

# Epigenetic Landscaping: Waddington's Use of Cell Fate Bifurcation Diagrams

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**ABSTRACT:** From the 1930s through the 1970s, C. H. Waddington attempted to reunite genetics, embryology, and evolution. One of the means to effect this synthesis was his model of the epigenetic landscape. This image originally recast genetic data in terms of embryological diagrams and was used to show the identity of genes and inducers and to suggest the similarities between embryological and genetic approaches to development. Later, the image became more complex and integrated gene activity and mutations. These revised epigenetic landscapes presented an image of how mutations could alter developmental pathways to yield larger phenotypic changes. These diagrams became less important as the operon became used to model differential gene regulation.

**KEY WORDS:** Epigenetic landscape, synthesis of evolution, genetics and development, Waddington.

## THE CONTEXT OF SYNTHESIS

Developmental biology is presently negotiating a synthesis between genetics, evolutionary biology, and embryology. On the one hand, there is the possibility that developmental biology will be taken over by molecular genetics. On the other hand, there is renewed interest in the developmental mechanisms that cause evolutionary changes in morphology. Developmental biology, seen as the study of how the inherited potentials become transformed into a changing organismal phenotype, must mediate between them. The result might be a synthesis that integrates these three disciplines of biology into one conceptual framework and is able to provide an integrated account for macroevolutionary events. Although this synthesis of evolution, embryology, and genetics is presently being worked out, ours is not the first attempt to do so. Earlier in the century, Richard Goldschmidt, E. E. Just, L. C. Dunn, and Julian Huxley, each had attempted to unite these disciplines into one conceptual framework. The person who probably went the furthest in forging such a synthesis was Conrad Hal Waddington whose work from 1936 to 1960 will be discussed here.

Negotiations among such disciplines, both then and now, are performed on several levels. First, there is the *conceptual* dimension in that the genes can only make RNA and proteins. They do not, of themselves, make an organism.

Between the base pairs of the genotype and the limb or eye of the phenotype lies development. Can morphogenesis be explained solely in terms of differential gene expression or is the phenotype dependent largely on other factors? Second, there is the *professional* dimension. Genetics, embryology, and evolutionary biology have become studied by different groups of people. The three sciences have their own journals, their own vocabularies, and their own rules of evidence. They also have their own niches within universities, medical schools, and museums. They have their own paradigmatic studies, their own textbooks, and their own professors to teach these courses. To affect any type of synthesis between these disciplines means renegotiating the professional boundaries that have been established.

Third, there is the *philosophical* dimension to any attempt at uniting or reuniting two separate disciplines. This is particularly evident in the attempts to reunite genetics with embryology. The geneticists of the 1930s (and the molecular geneticists of the 1980s) had a distinctly reductionist account of biology. An organism could be explained in terms of its genes. Development and evolution were merely epiphenomena of gene activity (see Gilbert 1988). Allen (1969, 1985) and Roll-Hansen (1978) have detailed the reductionist philosophy of Thomas Hunt Morgan's school of genetics which dominated American studies of heredity. Embryologists, on the other hand, have traditionally been (w)holistic thinkers who have stressed that "the organism in its totality is as essential to an explanation of its elements as its elements are to an explanation of the organism" (Haraway 1976). Embryologist Paul Weiss, for instance, thought it philosophically untenable to think that the organization of the embryo arose from disordered molecules. All order must proceed from pre-existent order. "The true test of a consistent theory of reductionism is whether or not an ordered unitary system...can, after decomposition into a disordered pile of constituent parts, resurrect itself from the shambles by virtue solely of the properties inherent in the isolated pieces." (Weiss, P. (1968) quoted in Haraway, 1976.) He graphically illustrated this point by including in one of his essays (1962) a photograph of an intact chick embryo, a chick embryo that had been blended through a homogenizer, and a chick embryo whose homogenized components had been centrifuged. The problem for reductionists, he maintained, was how to get the chicken back.

Fourth, there is a related, *aesthetic*, dimension that has to be considered in any synthesis. Embryology stands to genetics (both classical and molecular) as naturalism stands to abstract formalism. The contrast between them is like that between a Michaelangelo sculpture and a Brancusi sculpture. Abstract formalism, like that in modern art, seeks to pare away the observable phenomena to find an underlying reality "more real than the real". The aesthetic of genetics has traditionally been one of simplicity and uniformity. All organisms can be discussed as cybernetic systems whose genetic code contains the program specifying the flow of information in the particular cells. All cells use the same codescript and the same readout devices. As Monod claimed (quoted in Jacob 1988), an elephant is but *E. coli* writ large. Embryology, however, has tradition-

ally contained a naturalistic aesthetic that appeals directly to the senses. It celebrates, not the underlying unity, but the apparent complexity, of developing organisms. Each organism is seen to develop in its own unique fashion, often related directly to its external environment and almost always forming a coherent organism from a collection of semi-autonomous cellular components. Thus Holtfreter (1968) speaks of "the inner harmony, the meaningfulness, the integration, and the interdependence of structure and functions as we observed them in the embryo". Berrill (1961) writes repeatedly of the "rich and diverse material", "the complex reality" and "the amazing diversity of developmental performances". Reconciling embryology and genetics is part of the process of integrating the search for underlying unities with the search for the sources of individual variation. As Joseph Needham recognized in 1932, biology is a contest between Plato and Aristotle.

C. H. Waddington (1905–1975) was aware of all of these levels of negotiation. He was primarily concerned, as a scientist, with the conceptual level, for he sought the ways that development mediated genotype into phenotype, and he was one of the first biologists to look at genetic mutations that lead to developmental anomalies (Waddington 1939b; see Gilbert, *in press*, for details). On the professional level, he paid the price of trying to be an interdisciplinary scientist in a system which forced a scientist to belong to one field and not another. Waddington, who continually needed teaching and research fellowship during the 1930s and 1940s, did not have a "home" in any department. He had a number of part-time positions, occasional positions at private research laboratories, and was often a visiting investigator in someone else's laboratory. In 1936, he and Joseph Needham attempted to establish an interdisciplinary center at Cambridge University to look at the biochemistry and genetics of development. The Rockefeller Foundation was willing to partially underwrite this center for "physico-chemical morphology", but the proposal was turned down by Cambridge University which felt that the money would better go to the existing groups in physiology and anatomy (Abir-Am 1988). When the proposal was modified for a site at the Strangeways Laboratories, many of the embryologists polled by the Rockefeller Foundation were suspicious of attempts to integrate embryology with chemical disciplines. In the end, the Rockefeller Foundation decided not to fund the interdisciplinary project, largely, from the fact that Waddington and Needham were "working in the 'no man's land' between two more orthodox disciplines" and were "viewed somewhat skeptically by each."

