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Descended from Darwin

Insights into the History of Evolutionary Studies, 1900–1970

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Chapter 7

Homeotic Mutants and the Assimilation of Developmental Genetics Into the Evolutionary Synthesis, 1915–1952

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Introduction

In 1894 William Bateson described a class of discontinuous variation that he considered to be especially valuable for the study of evolution. This variation involved the repetition of a set of features typical of one member of a meristic series (e.g., a vertebra or a segment) in a new location in the series. Bateson referred to this process, whereby one body part is transformed into the likeness of another, as homeosis (from Greek *homoios* = same and *–osis* = condition or process, Bateson, 1894, pp. 84–85). Because phenomena such as homeosis could accomplish "at one step" a change similar to the differences observed between species, Bateson held that it was the discontinuity of variation itself, rather than the action of natural selection on continuous variation, that gave rise to the discontinuity of species (Bateson, 1894, pp. 568–570).

More than a century later, homeotic mutants play an important role in contemporary ideas of how genetics, development, and evolution intersect, and in large part have inspired the research program known as evolutionary developmental biology, or more popularly, "evo-devo" (e.g., Stern, 2000). The developmental genetics of Ed Lewis on homeotic mutants in *Drosophila* established the role homeotic genes play in specifying segmental identity during ontogeny (Lewis, 1951, 1964, 1978). Application of molecular techniques to these genes led first to the discovery of the homeobox, a conserved stretch of DNA sequence that codes for the DNA-binding portion of a large class of transcription factors (McGinnis, Levine, Hafen, Kuriowa, & Gehring,

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1984; Scott & Weiner, 1984), and later revealed gene expression patterns consistent with mutant phenotypes (for review, see Akam, 1987; Harding, Wedeen, McGinnis, & Levine, 1985). These studies, those that followed in vertebrates (Awgulewitsch, Utset, Hart, McGinnis, & Ruddle, 1986; Duboule & Dollé, 1989; Graham, Papalopulu, & Krumlauf, 1989; for review see McGinnis, 1994), and comparative studies of other arthropods (e.g., Averof & Patel, 1997) provided critical evidence for the commonality of the genetics of developmental programs across the bilaterian animals, and led to efforts at broadly integrating the genetics of homeosis with patterns of body plan evolution in the fossil record (e.g., Jacobs, 1990). In essence, homeosis has revealed commonalities in the way animals are structured and suggested ways in which those body-plan organizations evolve.

Yet, even before the advent of molecular biology, homeotic phenomena fueled attempts to integrate genetics, development, and evolution. Indeed, during the late 1920s through the 1950s, homeotic mutations in *Drosophila* were at the center of efforts to achieve conceptual or theoretical integration—to create an evolutionary-developmental synthesis. However, those who researched homeotic mutants were unable to convince their peers that such phenomena ought to play a defining role in the emerging evolutionary synthesis. Why not?

This chapter consists of three sections. The first will consider the history and historiography of developmental biology and the evolutionary synthesis, as well as the nature of the split between embryology and genetics. The second will consider early efforts to characterize homeotic mutants as developmental, evolutionary, and genetic phenomena. Although we will focus on homeotic mutants of *Drosophila*, we should note that in the early twentieth century homeotic mutants were widely recognized in arthropods more generally, as well as in plants (Sattler, 1988). The third section of this chapter will consider the reception of evolutionary interpretations of homeotic mutants by the primary architects of the evolutionary synthesis. We will argue, as have others, that the history of research on homeotic mutants reveals that the split between embryology and genetics was not absolute. Instead, a research program of developmental and physiological genetics grew around the analysis of homeotic mutants. Although this research program was ready to contribute to the evolutionary synthesis, attempts to integrate the developmental genetics of homeosis into the synthesis were complicated by their association with the controversial evolutionary views of their chief proponent, Richard Goldschmidt. Against the backdrop of this controversy, we argue that homeotic mutants failed to redefine the problems, concepts, or methodologies associated with the synthesis. To be sure, some aspects of developmental biology were assimilated into the synthesis; but mere assimilation failed to grant developmental biologists any authority to define the synthesis, and the phenomenon of homeosis was increasingly marginalized as the synthesis matured in the years following World War II (WWII).

Historicizing Evolutionary Developmental Genetics

Many contemporary historians of biology have documented how developmental biology was divorced from genetics in the early twentieth century (Allen, 1986; Gilbert, 1978, 1988, 1998; Kohler, 1994; Love, 2003; Love & Raff, 2003; Sapp, 1983, 1987). This split between embryology and genetics is often used to explain why embryology

was later excluded from the evolutionary synthesis (Gilbert, 2000; Hamburger, 1980; Love, 2003; Love & Raff, 2003). While it is occasionally claimed that the split in some way caused the exclusion, it has also been argued that the split is best viewed as a prerequisite for the exclusion in that it allowed a version of heredity bereft of ontogeny to be incorporated into evolutionary theory (Amundson, 2005, pp. 189–190).

While historians' accounts differ on whether Thomas Hunt Morgan and the *Drosophila* group at Columbia directly caused the split, all agree that Morgan and the Fly Group were at least instrumental in promoting it. Historical support for such a split comes from Morgan's own statements, such as his defense of such an approach as both temporary and strategic:

> On several occasions I have urged the importance of keeping apart, *for the present at least*, the questions connected with the distribution of the genes in succeeding generations from questions connected with the physiological action of the genetic factors during development, because the embryological data have too often been confused in premature attempts to interpret the genetic data. It has been urged that such a procedure limits the legitimate field of heredity to a process no more intellectual than that of a game of cards, for Mendelism becomes nothing but shuffling and dealing out new hands to each successive generation. My plea is, I fear, based largely on expediency, which may only too easily be interpreted as narrow-mindedness; yet I hope to be amongst the first to welcome any real contribution concerning the nature of genes based on the chemical changes that take place in the embryo where the products of the genes show their effects. (Morgan, 1917, p. 535)

The value that this strategy held for early transmission genetics is undeniable (Kohler, 1994). The alienating effect of Morgan's strategy on his contemporaries in embryology has also been well documented (Gilbert, 1988; Sapp, 1983). And yet despite Morgan's almost autocratic control of early *Drosophila* genetics, his strategies and pronouncements did not dictate research in all of genetics, especially for a younger generation of researchers. Indeed, historian Robert Kohler demonstrates that by the 1920s researchers in Morgan's own group had begun to make forays onto the edges of ontogeny (Kohler, 1994).

