical factor. It is an explanation of this kind which will be advanced here.

The first step in the argument is one which will scarcely be denied but is perhaps often overlooked. The capacity to respond to an external stimulus by some developmental reaction, such as the formation of a callosity, must itself be under genetic control. There is little doubt, though no positive evidence in this particular case so far as I know, that individual ostriches differ genetically in the responsiveness of their skin to friction and pressure. If we suppose, then, that in the early ostrich ancestors callosities were formed by direct response to external pressure, there would be a natural selection among the birds for a genotype which

gave an optimum response.

The next point to be put forward is the one which is, perhaps, new in such discussions, and which therefore requires the most careful scrutiny. It is best considered as one general thesis and one particular application of it.

The main thesis is that developmental reactions, *as they occur in organisms submitted to natural selection*, are in general canalized. 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.

The evidence for this comes from two sides, the embryological and the genetical. In embryology we have abundant evidence of canalization on two scales. On the small scale of single tissues, one may direct attention to the obvious but not unimportant fact that animals are built up of sharply defined different tissues and not of masses of material which shade off gradually into one another. Similarly, from the experimental point of view, it is usual to find that, while it may be possible to steer a mass of developing tissue into one of a number of possible paths, it is difficult to persuade it to differentiate into something intermediate between two of the normal possibilities. Passing from the scale of tissues to that of organs, it is not too much to claim it as a general rule that there is some stage in every life-history (though it may be an extremely early and short stage) when minor variations in morphology become 'regulated' or regenerated; and that is, again, a tendency to produce the standard end-product. Of course neither of these types of canalization is absolute. Morphological regulation may fail if the abnormalities are too great or occur too late in development; and intermediate types of tissue can occasionally be found, particularly in pathological conditions.

The limitations on canalization which are important for our present purposes can better be seen when the problem is viewed from the other, genetical, side. The canalization, or perhaps it would be better to call it the buffering, of the genotype is evidenced most clearly by constancy of the wild type. It is a very general observation to which little attention has been directed (but see Huxley 1942; Plunkett 1932; Ford 1940) that the wild type of an organism, that is to say, the form which occurs in

Nature under the influence of natural selection, is much less variable in appearance than the majority of the mutant races. In Drosophila the phenomenon is extremely obvious; there is scarcely a mutant which is comparable in constancy with the wild type, and there are very large numbers whose variability, either in the frequency with which the gene becomes expressed at all or in the grade of expression, is so great that it presents a considerable technical difficulty. Yet the wild type is equally amazingly constant. If wild animals of almost any species are collected, they will usually be found 'as like as peas in a pod.' Variation there is, of course, but of an altogether lesser order than that between the different individuals of a mutant type.

The constancy of the wild type must be taken as evidence of the buffering of the genotype against minor variations not only in the environment in which the animals developed but also in its genetic make-up. That is to say, the genotype can, as it were, absorb a certain amount of its own variation without exhibiting any alteration in development. Considerable stress has been laid in recent years on certain aspects of this buffering. Fisher (1928) and many authors following him have discussed 'the evolution of dominance,' by which the genotype comes to be able to produce the standard developmental effects even when certain genes have been replaced by others of less efficiency. Again, Stern (1929) and Muller (1932) directed attention to the phenomenon of 'dosage compensation,' by which it comes about that a single dose of a sex-linked gene in the heterogametic sex has the same developmental effect as a double dose in the homogametic. These two processes are part of the larger phenomenon which we have called the canalization of development. This also includes other, at first sight unrelated, features of the genotypic control of development. For example, attention has been directed (Waddington 1940a) to genes which cause certain regions of developing tissue to take an abnormal choice out of a range of alternative possible paths; K. and de Winton (1941) have recently spoken of such genes as 'switch genes.' Finally, Goldschmidt has shown that environmental stimuli may, by switching development into a path which is usually only followed under the influence of some particular gene, produce what he has called a 'phenocopy' of a previously known mutant type.