The philosophical and aesthetic dimensions of the synthesis were not lost on Waddington, either. He was a member of the Biotheoretical Gathering that discussed the philosophical relationships that biology had with mathematics, Marxism, and biochemistry. Of the fourteen people who attended these meetings, only Waddington, Needham, and the philosopher J. H. Woodger, attended them all (Abir-Am 1987). This group had espoused a Whiteheadian organicism, a holistic view of the organism that depended on the interrelationships between its developing parts (Haraway 1976; Abir-Am 1987). During the

time that Waddington was attempting to weld genetics and embryology together, Needham, using Woodger's philosophical foundations, was attempting to forge the union of embryology with biochemistry. They were both fighting similar battles. Biochemistry was a hybrid discipline that did not become recognized in England until after World War II (Abir-Am, in press). Needham spent a great deal of effort attempting to show that the biochemistry of the embryo would retain the vigor of biochemistry, while approaching subjects that were biologically relevant. Needham thought that 99% of the embryologists were "depressingly morphological and static" and that biochemistry would turn this vitalistic zoology into a real science. Few chemists thought it worthwhile to study the changing chemicals of embryos (Needham complained that "it was too biological for them"), and most embryologists regarded Needham's program as a reductionist threat. Embryologist E. E. Just (1939) characterized such research as "punitive expeditions against the egg", and using Needham's own term, wrote that "Living matter is never an excuse and living phenomena never an opportunity for the display of the investigator's physico-chemical knowledge." But Waddington and Needham were both dialectical thinkers. Waddington's dialecticism stemmed primarily from his reading of Whitehead; Needham's from a more complex brew of Whitehead, Woodger, and Marx (see Gilbert, in press). They felt that dialectic could create a synthesis between vitalism and materialism, reductionism and wholism, biology and chemistry, embryology and genetics, Aristotle and Plato.

Perhaps more than anyone else, it was Waddington who was aware of the aesthetic dimensions of the synthesis. Waddington eventually (1970) wrote a book on science and aesthetics, *Behind Appearances*, which saw similarities between the world view of mid-twentieth-century scientists and their artistic contemporaries. Science, like art, saw the complexities of appearances, and also, like art, sought the underlying structure that united these disparate elements.

Waddington's career as a biologist was largely concerned with the negotiations between genetics, evolution, and embryology. He sought to create a new "diachronic biology" where these three disciplines were integrated them into a coherent whole. In another paper, I have attempted to document the history of Waddington's integration of these disciplines. Here, I wish to use the context of resynthesis and negotiation to discuss one of Waddington's popular icons, the epigenetic landscape.

#### EMBRYOLOGY, EVOLUTION, AND GENETICS

The epigenetic landscape drawings of Conrad Hal Waddington are models having no grounding in physical reality. They are attempts to present a visual image for the processes by which a population of homogeneous cells differentiates into the diverse cell types of the organism. When these models were first presented in the early 1940s, biologists had no knowledge of DNA, and many researchers felt that there was no important relationship between genes and

embryonic development. When embryologist N. J. Berrill was asked to define the role of genes in development (1941), he called them "statistically significant little devils, collectively equivalent to one entelechy." Just (1939) contrasted the *geneticists*, who believed that genes controlled development, with *biologists*, who had their doubts.

In the early 1940s, there were three separate sciences of genetics, embryology, and evolutionary biology. This had not always been the case. Even as late as the 1890s, there was very little separation. The "hereditary" hypotheses of William Keith Brooks (1883) and August Weismann (1893), for instance, contained development and genetics in an evolutionary context. But in the 1880s, developmental mechanics (*Entwicklungsmechanik*) claimed that the proper way to study the heredity question was not as an adjunct to evolution, but as a partner to physiology. The physiology of embryonic development was to become a major research program in the United States and Germany. However, even Wilhelm Roux's (1894) rationale for developmental mechanics did not exclude evolution; it stated that first one has to know how the embryo is formed before one could start discussing how modifications of those processes could cause new types of organisms. By the end of the first decade of the twentieth century, developmental mechanics had become a science that had little reason to ground itself in evolutionary biology (Cassirer 1950; Gilbert 1979).

Shortly after this separation from evolutionary biology, a split was formed within the ranks of the developmental physiologists (Gilbert 1979). Until 1926, the problems of embryologists and the problems of geneticists were seen as being the same. This was changed when Thomas Hunt Morgan, an embryologist who was investigating whether the nucleus or the cytoplasm controlled developmental processes, showed that particular genes resided on specific chromosomes and that these genes determined the phenotype of the adult fruit fly. Whereas Mendel had shown the segregation of genetic traits, Morgan and his laboratory had shown the linkage of genes, and in so doing, created a new science. For about fifteen years after the discovery of gene linkage in *Drosophila*, one could be an embryologist working on genetic problems (indeed, that appears to be how Morgan saw himself). However, in *The Theory of the Gene*, Morgan (1926) explicitly stated that the problems of genetics and the problems of embryology were different. The problems of the geneticist involve the transmission of hereditary traits, while the problems of the embryologist concern the expression of those traits. Genetics and embryology went their separate ways, the geneticists claiming to be the newer and higher embryology (Sander 1986; Gilbert 1988).

Not all embryologists, geneticists, or evolutionary biologists were happy with this state of affairs. In the mid 1940s, the geneticists and the evolutionary biologists enjoyed a rapprochement that did not include embryology. This became known as the Modern Synthesis whereby evolution could be explained by the principles of population genetics.<sup>1</sup> Certain other scientists began to create broader syntheses that included embryology, as well. Richard Goldschmidt (1938), for instance, saw development and evolution as epiphenomena of gene

activity. Gene activity would create development, and changes in gene activity (especially in the rates of gene activity) would occasion evolution. Ernest Everett Just (1939) saw the cell surface as providing the basis for cell-cell cooperation during development, and claimed that the central nervous system was a product of this cortical cytoplasm. To him, the genes represented unused potentials that were locked away in the nucleus far from the cytoplasmic regions where the remaining potential was active. Just saw evolution as a product of development and of the specialization of the egg cell surface.