Although historians have recognized that the split between embryology and genetics in fact coincided with attempts to bridge the split, the exclusion of development from the evolutionary synthesis has instead been widely accepted. Alan Love has claimed "it is almost a truism that embryology was excluded from the Modern Synthesis (Hamburger, 1980), or at least embryologists did not want to participate (Mayr, 1993)" (Love, 2003, p. 313). This exclusion, Love argues, has its origins in the split between embryology and genetics, "codified" by Thomas Hunt Morgan in the early twentieth century. "If we assume genetics and embryology were separate by 1935," then, according to Love, "the tight connection between population genetics and evolutionary theory in the Modern Synthesis helps explain the exclusion of embryology" (Love, 2003, p. 313). Love recognizes that such an association does not mandate exclusion, but he writes, "although some participants had resources for bringing embryology into the discussion (e.g., Julian Huxley), by and large this simply did not occur" (Love, 2003, p. 313). But who counts as a "participant" in the *modern synthesis*? Love recognizes this problem in a footnote where he admits "if the national scope of the Modern Synthesis is construed broadly to include research that was not

widely known or incorporated, then evaluating the 'exclusion' of research emphases becomes more difficult (Reif et al., 2000)" (Love, 2003, p. 333n 9). In fact, the national scope of the synthesis does not need to be expanded to non-English-speaking countries to challenge this exclusion narrative. First, Love uncritically accepts Ernst Mayr's pronouncement as historical fact. Viktor Hamburger's much more informed evaluation of the place of developmental biology in the synthesis is at odds with Mayr's and we will return to it below. Second, the assumption that development and genetics were "separate" after 1935 exaggerates the absolute nature of the split and ignores the long history of work on gene action, known historically as physiological genetics, developmental genetics, and biochemical genetics, which continued into the late 1930s and 1940s.[1] That said, Love does much to reveal the important influence of a tradition of comparative morphology on the contemporary developmental synthesis, thereby supporting his argument that contemporary evo-devo research did not emerge solely from molecular developmental genetics. This claim, however, does not require the additional claim that developmental biology was by and large excluded from the evolutionary synthesis.

When Ernst Mayr and Will Provine organized their conference on the evolutionary synthesis in 1979, they asked the renowned developmental biologist Viktor Hamburger to comment on the role embryology played in the synthesis. Hamburger had been a prominent member of Hans Spemann's research group in Germany before WWII and subsequently went on to revolutionize research on nerve growth and regeneration (Allen, 2004). He opens his essay with the following question: "Did embryology and, more specifically, experimental embryology, assist in the creation of the modern synthesis during the thirties and early forties, or, on the contrary, was it a retarding element?" (Hamburger, 1980, p. 97). His answer is that the "synthesis did not receive any assistance from contemporary embryologists" (Hamburger, 1980, p. 98), and that while "evolutionists were aware of the role of embryology in evolutionary theory" (Hamburger, 1980, p. 99), "the modern synthesis as formulated at the time was incomplete without a chapter dealing with the effects of selection on gene controlled variability of developmental processes" (Hamburger, 1980, p. 100). Hamburger goes on to chart the strategic alienation of embryology from genetics and the response to this shift among biologists of a certain generation, notably T. H. Morgan, Hans Spemann, Ross Harrison, and E. B. Wilson. According to Hamburger, this "impasse" (Hamburger, 1980, p. 103) was overcome by "a younger generation, with open minds" (Hamburger, 1980, p. 104). This generation pioneered work in developmental genetics and included Richard Goldschmidt, C. H. Waddington, Alfred Kühn, Ernst Caspari, I. I. Schmalhausen, Curt Stern, George Beadle, Boris Ephrussi, and even Sewall Wright, to name only a few. Indeed, Hamburger himself argues that books such as Waddington's *The Strategy of the Gene* (1957) synthesized genetics, experimental embryology, and evolution to form a "draft of the 'missing chapter'" in the evolutionary synthesis (Hamburger, 1980, p. 108). Rather than argue that all participants excluded embryology from the evolutionary synthesis, Hamburger claimed that it was more specifically the architects of the synthesis who failed to embrace an active and well-known tradition of developmental genetics. A central feature of the latter, we claim, was the careful consideration of the developmental and evolutionary implications of research on homeotic mutants.

Homeosis and *Drosophila* Developmental Genetics

Following Bateson's 1894 definition and encyclopedic array of examples, reports of homeosis flourished as new mutants were reported in plants and arthropods, including, of course, *Drosophila* (Sattler, 1988; Villee, 1942b). In *Drosophila* alone, the number of recognized homeotic mutants grew steadily since the first was found in 1915. In September of that year, Calvin Bridges of the Morgan group noticed a few mutant flies of a "surprising nature." Although the phenotype was highly variable, extreme forms suggested a transformation of the third thoracic segment, the metathorax, into the likeness of the second thoracic segment, the mesothorax. Bristle-covered structures similar to those normally found only on the mesothorax covered the sides and most of the dorsal surface of the mutant metathorax. The metathoracic legs bore an apical tibial bristle normally found only on the mesothoracic legs. Most striking, however, was the transformation of the metathoracic halteres into mesothoracic wings, giving the appearance of a four-winged fly. The mutation was named bithorax (bx) and its first description was published in 1923 (Bridges & Morgan, 1923). In 1925, Curt Stern found a less variable and more dramatic allele of bithorax, and in 1934 Jack Schultz found an even more extreme allele with high penetrance. Although the bithorax mutation was clearly dramatic and "surprising" to the Morgan group, it did not become an object of further research until Ed Lewis began his work with it in the 1940s (Lewis, 1978, 1994, 1998).

Just as four-winged flies were cropping up in American *Drosophila* cultures they also began to appear in the Soviet Union. In 1927, Professor S. S. Tshetverikov at the Institute for Experimental Biology, in Moscow, discovered a mutant whose phenotype was similar to that of bithorax. The mutant was named tetraptera and was described in 1927 and 1929 by B. L. Astauroff, a member of Tshetverikov's group (Astauroff, 1927, 1929). One year earlier, in 1926, another member of Tshetverikov's group, E. I. Balkaschina, had discovered a remarkable mutant whose antennae had been replaced by leg-like structures. The mutation was named aristapedia and its description published in 1929 (Balkaschina, 1929).[2] Like the tetraptera mutants, aristapedia mutants were highly variable and presented a range of phenotypes. Balkaschina included with her description of the adult phenotype a detailed description of the differences in its development (Balkaschina, 1929). This description included the important observation that aristapedia antennal imaginal discs undergo precocious segmentation relative to wild type antennal discs. By the time a wild type antennal disc has completed its segmentation into 3 segments, for example, an aristapedia antennal disc has already segmented into 7–8 segments. From then on an aristapedia disc continues to develop as a leg rather than an antenna. By interpreting aristapedia antennal disc development as fundamentally leg-like, Balkaschina made the crucial connection between homeotic mutants and their effects on development.