There seems, then, to be a considerable amount of evidence from a number of sides that development is canalized in the naturally selected animal. At the same time, it is clear that this canalization is not a necessary characteristic of all organic development, since it breaks down in mutants, which may be extremely variable, and in pathological conditions, when abnormal types of tissue may be produced. It seems, then, that the canalization is a feature of the system which is built up by natural selection; and it is not difficult to see its advantages, since it ensures the production of the normal, that is, optimal, type in the face of the unavoidable hazards of existence.

The particular application of this general thesis which we require in connexion with 'the inheritance of acquired characters' is that a similar canalization will occur when natural selection favours some characteristic in the development of which the environment plays an important part. It is first necessary to point out the ways in which the environment can influence the developmental system. If we conceptually rigidify such a system into a definite formal scheme, we can think of it as a set of alternative canalized paths; and the environment can act either as a switch, or as a factor involved in the system of mutually interacting processes to which the buffering of the paths is due. This is, of course, too dead and formal a scheme to be a true picture of development as it actually occurs. In so far as it is always to some extent, but not entirely, a matter of convenience what we decide to call a complete organ, so far will it be a matter of convenience what we consider to be different alternative paths; and the question of whether a given influence is thought of as a switch mechanism or a modification of a path will depend on how we choose our alternatives. There are some cases, however, in which the alternatives are very clearly defined. Thus it is commonly assumed that the evolution of sexuality passed through a stage in which, as in Bonellia, the environment acted as a switch between two well-defined alternatives; later, genetic factors arose which superseded the environmental determination by an internal one.

More commonly, however, the original environmental effect will be to produce a modification of an already existent developmental path. Thus in the case of the ostrich ancestors, the formation of callosities following environmental stimulation is a response by a developmental

system which is normally present in vertebrates. This system must, in all species, be subject to natural selection; outside certain limits, too great or too low a reactivity of the skin would be manifestly disadvantageous. If we suppose that the callosities, when they were first evolved, were dependent on the environmental stimulus, then the evolution appears as a readjustment of the reactivity of the skin to such a degree that a just sufficient thickening is produced with the normally occurring stimulus.

There would appear to be two possible ways in which such a development might be organized. It might on one hand remain uncanalized, the formation of the thickening in each individual depending on the reception of the adequate stimulus, to which the response remained strictly proportional. If this possibility was realized, the well-known difficulty of accounting for the hereditary fixation of the character remains unimpaired. The alternative is that the development does become canalized, to a greater or lesser extent. In that case, the magnitude of the response would not be proportional to that of the stimulus; there would be a threshold of stimulus, above which the optimum (that is, naturally selected) response would be formed. In so far as the response became canalized, the environment would be acting as a switch.

Systems of either type can be built up by natural selection, and one can point to examples of them in animals at the present day. The reaction of the patterns on Lepidopteran wings (for example, in Ephestia, Kühn 1936) to temperature during the sensitive period scarcely seems to involve thresholds, while the metamorphosis of the axolotl, for example, clearly does. In general, it seems likely that the optimum response to the environment will involve both some degree of proportionality and some restriction of this by canalization. The most favourable mixture of the two tendencies will presumably differ for different characters. It is easy to see why a much sharper distinction between alternatives is generally evolved in connexion with sex differences than with the degree of muscular development, for example; but even the former is to some extent modifiable by extreme and specialized environmental disturbances (heavy and early hormone treatment), and even the latter has some degree of genetic determination.