But neither Just nor Goldschmidt took Morgan's genetics seriously. A new synthesis of genetics, embryology, and evolution would have to take into account genes, organizers, and differential fitness. Such a person would have to be familiar with the most current knowledge of these three areas. That task was taken on by C. H. Waddington.

#### THE PRIMACY OF COMPETENCE

Conrad Hal Waddington was trained in evolutionary embryology (of cephalopods) before becoming trained in genetics and development. (For a more detailed biography, see Robertson 1977; Gilbert, in press.) In 1932–1933, he visited Spemann's laboratory in Freiburg and brought back to Cambridge the embryological techniques to study the amphibian organizer. Forming a team with Dorothy and Joseph Needham and Jean Brachet, he attempted to find the evocator substance, a chemical that was able to direct ectoderm to become neural tissue. Preliminary studies had shown that this substance might be a steroid, since several artificial and natural steroids were capable of forming neural tissue out of competent amphibian ectoderm. In 1936, however, Waddington, Joseph Needham, and Brachet made an unexpected discovery. Rather than finding a specific factor from the notochord that would induce neural plates, they observed that a large variety of natural and artificial compounds were able to cause this induction. They reinterpreted their data to suggest that the actual neuralizing factor lay dormant in an inhibited state within the competent ectoderm, and that many different types of compounds could release the neuralizing factor from its inhibitor. Waddington then began to focus his attention on the competent cells, rather than on the inducing cells. Since many things could act as inducers, the specificity of the developmental reaction wasn't in the inducer but in the competent tissue. The inducer, he wrote (1940), was only the push. It was the *competence* that was genetically controlled and which was responsible for the details of the development. Not all cells could form neural tubes; only the competent ectoderm could. Thus, the genes of this tissue were seen as having a different activity than genes in other tissues. This led Waddington to propose that this competence was due to the existence of genetically controlled pathways. If the developmental pathway is advantageous to the organism, that path from one state to another (say, from ectoderm to neural tube) became *canalized* by natural selection. Canalization meant that the

pathway was “buffered” such that it would be difficult to get out of the channel once into it. Once the pathway had been entered, cell fate was rigidly fixed if the pathway were sufficiently canalized. Competent tissues were tissues in which such pathways were present. All that the inducer did was shove a cell into such a path.

#### MOLDING THE LANDSCAPE: THE CELL FATE DIAGRAM

Waddington visually represented canalization in an image called the *epigenetic landscape*. This image graphically portrayed a process that has no physical counterpart to the valleys and hills of the model, namely, the mechanisms which cause a cell to differentiate into one cell type and not another. It represents the paths within a competent cell which allowed certain cell fates to be achieved more readily than others. Waddington (1956) called it “a symbolic representation of the developmental potentialities of a genotype in terms of surface.”

The epigenetic landscape was first introduced in Waddington’s *Introduction to Modern Genetics* (1939a) and given extended treatment in his *Organisers and Genes* (1940). In these books, the landscape can be seen as an extension of another Waddington conceit, “the branched track system”. Such a branched track system is seen in Figure 1. This is the developmental (and genetic and biochemical) path leading to the formation of the wild-type red pigment of

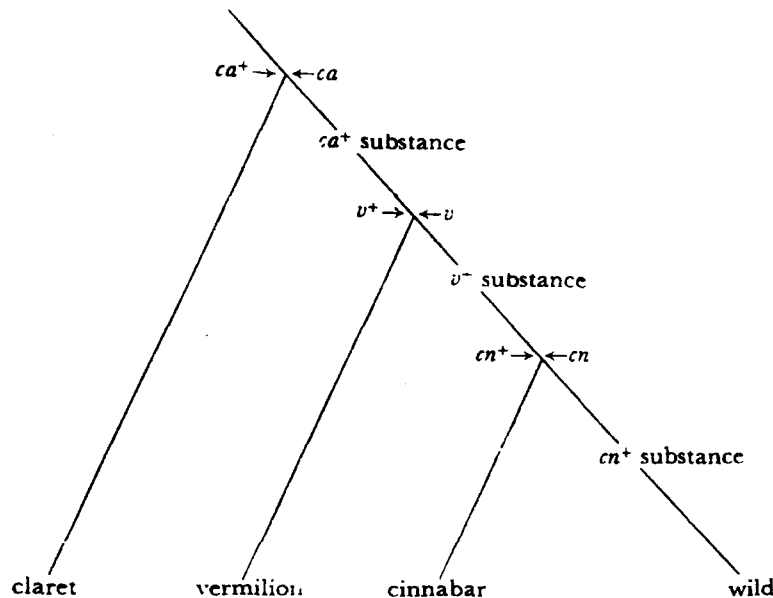


Fig. 1. The formation of eye colours in *Drosophila*. The pigment-forming process normally runs down the line through the  $ca^+$  substance, the  $v^+$  substance, to give wild type pigment. The genes,  $ca$ ,  $v$  and  $cn$  interrupt this sequence, so that the process takes an altered course, to give claret, vermillion or cinnabar pigmentation. (Caption from Waddington 1940.)