In 1931, Bridges discovered yet another homeotic mutant. In this mutant, named proboscipedia, the unsegmented sponging-type oral lobes of the proboscis develop as two segmented appendages possessing characteristics of both the aristae of antennae and the tarsi of legs. Working with Dobzhansky, Bridges offered an evolutionary interpretation of this new mutant: the mutant oral lobes, albeit nonfunctional and completely different from any dipteran species, nevertheless closely resemble the mouth parts of some biting insects, providing new evidence that dipteran oral lobes

evolved from the labium of lower insects (Bridges & Dobzhansky, 1933). The authors go on to ascribe more general evolutionary importance to the homeotic mutants bithorax, bithoraxoid, tetraptera, and proboscipedia, by arguing that these examples should be adequate to overcome the objections that genetic mutations were capable of producing only superficial changes of the sort that distinguish varieties within the same species or genus:

> A single gene-mutation is, therefore, able to change characters of the kind to which taxonomists ascribe considerable significance.
>
> This fact seems to be contradictory to the view repeatedly expressed by certain authors, according to which mutation changes affect only "superficial" structures, of the kind distinguishing different varieties of the same species or, as a maximum, different species of the same genus. . . . The "fundamental" characters, such as those distinguishing families, orders, and classes, are supposed to be determined not by genes, but by some "central" part of the germplasm, not divisible into genes, and associated with the cytoplasm. (Bridges & Dobzhansky, 1933, p. 589)

Bridges and Dobzhansky were careful not to advocate a macroevolutionary role for homeotic mutations: although they appear to produce "fundamental" phenotypic differences, such mutations could never create a new species.[3] "It is obvious, of course, that mutations similar to bithorax and proboscipedia do not represent appearances of new species. . . . It is interesting, however, to know that even the most 'fundamental' structures can be 'fundamentally' changed by a single gene-mutation" (Bridges & Dobzhansky, 1933, p. 589). For Bridges and Dobzhansky, the dramatic alterations produced by homeotic mutations were of "fundamental" importance to an organism's phenotype, but not necessarily relevant to the evolutionary process.

Balkaschina's developmental perspective and Bridges and Dobzhansky's evolutionary perspective would soon be combined in Richard Goldschmidt's interpretation of homeotic mutants. Drawing on his theory of physiological genetics, Goldschmidt developed what he called a "phenogenetic analysis of homeosis," by which he meant an analysis of the action of homeotic mutations upon development (Goldschmidt, 1938, p. 23).

Beginning in 1911, Goldschmidt, working with Richard Hertwig in Munich and later as Director of the Kaiser Wilhelm Institute for Biology, had been analyzing gene action and developing his theory of physiological genetics. Although his primary concern was the problem of sex determination in gypsy moths and the experimental production of intersexes, he developed a general account of physiological gene action that emphasized rates of reaction and developmental timing. His new field of "physiological genetics" attempted to link development specifically to the "function and action of genes" (Gilbert, 1988). Here genes were visualized as catalysts that affected the velocities of developmental reactions. Under this approach, the normal expression of a trait depended on the corresponding gene's ability to produce enough substance at the right rate during critical periods of development (Goldschmidt, 1938, p. 65). If not enough substance was produced, then the threshold for expression would not be crossed. If the threshold was crossed at the wrong time, the trait would be expressed, but not in its normal form.

Goldschmidt interpreted Balkaschina's work in the light of his theory of developmental velocities. According to Goldschmidt, the mechanism producing the aristapedia

phenotype was a change in the developmental rate of the antennal disc (Goldschmidt, 1938, p. 36). Here the mutant gene alters the process so that development of the antennal disc is accelerated relative to the rest of the larva, the result being that the antennal disc is competent to respond to a putative leg evocator (diffusible inducer, see below) when it is first released in the tissue:

> The mutant gene [aristapedia], which speeds up antennal differentiation . . . makes the antennal disk mature simultaneously with the leg disks; and the evocator substance, which "orders" the formation of tarsus segments, therefore also acts on this disk. Here we have a case where a simple shift in the time element of gene action results automatically in a complicated morphogenetic change. (Goldschmidt, 1938, p. 209)

In this scheme the wild type antennal disc would not become competent in time to respond to the early release of a leg evocator; instead it must wait to be induced by a later antenna evocator. Homeotic mutants such as aristapedia, Goldschmidt believed, were "of the greatest importance in linking gene action with developmental processes" (Goldschmidt, 1938, p. 208). His interpretation of the developmental role of homeotic mutants drew on the embryological work of Hans Spemann and his students as well as the interpretation of this work by Conrad Hal Waddington in Cambridge, England.

Although trained as a paleontologist, Waddington was drawn to embryology by the path-breaking work of Hans Spemann and Hilde Mangold on embryonic induction and the organizer. The organizer is a small group of cells on the dorsal blastopore lip of amphibian blastulas that, when transplanted into another area of the embryo, can induce gastrulation and differentiation of the ectoderm where it does not usually occur. Research on the organizer and embryonic induction was some of the most exciting work done in experimental embryology and dominated the field before WWII. Waddington tracked the results of the Spemann group closely. In 1933 he located the equivalent of the organizer in the chick embryo (Waddington, 1933). Like his counterparts in Germany, Waddington was interested in what allowed the organizer to induce changes. For Spemann, the organizer was an irreducible, holistic phenomenon. For Spemann's student, Johannes Holtfreter, and for Waddington himself, the organizer was instead in need of experimental dissection. In part to put to rest vitalist speculation about the action of the organizer, Holtfreter and Waddington, using amphibians and chicks, respectively, demonstrated that dead organizer tissue could induce gastrulation (Bautzmann, Holtfreter, Spemann, & Mangold, 1932; Waddington, 1933, 1934). This discovery suggested that the organizer must act via an inducing substance. The search for the exact nature of the inducing substance marked the beginning of biochemical embryology. While Waddington engaged in some of this early work on biochemical induction, he was more interested in the connection between embryonic induction and genetics.