The canalization of an environmentally induced character is accounted for if it is an advantage for the adult animal to have some optimum degree of development of the character irrespective of the exact extent of stimulus which it has met in its early life; if, for example, it is an advantage to the young ostrich going out into the hard world to have adequate callosities even if it were reared in a particularly soft and cosy nest. Now in so far as the development of the character becomes canalized, the action of the external stimulus is reduced to that of a switch mechanism, simply in order that the optimum response shall be regularly produced. But switch mechanisms may notoriously be set off by any of a number of factors. The choice between the alternative developmental pathways open to gastrula ectoderm, for example, may be made by the normal evocator or by a number of other things (the mode of action of which may be through the release of the normal evocator (cf. Waddington 1940b), but which remain different to the normal evocator nevertheless). Again, we know many instances in which several different genes, by switching development into the same path, produce similar effects; and attention has already been directed to the 'phenocopying' of a gene by a suitable environmental stimulus. Thus once a developmental response to an environmental stimulus has become canalized, it should not be too difficult to switch development into that track by mechanisms other than the original external stimulus, for example, by the internal mechanism of a genetic factor; and, as the canalization will only have been built up by natural selection if there is an advantage in the regular production of the optimum response, there will be a selective value in such a supersession of the environment by the even more regularly acting gene. Such a gene must always act before the normal time at which the environmental stimulus was applied, otherwise its work would already be done for it, and it could have no appreciable selective advantage.

Summarizing, then, we may say that the occurrence of an adaptive response to an environmental stimulus depends on the selection of a suitable genetically controlled reactivity in the organism. If it is an advantage, as it usually seems to be for developmental mechanisms, that the response should attain an optimum value more or less independently of the intensity of stimulus received by a particular animal, then the reactivity will become canalized, again under the influence of

natural selection. Once the developmental path has been canalized, it is to be expected that many different agents, including a number of mutations available in the germplasm of the species, will be able to switch development into it; and the same considerations which render the canalization advantageous will favour the supersession of the environmental stimulus by a genetic one. By such a series of steps, then, it is possible that an adaptive response can be fixed without waiting for the occurrence of a mutation which, in the original genetic background, mimics the response well enough to enjoy a selective advantage.

REFERENCES

C., Robson G., and O. W. Richards. 1936. *The Variation of Animals in Nature.* London, UK: Longmans, Green / Co.

Darwin, C. 1901. *The Descent of Man, and Selection in Relation to Sex.* London, UK: John Murray.

Detlefsen, J. A. 1925. "The Inheritance of Acquired Characters." *Physiological Reviews* 5 (2): 244–278.

Duerden, J. E. 1920. "The Inheritance of the Callosities in the Ostrich." *The American Naturalist* 54:289.

Fisher, R. A. 1928. "The Possible Modification of the Response of the Wild Type to Recurrent Mutations." *The American Naturalist* 62 (679): 115–126.

Ford, E. B. 1940. "Genetic Research in the Lepidoptera." *Annals of Human Genetics* 10 (1): 227–252.

Huxley, J. H. 1942. *Evolution: The Modern Synthesis.* 74. London, UK: Allen & Unwin.

K., Mather, and D. de Winton. 1941. "Adaptation and Counter-Adaptation of the Breeding System in Primula." *Annals of Botany* 5 (2): 297–311.

Kühn, A. 1936. "Versuche über die Wirkungsweise der Erbanlagen." *Naturwissenschaften* 24:1–10.

Muller, H. J. 1932. "Further Studies on the Nature and Causes of Gene Mutations." In *Proceedings of the Sixth International Congress of Genetics,* edited by D. F. Jones, 1:213–255. Menasha, WI: Brooklyn Botanic Garden.

Plunkett, C. C. 1932. "Temperature as a Tool in Research in Phenogenetics." In *Proceedings of the Sixth International Congress of Genetics,* edited by D. F. Jones, 2:158–160. Menasha, WI: Brooklyn Botanic Garden.

Stern, C. 1929. "Über die additive Wirkung multipler Allele." *Biologisches Zentralblatt* 49:261–290.

Waddington, C. H. 1940a. "Genes as Evocators in Development." *Growth (Supplement),* 37–44.

———. 1940b. *Organisers and Genes.* Cambridge, UK: Cambridge University Press.