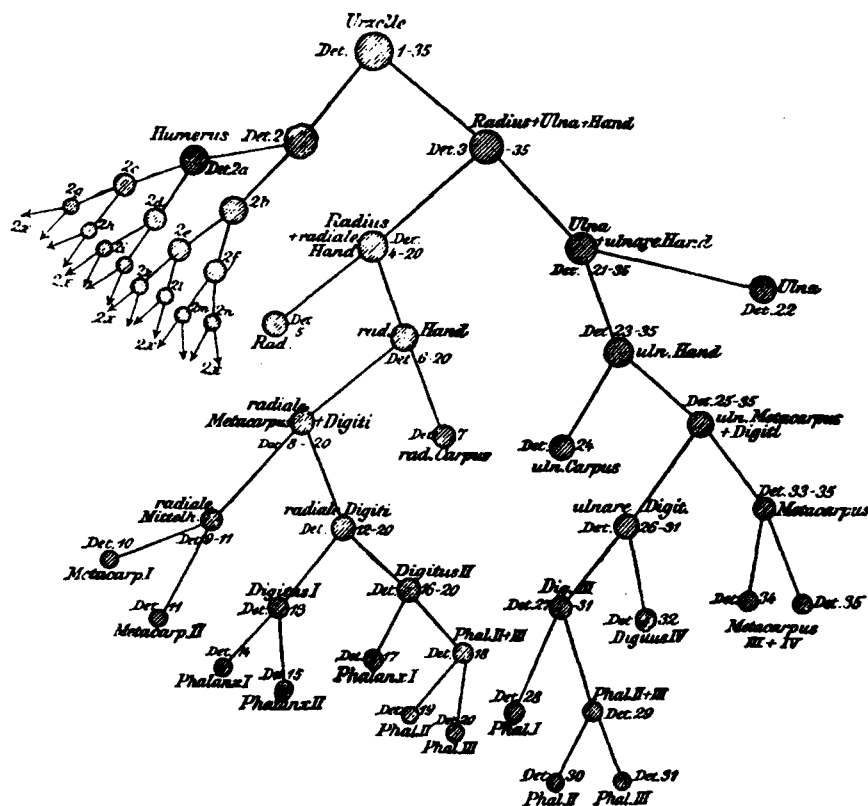


Fig. 2.

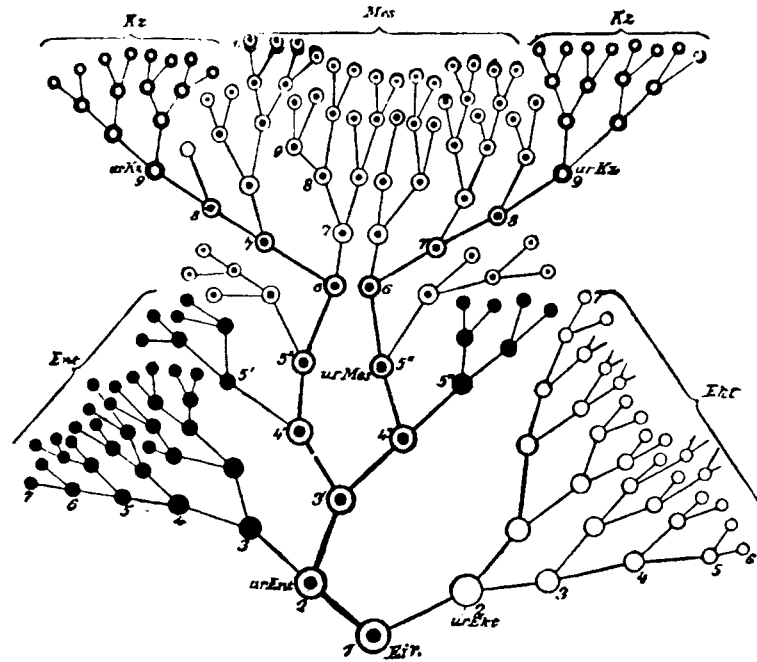
*Drosophila*. It is, claimed Waddington, "a purely diagrammatic representation of the track of the reaction in which these substances are concerned. The path is, of course, a branching one: if  $v^+$  substance is formed, the pigment system can develop a cinnabar pigment, if not, then it must develop along the track to vermilion pigment, and so on."

Waddington's "of course" statement was rhetorical. There is no "of course" about it. The branched track diagram was not the way that Beadle and Ephrussi presented their data (and after all, it was their data, not Waddington's!)<sup>2</sup> Rather, they routinely placed their compounds in a linear array which they called (1937) "substances in a chain reaction." Their representation of their studies looked like:



Why, then, did Waddington use a branch-track model rather than the linear one? The answer, I believe, lies in his desire to synthesize embryology and genetics. Waddington would use the branched-chain diagram to show that the theories in genetics and the theories in embryology were saying the same thing. To do this, he put the genetic data into the branch-track diagram that was





(Caption from Weismann 1893; presented by Griesemer and Wimsatt 1988.)

already commonplace in embryology. James Griesemer and Bill Wimsatt (1988) have shown that this type of embryological bifurcation diagram has a history that goes at least as far back as Weismann. Figure 2 shows Weismann's 1893 diagram for the cell fates in the salamander forelimb. This hypothetical cell descent drawing (it has to do with specification of position, not the differentiation into chondrocytes, muscle cells, bone cells, and so forth) was used to show Weismann's mosaic theory of development. The determinants (1–35) that were present in the limb precursor cells are distributed such that in the final portion of the organ, only one determinant remains for each part. A diagram with more physical reality is shown in Figure 3. Also from Weismann's book, this diagram shows the cell lineages of the nematode *Rhabditis*. It is especially clear at showing the relationships between the germ cell precursors and the mesodermal cells. Here, each bifurcation stands for an actual cell division and each circle represents a single cell. According to this diagram, at the eighth division, two mesodermal precursor cells generate two more mesodermal precursors and two