In 1934 Waddington coined the term "evocator" to describe inducing substances, because he believed that they evoked potentialities already existing within embryonic tissue (Hall, 1992; Needham, Waddington, & Needham, 1934). Translating the German concept of *Reaktionsfaehigkeit* as competence, tissue responding to an evocator could show a range of induced responses depending on its ability or competence to react. For Waddington, the differentiation of competent tissue in response

to evocators served as an analogy for gene action. Tissue was competent when it was "in a condition of instability in which several types of differentiations are possible" (Waddington, 1939, p. 37). An evocator was the "Active chemical substance of the organizer," which "decides which of the alternative modes of development shall be followed" (Waddington, 1939, p. 37). Waddington articulated a view of development as a series of choices among a restricted number of developmental pathways. In this conception, genes may act in one of two ways. First, they may define the characteristics of each developmental pathway available to the competent tissue. Second, genes act "in a way formally like that of evocators, in that they control the choice of alternatives" (Waddington, 1939, p. 37). For Waddington, the most important example of this latter form of genetic control was the homeotic mutant of *Drosophila*, aristapedia.

Aristapedia was a primary focus of Waddington's research in the late 1930s and 1940s. In his 1940 book, *Organisers and Genes*, he reviewed the aristapedia alleles, ordering their strength in producing the aristapedia phenotype as follows: aristapedia Bridges (ss^{aB}), aristapedia (ss^{a}), aristapedia Spencer (ss^{aSp}). In looking specifically at intermediate forms of the phenotype, Waddington noted that in actuality there is no "intermediate" at the tissue level, because a segment must develop as either an arista or a tarsus. Since it is typically the proximal parts of the arista that become tarsus-like, Waddington proposed that various thresholds exist for the switch to tarsus development as one moves down the length of the arista. Waddington was particularly interested in the effects of other mutants known to affect *Drosophila* legs and antennae. Waddington found that both tarsus mutants and antenna mutants had an effect on aristapedia (ss^{a}) antennal discs. Waddington interpreted these results with his branching track model (see Figure 7.1). In this model, genes are characterized as acting on various points along the developmental tracks available to antennal disc tissue. First, major evocator genes, such as aristapedia, determine which track (either the tarsus-track or the arista-track) the imaginal disc tissue will follow. One of the two paths must be followed, thus accounting for Waddington's observation that no real transitional zones exist with aristapedia mutants. Second, additional evocator genes may alter the form of the tracks as follows: mutant alleles affecting the phenotype regardless of whether tissue develops along the tarsus-track or the arista-track probably act before the main fork (producing the alternate dotted track in Figure 7.1), whereas mutant alleles affecting only aristae or tarsi are likely to act after the main fork. With this scheme, Waddington was able to make sense of the range of mutants affecting how the antennal disc develops (Waddington, 1940).

Waddington developed his model of branching tracks, later known as the epigenetic landscape, in response to the path-breaking work of Boris Ephrussi and George Beadle on eye color mutants in *Drosophila* (Gilbert, 1991a). Beadle and Ephrussi adapted the concepts and transplantation techniques of the Spemann and Kuhn groups to study the extent of induction on imaginal eye discs transplanted into the abdomens of genetically different adult flies. The result of their painstaking series of experiments was a proposed biochemical pathway for the formation of eye color (Beadle & Ephrussi, 1937a, 1937b; Berg & Singer, 2004). The notorious difficulty of Beadle and Ephrussi's experiments made research on homeotic mutants much more appealing, since they represented natural experiments in *Drosophila* developmental genetics. Applied to the problem of antennal development, Waddington transformed

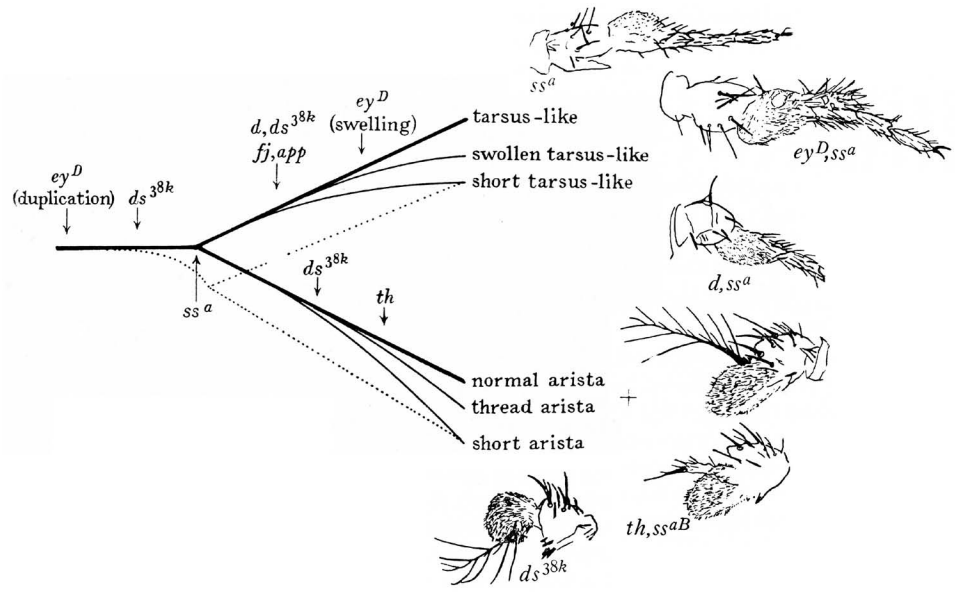

Figure 7.1. Forms of aristapedia mutants in *Drosophila* and their developmental track system. Abbreviations: ey^D = eyeless-Dominant, ds^{38k} = dachsous 38k, ss^a = spineless-aristapedia, *d* = dachs, *fj* = four-jointed, *app* = approximated, *th* = thread. From Waddington (1940), composite of figures 8 and 9. Note that Waddington did not include an illustration of the *th* mutant alone. Instead he drew *th* with ss^{aB}, a weak allele of *ss*, which we have included here as a stand-in. Reprinted with the permission of Cambridge University Press.

Beadle and Ephrussi's notion of a linear pathway into a system of branching pathways (Gilbert, 1991a, 1991b).

At the same time that Waddington was developing his branching track model, Werner Braun, working in Goldschmidt's laboratory in Berkeley, was conducting experiments concerning the impact of evocators in aristapedia mutants. Braun, like Goldschmidt, was forced to leave Nazi Germany and Goldschmidt accepted him as a graduate student. Because Goldschmidt had suggested that the development of aristapedia antennal discs should be identical to that of leg discs, Braun sought to test the idea that aristapedia antennal discs were under the control of the genes that usually control leg development. Genes, such as dachs and thickoid, which normally shorten legs, should then presumably cause a shortening of aristapedia antennae. Conversely, mutations such as aristaless, which normally affect only antennae, should not affect the aristapedia antennae. In a series of crosses, Braun was able to show that this was indeed the case (Braun, 1940, pp. 144–146).

Braun also sought to test Goldschmidt's conjecture that the aristapedia gene (ss^a) acted by altering the competency of antennal discs rather than by altering their evocator or inducing substance (Braun, 1940, pp. 146–148). Using the transplantation technique adapted to *Drosophila* by Ephrussi and Beadle, Braun transplanted ss^a antennal discs into wild type larvae and vice versa. Braun's experiments revealed that ss^a antennal discs, transplanted into wild type hosts of varying age from 2 days to pupation, developed as legs. This was consistent with Goldschmidt's hypothesis, since the mutant discs were not "rescued" by the release of a normal evocator. Conversely, wild type antennal discs transplanted into ss^a hosts retained their tendency to develop

normally as antennae. Supporting Goldschmidt's interpretation, Braun claimed that his experiments indicated that ss^{a} altered the antennal disc itself, making it competent to respond to the release of a leg evocator (Braun, 1940, pp. 148–149).

Waddington believed that his branching track model explained both his and Braun's data on aristapedia and other leg and antenna mutants. He did not comment on Goldschmidt's proposal for the role of developmental velocities in determining the developmental fate of antennal discs. The connection between Waddington's and Goldschmidt's schemes, however, was articulated by another of Goldschmidt's students, Claude Villee. Villee also worked on aristapedia mutants during the early 1940s, first as a graduate student and later as a faculty member at the University of North Carolina. His research adopted a phenogenetic approach that he believed offered special insight into the normal mechanisms of development. He was especially interested in using temperature effects to analyze the expression of homeotic mutants, such as aristapedia.

Villee found that increases in temperature tended to decrease the expression of ss^{aB} to the point that it was indistinguishable from wild type. Conversely, decreases in temperature tended to increase the expression of ss^{aB} to the point where its phenotype approached that of the stronger allele ss^{a}. It thus appeared that higher temperatures promoted antennal development while lower temperatures promoted tarsal development. Applying Goldschmidt's model of developmental velocities, Villee suggested that the effect of temperature on development was the "differential acceleration or retardation of certain processes in relation to others, since the processes involved probably have different temperature coefficients" (Villee, 1943, p. 94). Villee's interpretation was faced with a theoretical problem, however. Temperature treatments on aristapedia mutants were most effective in altering development at 4 days, 2 days after the fate of the antennal disc was supposed to have been determined. This suggested to Villee that either Waddington's tarsus/arista fork occurred later in time or that the branching point was not final, with some time remaining for the possibility of jumping to another track (Villee, 1943, p. 95). Villee conducted similar phenogenetic studies of temperature in relation to homeotic mutants, including tetraltera, proboscipedia, and bithorax (Villee, 1942a, 1944, 1945). Each of these mutants demonstrated variable expression in response to temperature shifts, but they did not display the same type of response; in some cases, increased temperature led to a more pronounced mutant phenotype.

Interpretations of the developmental genetics of homeotic mutants such as aristapedia have since significantly departed from both Waddington's evocator switch genes and Goldschmidt's developmental velocities (Ouweneel, 1976).[4] Nevertheless, the research of Waddington, Goldschmidt, and Villee on homeotic mutants demonstrates that there were significant research programs underway during the period of the evolutionary synthesis that took the best experimental embryology of the day and sought to integrate it with genetics. Of course, this is not to say that work on induction captures the entire scope of embryological research at the time. Embryology, and later developmental biology, included a diverse set of research areas including fertilization, cell cleavage, gastrulation, differentiation, regeneration, organogenesis, growth, and metamorphosis (Willier, Weiss, & Hamburger, 1955). Our claim is that an important area of experimental embryology was integrated with genetics beginning in the 1930s and that research on homeotic mutants was a key site for this integration.

Evolutionary Interpretations

As we previously noted, Bridges and Dobzhansky were the first to draw evolutionary implications from an analysis of homeotic mutations in *Drosophila*. For them, homeotic mutants could reveal not only serial homology between structures at different locations along the body axis but also homology between structures in *Drosophila* and those of other insects. Such arguments, based on genetic evidence but grounded in comparative morphology, were one way to construct an evolutionary interpretation of homeotic mutants. Another was to integrate an account of the developmental genetics of a mutant with an evolutionary account of its origin and spread. As we shall see, Richard Goldschmidt and Claude Villee actively pursued both avenues of evolutionary interpretation with regard to homeotic mutations.

In *The Material Basis of Evolution* (1940) Goldschmidt sought to shake neo-Darwinian confidence in the idea that the gradual accumulation of small mutations could lead to speciation. He argued for the differentiation of micro- and macroevolution by proposing two alternative processes of macroevolution, both distinct from microevolution. The so-called "bridgeless gaps" between species could be spanned by what Goldschmidt called macromutations. These could be either systemic mutations or mutations that produce large phenotypic effects by affecting developmental processes. Systemic mutations were large-scale rearrangements or repatternings of the chromosome. According to Goldschmidt, "A complete repatterning might produce a new chemical system which as such, i.e., as a unit, has a definite and completely divergent action upon development, an action which can be conceived as surpassing the combined actions of numerous individual changes by establishing a new chemical system" (Goldschmidt, 1940, p. 203). A systemic mutation could potentially produce a significant phenotypic shift in a relatively short period of time. Goldschmidt thought of these types of mutations as "phylogenetic consequences" of his rejection of the particulate gene concept (Dietrich, 2000). Drawing on position effect research, H. J. Muller's research on chromosomal rearrangement, and his own work on rearrangements and mutability, Goldschmidt had postulated that all mutations were in fact rearrangements and that a hierarchy of genetic units was preferable to Morgan's bead-on-a-string model. Not having any direct evidence of systemic mutation, Goldschmidt did as Darwin and argued by analogy to developmental macromutations. The developmental macromutations discussed in the last third of *The Material Basis of Evolution* captured Goldschmidt's understanding of the importance of developmental genetics for evolution. "A single mutational step affecting the right process at the right moment can accomplish everything," Goldschmidt claimed, "providing that it is able to set in motion the ever present potentialities of embryonic regulation" (Goldschmidt, 1940, p. 297). The results of these macromutations were what Goldschmidt called hopeful monsters and, as examples, Goldschmidt marshaled literally every homeotic mutation available to him. He noted the macroevolutionary leap of dipterans to two wings from four wings suggested by bithorax and tetraptera, a connection that would later be articulated somewhat differently by Ed Lewis (Lewis, 1978). He also pointed out that the structures intermediate between wings and halteres seen in his own homeotic mutant tetraltera were strikingly similar to the rudimentary wings of the termitophile fly *Termitoxenia* (Goldschmidt, 1940, p. 36). In sum,