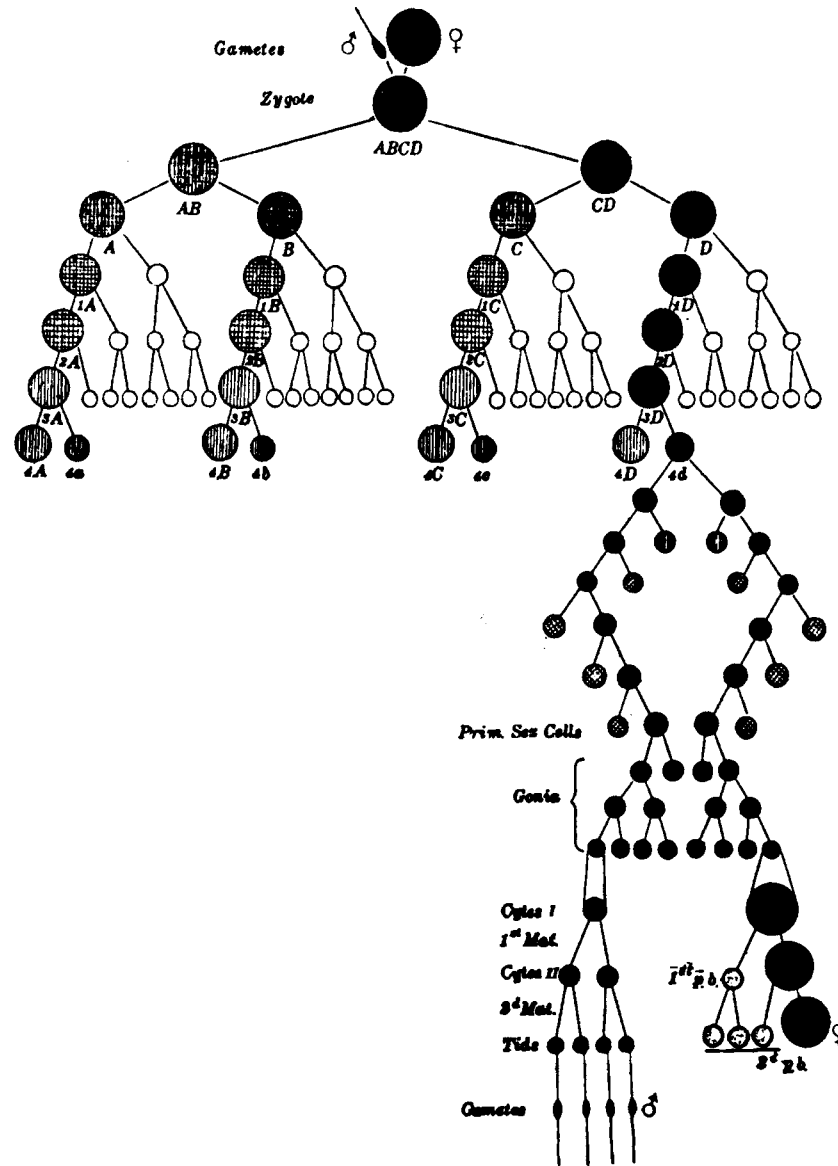


Fig. 4.

cells that will give rise to all the germ cells in the nematode. Embryologists such as Edwin Conklin took these diagrams and standardized the way in which cell fate dichotomies were represented (Griesemer and Wimsatt 1988). Figure 4 shows such a diagram. Here, the "either/or" nature of the cell's "decision" is emphasized. Each division can present a dichotomous either/or decision to the

cell. Eventually, the choice does not matter because the cell fate is fixed, and the progeny of the cell are all going to be of one kind. In early development, however, each division may change the cell's fate.

These cell fate diagrams were made for organisms with a preponderance of mosaic determination. In such animals, cell fate is determined very early in development. In organisms such as amphibians (the subjects of embryological experiments) or *Drosophila* (the standard genetic animal), there were no such cell lineage diagrams in the 1940s. There were too many cells for such an analysis, cell fate being determined relatively late in development when there were tens or hundreds of thousands of cells. However, Waddington will use this concept of bifurcation to show that *Drosophila* genetics and amphibian embryology were talking about the same things.

In *Organisers and Genes*, Waddington uses branched track diagrams to model the effects of homeotic genes that change the fates of cells in *Drosophila*. In Figure 5, he models the developmental track of *aristopedia*. The track that the cell takes is determined by the *aristopedia* gene (*ss-a*). If the allele is wild-type, the imaginal disc develops normal arista (antenna) segments. If the allele is mutant, the same cells develop into tarsus (foot) segments, giving the fly two limbs sprouting from its head. Other genes can modify the shape of the resulting appendages, but the main switch is *aristopedia*. (The *dachous* gene [*ds*], for instance, shortens both appendages).

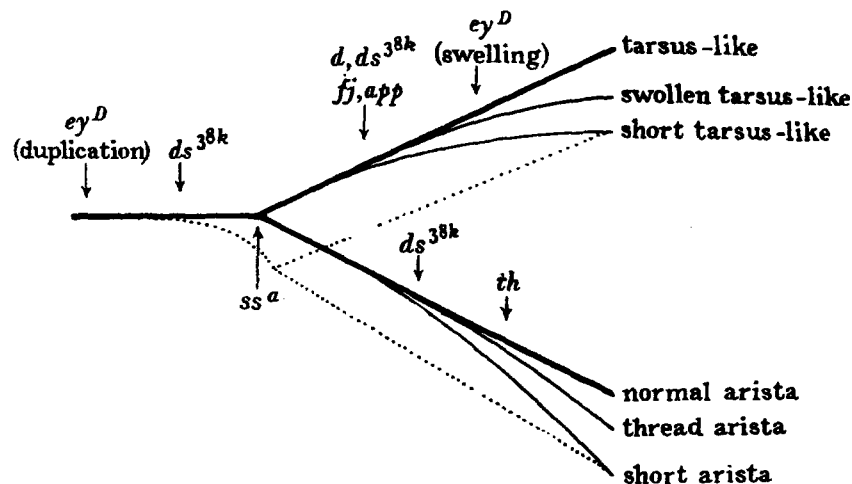


Fig. 5. The *aristopedia* developmental track system. The developmental process runs from left to right, either into the tarsus track above or the arista track below. Both these tracks are affected by various genes. The dotted lines represent one interpretation of the actions of *ds*<sup>38k</sup>, which affects both normal and tarsus-like antennae. Only the mutant genes have been inserted; their normal allelomorphs would act in the opposite sense.

(Caption from Waddington 1940.)

According to this model, "the sequences of gene reactions must be described in terms of branching tracks, and that the presence or absence of particular genes acts by determining which path shall be followed from a certain point of divergence." This was not a genetic way of showing mutant versus wild-type phenotypes. Rather, it was the type of depiction used by embryologists to show cell lineage relationships. This depiction allows him to compare the genetic data with the embryological. In *Organisers and Genes*, it becomes apparent that the major cell lineage bifurcation for Waddington is the induction of the neural tube by the notochord. In the presence of the notochord, the competent ectoderm becomes neural. In the absence of this inducer, the competent ectoderm enters another pathway and becomes epidermal. He relates this choice to the presence of a wild-type or a mutant allele of *aristopedia*. Waddington believed that genetics and embryology were two ways of describing the same phenomenon. He would represent them the same way. He described several genetic and embryological phenomena in terms of bifurcations of a path and a choice to follow one of the other. In embryology, one saw that an external factor (the evocator) pushed the competent ectoderm into the neural track rather than the epidermal track. Similarly in genetics, another external factor, the soluble product of the *cn*<sup>+</sup> gene, caused the *Drosophila* eye to develop red pigment instead of cinnabar pigment. The inducing factors need not come from outside the cell, either. In embryology, one saw that the fates of tunicate cells were determined by the type of cytoplasm that they had received from the oocyte. In genetics, the *Drosophila aristopedia* gene was an internal inducer that could switch the fate of a cell from being part of an antenna to being part of a leg. Both embryology and genetics, then, could be represented by branched track systems. His words could be diagrammed as in Figure 6:

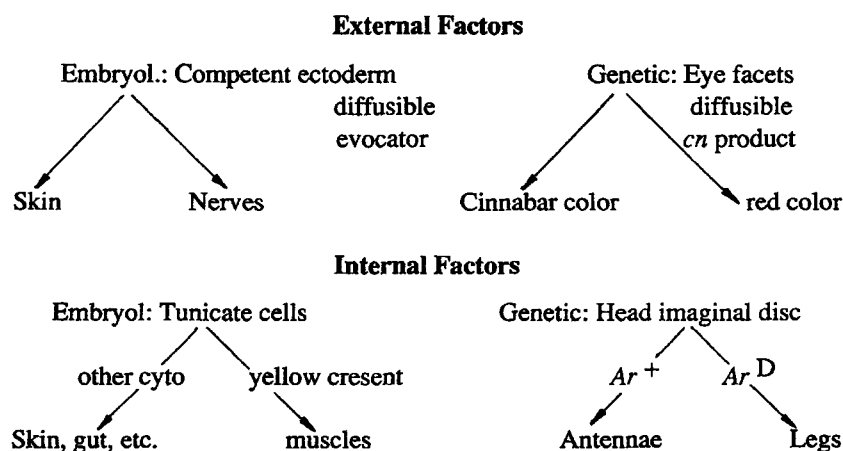


Fig. 6.

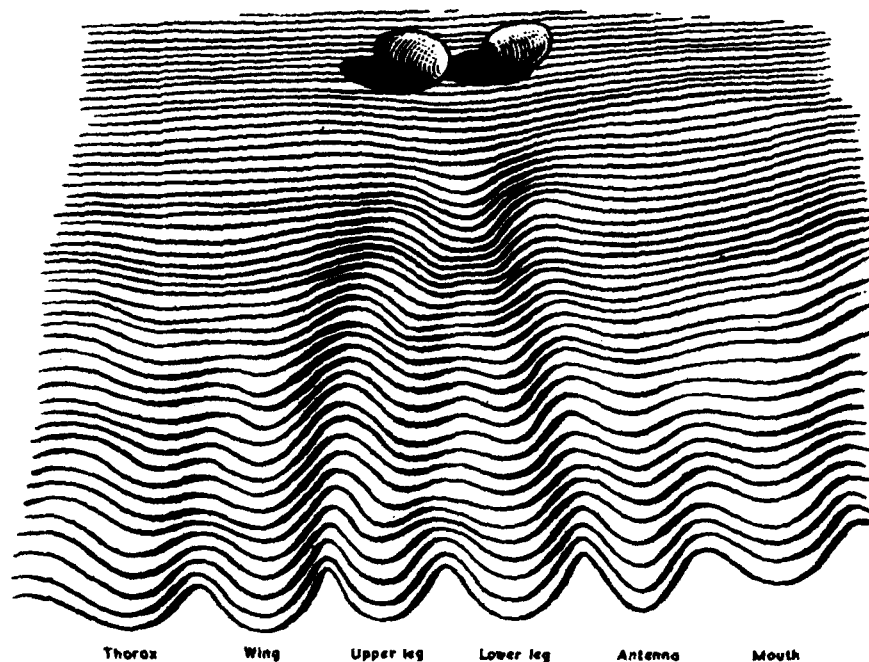


Fig. 7. The 'epigenetic landscape'. A symbolic representation of the developmental potentialities of a genotype in terms of a surface, sloping towards the observer, down which there run balls each of which has a bias corresponding to the particular initial conditions in some part of the newly fertilised egg. The sloping surface is grooved, and the balls will run into one or other of these channels, finishing at a point corresponding to some typical organ. (Caption from Waddington 1956.)

Waddington claimed that "the genes we have just considered control the choice between two alternative modes of development which are sharply contrasted." He linked this to his earlier discussions of ectodermal cell competence wherein two choices were also given the cell. Waddington then equates the two schemes:

The similarity between the theoretical schemes we have arrived at on embryological and genetic grounds is immediately apparent. In embryonic development we are confronted with alternative modes of development, the choice between which is taken in reference to an external stimulus, in inductive development or to an internal one, in mosaic development. In considering the effects of genes, we find alternatives the choice between which may be taken in response to diffusible substances, as in the *Drosophila* eye colours, or apparently in response to internal factors as in aristopedia. It is clear that we have merely followed two different methods of approach to the same phenomena, and that the two schemes are in fact identical.

Here, Waddington can make his synthesis of embryology and genetics. The diagrammatic unity of these two sciences bolsters his case. Thus, one of the first "political" uses of Waddington's diagrams is to show the unity of genetics and embryology.

## THE CONTOURS OF THE EPIGENETIC LANDSCAPE

After presenting this data in *Organisers and Genes*, Waddington remarks that a fuller picture of the branching developmental paths would be that of "a system of valleys diverging down an inclined plane." Here we have the epigenetic landscape. The first depiction of such a landscape was drawn by a friend of his, John Piper,<sup>2</sup> where it serves as the frontispiece to this book. A less Romantic diagram is shown in Figure 7. Here we see a set of valleys or channels separated from one another by hills. The inclined plane of the landscape represents the tendency of cells to pass from an immature to adult condition. The steepness of the valley walls indicate the changing equilibrium state of the track. It is a depiction of how canalized the reaction is. If the walls are steep, it would be difficult to escape from that valley once inside it. However, if the hill separating two valleys were small, it would be possible for the cell fate (represented here in Figure 7 by the eggs, but often as spheres) to change from one cell type to the other.