> the facts concerning the range of potential changes of development caused by a single or a few genetic steps, which are small from the genetic point of view but large in the morphogenetic result, demonstrate that it is possible, and even probable, that macroevolution takes place without accumulation of micromutations under pressure of natural selection. (Goldschmidt, 1940, p. 331)

More important is the fact that, for Goldschmidt, homeotic mutations provided a glimpse into his dream of a fully integrated biology, which contained elements of genetics, embryology, and evolutionary theory:

> The real importance of these facts [homeotic mutations] for a general analysis of evolution appears only in the light of our interpretation. If an embryological system of the type described underlies the process of segmental differentiation of appendages, and if this system is controlled by the genotype in the way described in the theory of balanced reaction [i.e., developmental reaction] velocities, a system obtains in which very small genetic changes in that part of the genotype which controls the speed of differentiation . . . may lead to sudden macroevolutionary steps in all details of segmental divergence. (Goldschmidt, 1940, p. 208)

This idea of macromutations in developmentally significant genes attracted significant support, but it did nothing to convince Goldschmidt's critics of the value of systemic mutations. Moreover, most biologists thought that Goldschmidt had overstated the potential for macromutations to produce new species: their phenotypic effects could be quite striking but they were unlikely to represent new species.

The controversy over Goldschmidt's evolutionary interpretation certainly made it difficult to advocate a more modest role for macromutations in evolution. In his second edition of *Genetics and the Origin of Species* (1941), for instance, Theodosius Dobzhansky, who earlier had suggested that homeotic mutants could offer insights into homology, argued vehemently against the idea of homeotic mutants as hopeful monsters. Drawing on his earlier distinction between fundamental and superficial changes, Dobzhansky asked, "is the appearance of a four-winged *Drosophila* a fundamental or superficial change? Is a mutation which diverts the embryonic development to a wrong course and thus causes death fundamental or superficial?" Note that these two questions could afford very different answers. The second question presumes that any homeotic change is to a "wrong course." Dobzhansky continues his argument by claiming, "Those who would like to see a mutant fly without an alimentary canal, or with the location of the heart and nerve cord exchanged, overlook the fact that such a mutant could not survive and hence could never be detected" (Dobzhansky, 1941, p. 24). While bithorax mutants are viable, they are clearly less fit than other fruit flies. Dobzhansky raised in his objection a line of reasoning that would be echoed by others, namely that Goldschmidt had not given enough careful consideration to the population dynamics necessary for a new mutant to succeed and spread. This line of argument would be taken up by G. G. Simpson, as well as by Sewall Wright.

In his *Tempo and Mode of Evolution* (1944) G. G. Simpson raised a number of objections to Goldschmidt's evolutionary claims concerning homeotic mutants. Simpson argued that homeotic mutants may have large effects, but they do not create new species, and hence are no different from other mutations evolutionarily. In addition, Simpson argued "the appearance of a mutant individual is not evolution"

(Simpson, 1944, p. 53). Homeotic mutants, according to Simpson, were still subject to selection and still had to spread through a population (Dietrich, 1995, 2000). Sewall Wright raised similar criticism in his own review of Goldschmidt's views in 1941. According to Wright, "Goldschmidt gives no serious discussion of questions of dynamics. . . . Yet the dynamics of the postulated accumulation of subliminal steps in chromosome repatterning and of the establishment of the systemic mutations, once the threshold has been passed, are questions which must be considered" (Wright, 1941, p. 166). Interestingly, Goldschmidt and Wright would later collaborate to address exactly this issue of the population dynamics needed for large mutations. Wright and Goldschmidt never published a paper together, but, by 1950, Wright included large-effect mutations as a part of his shifting balance theory of evolution (Dietrich, 2000; Wright, 1950, 1977). Goldschmidt gladly accepted Wright's model of the evolution of large-effect mutations and began to argue for the importance of population structure and natural selection with regard to their fixation (Goldschmidt, 1952b, pp. 101–103). However, while Wright emphasized population structure and the elements of his shifting balance theory, Goldschmidt continued to emphasize developmental processes. According to Goldschmidt, regulatory and integrative processes of development relieved "the evolutionary processes, in the case of macromutations, of a good deal of the work which would be necessary if everything were based upon more and more modifiers for a thousand details." For this reason he tried to "convince evolutionists that evolution is not only a statistical genetical problem but also one of the developmental potentialities of the organism" (Dietrich, 2000; Goldschmidt, 1952b, p. 103).

A different type of objection to evolutionary interpretations of homeosis came from Gordon Ferris. A Professor of Entomology at Stanford University, Ferris was an expert on the comparative morphology of insects. His careful studies of insect homology bolstered his gradualist perspective on evolution. Ferris did not object to Goldschmidt's saltational interpretation of homeosis directly, however. In a 1942 review article on homeosis, Claude Villee used his own research to extend Goldschmidt's claims for homeotic mutants as homologous structures (Villee, 1942b). Villee claimed that homeotic phenomena had much to offer both embryology and comparative anatomy. In particular, he argued that mutants such as aristapedia demonstrated the serial homology between antenna and tarsus while proboscipedia corrected the older comparative morphology literature by demonstrating that "the oral lobes of Diptera are homologous to the labium of other insects" (Villee, 1942b, p. 502). Villee's pronouncements on proboscipedia in fact merely summarized the interpretation of Bridges and Dobzhansky from 1933, but Ferris did not appreciate the source of the claim. Ferris castigated Villee for his genetic chauvinism, rightly pointing out that he had skipped over a large body of work on comparative morphology that had already demonstrated that "the 'oral lobes' of flies are in fact nothing more than the labial palpi" (Ferris, 1943). In a rather pointed fashion, Ferris remarked that comparative morphologists did not need a geneticist pointing out something that they already knew.

Never one to shy away from an argument, Goldschmidt defended his former student by responding to Ferris on Villee's behalf. In his reply, Goldschmidt assumed his mantle as a classically trained German morphologist asserting that he "cannot be accused of lack of understanding for the morphologist's point of view, having spent

many years of his life in work on comparative morphology and having been guilty of many more or less good phylogenetic homologisations on the basis of such work" (Goldschmidt, 1945b, p. 42). He then launches into an extensive review of the literature on insect morphology demonstrating that the issue of mouthpart homology was still controversial and could therefore still benefit from genetic evidence. Of course, Goldschmidt could not resist taking a jab at Ferris, commenting that geneticists "do not want to parade any superiority but just to make the proper use of a superior tool, which they happen to wield" (Goldschmidt, 1945b, p. 44).

Ferris's true venom was reserved for Villee's embrace of Goldschmidt's saltational interpretation. Villee claimed that the analysis of homeotic mutants demonstrated that dipteran oral structures did not have to evolve in a process of gradual modification. In fact, insects with intermediate mouthparts, according to Villee, would not have been able to feed (Villee, 1942b). Such a comment spurred Ferris to respond with "All of which can but wring an agonized scream from the depths of a morphologist's soul. The writer of that statement, like most nonentomologists, seems to be quite unaware of the fact that there are thousands upon thousands of species of flies other than *Drosophila melanogaster* and that these flies present probably hundreds of those curious 'intermediate types of mouth parts' condemned by him, with which they get along very nicely" (Ferris, 1943, p. 4). Evidence of an evolutionary series was exactly what Goldschmidt had used to distinguish microevolution from macroevolution, however. For Goldschmidt, quantitative variation was the hallmark of evolution within a species. The transition from one species to another, however, required a change in the kind of morphological structure in question. Ferris's appeal to innumerable transitions, according to Goldschmidt, confused the many variations typical within species diversification with the decisive "first step from a biting labium to a sucking one, from a palpus to a labellum" (Goldschmidt, 1945b, p. 46). Goldschmidt believed that homeotic mutants demonstrated that this first step was the product of a large, single mutational event.

Irwin Herskowitz, a graduate student of Dobzhansky's at Columbia in the late 1940s, also called Goldschmidt's homology claims into question in a 1949 paper on the homeotic mutant hexaptera, which possessed ectopic structures resembling wings, halteres, and legs on the dorsal prothorax (Herskowitz, 1949). Herskowitz argued that the different phenotypes produced by homeotic mutations do reveal information about ancestral structures. However, if homology is understood as similarity based upon a common evolutionary past, then the serial "homologies" Goldschmidt identifies between different organs in *Drosophila* cannot properly be regarded as true homology (Herskowitz, 1949, p. 24). Because Goldschmidt's interpretation depended on imaginal discs having the potential to become eyes, antennae, legs, or wings, the phenomenon whereby antennal discs produce legs after exposure to a leg evocator does not support the claim that legs and antennae are derived from a shared ancestral structure (Herskowitz, 1949, p. 24).

While the exact message of homeotic homologies was clearly open to interpretation, these discussions of the evolutionary implications of homeotic homologies represent an important intersection between traditions in genetics and comparative morphology. Goldschmidt's training and early research in comparative morphology allowed him to explore this connection with ease. Nevertheless, his use of homology

to argue for macroevolution was controversial and tainted the evolutionary interpretation of homeotic mutants.

By the 1950s, Dobzhansky, Mayr, and Simpson split Goldschmidt's work on the genetics of homeosis apart from its evolutionary interpretation. Goldschmidt's work on the genetics of homeotic mutants and other mutations affecting development was widely recognized and assimilated into the neo-Darwinian literature as a source of variation. Dobzhansky's third edition of *Genetics and the Origin of Species* (1951 [1939]), for instance, claims that mutations affecting early development can have massive phenotypic effects. Developmental mutations were recognized as one of the wide variety of genetic changes possible. Developmental mutations, however, were not accepted as a mechanism for species formation. Echoing his previous position from as early as 1933, Dobzhansky argued that the genetic and morphological change that homeotic mutations produced contributed to the same process of selection and speciation as any other type of mutant. By 1953, Simpson also acquiesced a bit to Goldschmidt's proposal concerning phenogenetics and the variable expression of homeotic mutants. To Simpson, Goldschmidt's scheme appeared to be "at least a possible physiological mechanism for the production of the observed variations" (Simpson, 1953, p. 76). Simpson continued to deny, however, that these mutations (homeotic or otherwise) could produce new species.

Conclusion

C. H. Waddington and Richard Goldschmidt and his students perceived the synthetic potential of homeotic mutation research. Mutants in *Drosophila*, such as aristapedia, afforded opportunities to integrate genetics and development. Morphological similarities suggested one type of evolutionary implication in terms of homology, while work on developmentally significant mutations suggested another. As such, homeotic mutants had the potential to become unifying objects of research, to transform the evolutionary synthesis into an evolutionary-developmental synthesis.

Constructing homeotic mutants as a unifying object of research required a system of claims linking the genetic, developmental, and evolutionary interpretations of these phenomena (see Figure 7.2). The connection between genetic and developmental approaches to homeotic mutants was established early in the work of Balkaschina and strengthened by Waddington and Goldschmidt throughout the 1930s and 1940s. Of all the connections between different interpretations of homeosis, this was the most carefully explored by 1950. The evolutionary implications of interpreting homeotic mutants as developmental phenomena were more fraught.

Goldschmidt tied his interpretation of homeosis as a product of induction and timing with an extremely controversial saltationist argument for macroevolution. Only after years of debate did architects of the synthesis somewhat begrudgingly accept that mutations affecting developmental processes, such as homeotic mutants, could have large phenotypic effects and constitute an important source of genetic variability. This effectively downplayed their importance relative to larger numbers of genes of more modest effect.