The normal developmental path is also the one to which the embryo will return if perturbed. Regulation can occur only when the valley walls are low, but after a time, the valley walls steepen and regulation would not be possible. It is important to remember that this is a landscape within a competent cell. As Waddington frequently noted, the valleys or channels are produced by the interaction of genes with one another and with their environment. Some genes might push the valley one way or attempt to push the ridges higher. Other genes might effect the depth of the valley. "One might roughly say that all these genes correspond to the geological structure that moulds the form of the valley. Genes like vermilion which have their main effect at certain branching points are like intrusive masses which can divert the course of the developmental stream down a side valley" (Waddington 1939a).<sup>3</sup> In 1956, Waddington represented this by depicting the underside of the genetic landscape (Figure 8). The pegs in the ground represent the genes. The guy ropes shaping the genetic landscape are the gene products. Here is, then, another way in which Waddington uses concrete diagrams to model an abstract topic. Having used the bifurcation diagram to show that genetics and embryology are really the same thing, he then uses the epigenetic landscape diagrams to show how genes can act upon developing tissues.

Waddington's next use of these diagrams is to integrate genetics and development into evolutionary biology. He does this by bringing us back to the notion of competence. Since different compounds could induce the same developmental process in competent tissue (such as amphibian ectoderm), Waddington (1942) proposed that a given competent tissue could transfer its responsiveness from one inducing stimulus to another. The important thing was to have the pathway canalized. The inducer could be anything. Moreover, these inducers could be either internal or external. As an example, he used the ability to form calluses on those areas of skin that abrade the ground. Here, the skin cells had the ability to form a callus if induced by friction. In other words, they were

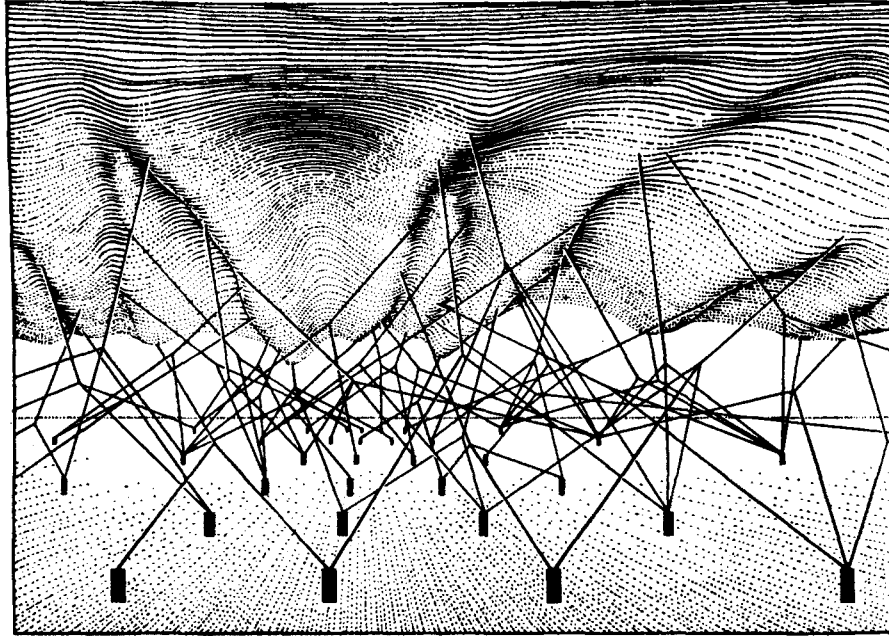


Fig. 8. The complex system of interactions underlying the epigenetic landscape. The pegs in the ground represent genes; the strings leading from them the chemical tendencies which the genes produce. The modelling of the epigenetic landscape, which slopes down from above one's head towards the distance, is controlled by the pull of these numerous guy-ropes which are ultimately anchored to the genes. (Caption from Waddington 1956.)

competent to form calluses. The genes could respond by causing the proliferation of cells to form the callus structure. While such examples of environmentally-induced callous formation are widespread, the ostrich is *born* with calluses. Waddington hypothesized that since the skin cells were already competent to be induced by friction, they could be induced by other things as well. As ostriches evolved, a mutation appeared that enabled the skin cells to respond to a substance within the embryo. In this way, a trait that had been induced by the environment became part of the genetic heritage of the organism and could be selected. He called this phenomena *genetic assimilation*.

Thus once a developmental response to an environmental signal has been canalized, it should not be difficult to switch development into that track by mechanisms other than the original external stimulus, for example by the intrinsic mechanism of a genetic factor... Once the developmental path has been canalized, it is to be expected that different agents, including a number of mutations available in the germline of the species, will be able to switch development into it... (Waddington 1942).

Waddington uses these diagrams to represent genetic assimilation (Figure 9).

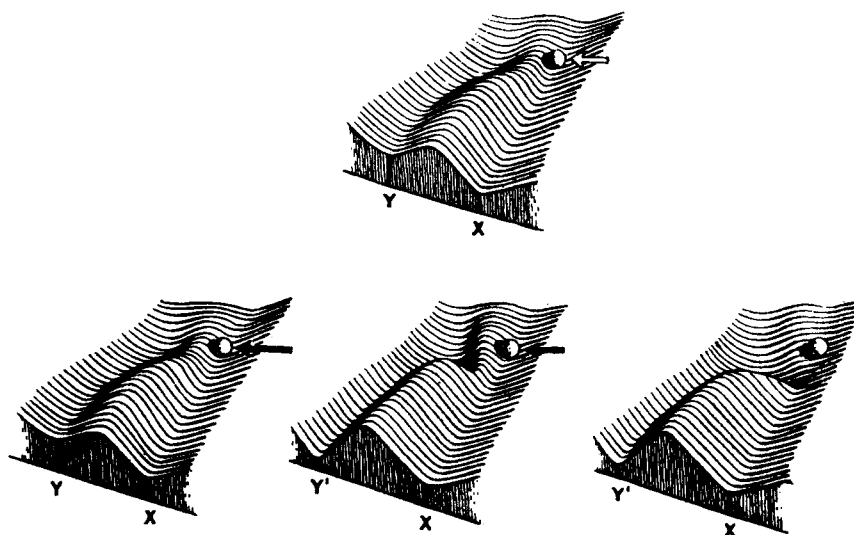


Fig. 9. 'Organic selection' (the Baldwin effect) and genetic assimilation. The diagram above shows part of an epigenetic landscape, with a main valley leading to the adult character *X* and a side branch leading to *Y*; the developing tissue does not get into the *Y* path unless an environmental stimulus (hollow arrow) pushes it over the threshold. The three diagrams below show ways in which the 'acquired character' *Y* might become incorporated into the genotype. On the left, the original environmental stimulus is replaced by a mutant allele (dark arrow) which happens to turn up; this is 'organic selection'. On the right are two modes of 'genetic assimilation'. In the central one, the threshold protecting the wild type is lowered to some extent, but there is an identifiable major gene which helps push the developing tissues into the *Y* path. On the right, the genotype as a whole causes the threshold to disappear and there is no identifiable 'switch gene'. Note that in both the genetic assimilation diagrams there has been a 'tuning' of the acquired character, i.e. the *Y* valley is deepened and its end-point shifted from *Y* to *Y'*. (Caption from Waddington 1957.)