The evolutionary significance of homeotic phenomena in revealing homologies was suggested by Bridges and Dobzhansky in 1933, but actively pursued by Goldschmidt, Villee, and others. Homeotic homology claims represent a connection to

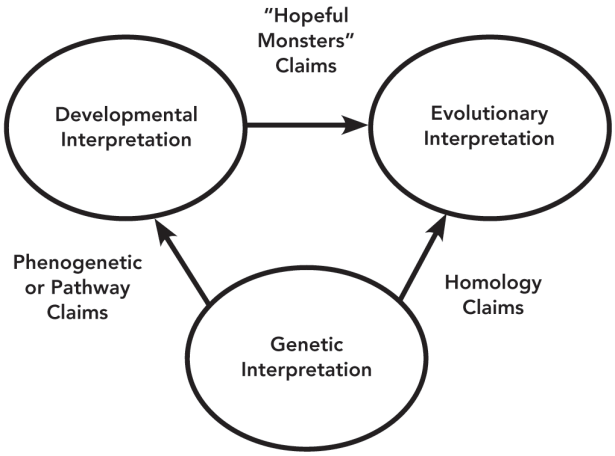

Figure 7.2. A schema for the construction of homeotic mutants as unifying objects of research based on Richard Goldschmidt's efforts from 1933 to 1952.

evolution independent of developmental biology, but not independent of comparative insect morphology. The exchange between Ferris and Goldschmidt did not foster a stronger connection between geneticists and comparative morphologists. Indeed, we have found no evidence that Mayr and Simpson were even aware of the evolutionary homologizing produced by comparative insect morphologists, such as Ferris.

It is tempting to ascribe the general disregard for homeosis as a unifying object of research to the controversial status of its chief advocate, Richard Goldschmidt. This narrative, however, fails to do justice to the complexities of homeotic research in the synthesis period. While Goldschmidt's views on macroevolution, especially his model of systemic mutation, were severely criticized, his interpretation of the significance of homeotic mutants was given more credence (Dietrich, 1995). Goldschmidt advocated a system of claims that integrated and unified the genetic, developmental, and evolutionary interpretations of homeosis he had proposed. His critics, however, were more interested in the status of individual claims and interpretations than in the integrated system that could have seeded an evolutionary-developmental synthesis. The result was that Goldschmidt engaged paleontologists, morphologists, and geneticists on those aspects of his approach to homeosis that were relevant to their particular specialties. Seeing problems within their own domains regarding the interpretation of homeotic mutants, researchers were often unwilling to draw connections to other domains. Geneticists such as Curt Stern and Ed Lewis, for instance, believed that the genetic understanding of homeotic mutants and their action during development demanded further resolution before evolutionary claims could be ventured. Through the 1950s and 1960s, Stern and Lewis would continue research programs that integrated development and genetics. It is worth noting that neither Stern nor Lewis lost sight of the evolutionary implications of their research; they were just very cautious about articulating those implications (Lewis, 1964; Stern, 1955). That homeotic mutants failed to facilitate a synthesis of evolution, development, and genetics on a

large scale did not result from a failure to integrate development and genetics, but from the difficulty of providing an evolutionary interpretation for these phenomena. Homeotic mutants did not go unrecognized, and yet their assimilation into the evolutionary synthesis did not fundamentally alter the nature of neo-Darwinism.

It is clear that substantial differences did arise between synthesis architects and developmental biologists such that the latter were unable to play a defining role in the synthesis (Amundson, 2005). However, rather than bemoan the exclusion of development from the evolutionary synthesis, we suggest bemoaning its assimilation. In the effort to define the emerging field of evolutionary biology, developmental issues were subsumed within evolutionary genetics without significantly altering the issues and problems seen as central to the evolutionary synthesis. Homeotic mutants, when they were recognized, became merely another source of genetic variation. Indeed, similar cases of conceptual assimilation, and even co-option, into and by the synthesis have been documented (for review, see Amundson, 2005, pp. 152–155, 194–195). These include, for example, Mayr's recasting of Waddington's concepts of canalization (Waddington, 1940) and genetic assimilation (Waddington, 1942) as merely additional ways to increase adaptiveness in a stable environment (Amundson, 2005, p. 194; Mayr, 1970, p. 108). In this regard it is interesting to note that I. I. Schmalhausen's similar concept of stabilizing selection may have been more palatable to Dobzhansky, because it was offered as merely a missing detail of the synthesis rather than, as Waddington claimed, an essential complement (Gilbert, 1994).

By assimilating developmental phenomena such as homeotic mutations, or the process Waddington observed and referred to as genetic assimilation, developmental biologists were denied authority to speak to the questions and approaches that characterized research in evolutionary biology. Understanding the synthesis as a struggle for authority (Sapp, 1987) allows us better to grasp the process of disciplinary negotiation that marked the period. The struggle is evident in Waddington's 1953 objections to the supposed contributions of the synthesis. In an essay entitled "Epigenetics and Evolution," Waddington attacked the evolutionary synthesis for its inordinate emphasis on population genetics. Noting that those who raised objections to the synthesis tended to be "biologists with an embryological background," he argued that mathematically modeling changes in genotypes and phenotypes ignored what connected genotype to phenotype (Gilbert, 2000; Waddington, 1953). Although Waddington goes on to argue for his theory of genetic assimilation and canalization, what is significant about Waddington's argument for present purposes is his articulation of how the problems and concepts at the core of the evolutionary synthesis could be reconsidered from a developmental point of view. Waddington's complaint does not demonstrate the exclusion of embryology from evolution, but rather, that he, Goldschmidt, and others were actively engaged in a struggle for authority within evolutionary biology.

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NOTES

1. In an article entitled "Know your ancestors: themes in the history of evo-devo," Love and Rudolf Raff additionally deny the deep "ancestry" of developmental genetics by producing timeline diagrams where developmental genetics appears only after molecular genetics in the 1970s (Love & Raff, 2003, pp. 328–329).
2. When Alfred Sturtevant read Balkaschina's paper he realized that the aristapedia mutation mapped to the already known spineless (ss) locus and so assigned the notation ss^a to aristapedia. A dominant mutant exhibiting a similar phenotype, produced by a gain-of-function mutation in the Antennapedia locus, was first identified and named in 1948 by Sien-chiue Yu, a graduate student of Ed Lewis (Gerhing, 1998, pp. 32–34). A phenotypically similar dominant allele of Antennapedia was described in the same year by Jean Le Calvez, but misidentified as a dominant allele of aristapedia (Le Calvez, 1948; Gerhing, 1998, pp. 32–34).
3. For a discussion of "fundamental" and "superficial" changes see Amundson, 2005, pp. 180–186, and Sapp, 1987.
4. Issues of timing and determination in imaginal discs were questioned by Marguerite Vogt. Daughter of the well-known German biologists Oskar and Cecile Vogt, Vogt conducted a series of experiments on labile periods of determination in *Drosophila* (Vogt, 1946, 1947). Her results argued against Goldschmidt's earlier interpretation of homeotic gene action resulting from timed exposure to evocators and seemed to support Waddington's branching track model.

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