Here, he returns to three critical ideas. First, the specificity of the embryonic reactions reside in the competent tissue. Second, the genes of the competent tissue make the paths of the epigenetic landscape. The more buffered paths are called canalized paths, and these paths exist in the competent cell prior to induction.<sup>4</sup> Third, the inducer can be internal or external to the cell. In genetic assimilation, the height of the hills can be modified to allow the cell fate (spheres) to enter a path that would not have otherwise been accessible. Or alternatively, the competent cell can transfer its competence from one inducer to another (as Waddington thought occurred in the formation of ostrich calluses).

In the top diagram in Figure 9, developing tissue would normally go down the



path to *X* unless an environmental stimulus (hollow arrow) would push the tissue into the path of *Y*. Below this diagram are three ways in which the same effect could be incorporated internally into development. First, the environmental effect could be mimicked by a mutant allele (dark arrow). This would explain the Baldwin effect. In the second mechanism, a gene mutation causes the hill between paths *X* and *Y* is lowered, but a major gene is still required to push the tissue over the threshold from *X* to *Y*. Last, the genotype can be changed causing the hill to disappear altogether. No switch gene would be needed to go to path *Y*.<sup>5</sup>

In this way, Waddington used the epigenetic landscape to model macroevolutionary change. Thus, the epigenetic landscape enabled Waddington to present a visual image of the hidden processes of cell fate determination. Moreover, these depictions permitted him to equate development with genetics and to link this united discipline back to evolution.

## EPILOGUE

Waddington's synthesis was only partially successful, a truce more than a synthesis. It formed a context in which embryologists could work without fearing that geneticists could take over their discipline. However, few scientists shared Waddington's belief that organizers and genes were identical, nor did many embryologists know what to do with the notion of canalization. Before the advent of molecular biology, embryologists shied away from theory making, generally holding that each species developed in its own peculiar way. Even today, formal model building is not the forte of developmental biology. Moreover, given that the channels and spheres had no physical reality, what was an embryologist supposed to do with them? Very little. They cannot be purified, transplanted, cloned, or localized with a monoclonal antibody. Waddington, himself, eventually downplayed the epigenetic landscape pictures for newer images: cybernetic contour models and the wiring diagrams of the operon. Evolutionary biologists similarly ignored Waddington's genetic assimilation proposals. Although Lerner (1958) and Merrell (1962) saw genetic assimilation as a means of circumventing Lamarckian explanations for certain types of inheritance, Mayr (1963) and Dobzhansky (1970) claimed that genetic assimilation was artefactual.

Waddington was important in promoting the disuse of his epigenetic landscape pictures, as he helped introduce the operon model into developmental biology. Within a few months of its publication by Jacob and Monod, Waddington (1962) reported on the bacterial operon as a useful model for embryonic induction. Here were chemicals that determined which path a cell was to take. With lactose in its environment, the bacterium produced one set of enzymes; without lactose, they synthesized another set. This provided the model that studies of cell differentiation were to follow for the next decade. In so reifying the hypothetical chemical switches, molecular biology did away with the need for such abstractions as the epigenetic landscape.

## NOTES

<sup>1</sup> For possible explanations as to why the Modern Synthesis left out developmental biology and asserted that macroevolutionary events could be explained by microevolutionary processes, see Mark Adams, "Little Evolution/Big Evolution" (manuscript submitted).

<sup>2</sup> In his 1970 volume on modern art and science, *Beyond Appearance*, Waddington mentions John and Myfanwy Piper as his closest friends. He related (p. 232) that Piper made the illuminating statement that Giacometti wanted to make a statement about reality, not a description. This may be the case for Waddington's epigenetic landscape pictures.

<sup>3</sup> Stream images have always been common in developmental biology and were used frequently in the first half of this century. Probably the most famous was F. R. Lillie's trope in his 1927 paper "The gene and the ontogenetic process." Here he said that, "Those who desire to make genetics the basis of physiology (of development) will have to explain how an unchanging complex can direct the course of an ordered developmental stream." This, of course, was precisely what Waddington was trying to do. Goldschmidt (1938) wrote of developmental streams, and E. E. Just (1939), who was also trying to unite genetics and embryology, probably came the closest to Waddington's ideas of streams: "Studying cleavage we approach the source whence emerges the progressively branched streams of differentiation that end finally in almost quiet pools, the individual cells of the completed adult organism." Waddington's trope of an obstruction redirecting the stream was anticipated by Spemann (1903) who saw the flow of dorsal forming material split by his constrictions "like the river which is divided by the pier of a bridge." Such images are heard today when one speaks of "downstream genes" (as in a developmental pathway) or upstream promoter elements (that may be regulating these genes). Landscape metaphors had, of course, been common in evolutionary biology through Sewall Wright's trope of adaptive peaks separated by inadaptive valleys.

<sup>4</sup> This means, of course, that the channels were the product of an earlier inductive event which may have turned some gene activity on or off.

<sup>5</sup> Waddington modified the epigenetic landscape over the years, and in 1957, he replaced the term epigenetic landscape with "chreodes", a term used to describe a canalized pathway of developmental change. He would return to the epigenetic landscape in 1974, when he proposed a mathematical model of development that used these concepts. These concepts have been revitalized by individuals looking at developing embryos in terms of dynamic systems theory (see Kauffman 1987). Here the canalized pathways are produced by a set of genes integrated together in a Boolean network. The cell types, themselves, are attractors (or reside in basins of attraction) that are separated from one another by separatrices, roughly analogous to the hills of Waddington's epigenetic landscape.

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