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TIMELINE

Richard Goldschmidt: hopeful monsters and other 'heresies'

Michael R. Dietrich

Richard Goldschmidt is remembered today as one of the most controversial biologists of the twentieth century. Although his work on sex determination and physiological genetics earned him accolades from his peers, his rejection of the classical gene and his unpopular theories about evolution significantly damaged his scientific reputation. This article reviews Goldschmidt's life and work, with an emphasis on his controversial views.

Reputations, both good and bad, are context dependent: as science and circumstances change, so can they. Richard Goldschmidt's rejection of the classical gene and his controversial views on evolution have earned him a reputation as a 'scientific heretic'[1]. During his lifetime, Goldschmidt certainly sought controversy and even referred to some of his ideas as 'heresy'. However, by the end of his life, Goldschmidt had also earned important accolades, such as election to the National Academy of Science and the Presidency of the International Congress of Genetics[2] (TIMELINE).

For historians of science, Goldschmidt's enduring reputation as a 'scientific heretic' presents several challenges as we seek to understand his role in twentieth century biology. His positive contributions to genetics made him an important and respected scientist during the first half of the twentieth century. However, his controversial rejection of the classical, particulate gene concept and gradual evolution put him at odds with many leading biologists in the United States. Why did he lose faith in the classical gene and neo-Darwinian evolution? Answering this relatively straightforward historical question is complicated by the fact that Goldschmidt's negative reputation among scientists remains strong. Histories that do not begin with the assumption that Goldschmidt was and is a 'heretic' run the risk of appearing as if they are defending his science. Indeed, several biologists in the past 25 years have tried to rehabilitate his theories, as they extol the merits of some aspect of his work[1,3,4]. I have no desire to rehabilitate or defend all of Goldschmidt's science, but I believe that his reputation as a heretic obscures important features of his life and work. In this article, I emphasize the development of his controversial views, as well as his broader scientific ambition of integrating evolutionary biology, developmental biology and genetics.

Becoming a biologist
Goldschmidt was born into an upper-middle-class family in Frankfurt am Main, Germany, in 1878. He received a classical education that emphasized Latin and Greek, and read widely in literature, history and science. His interest in natural history was fostered as a student at
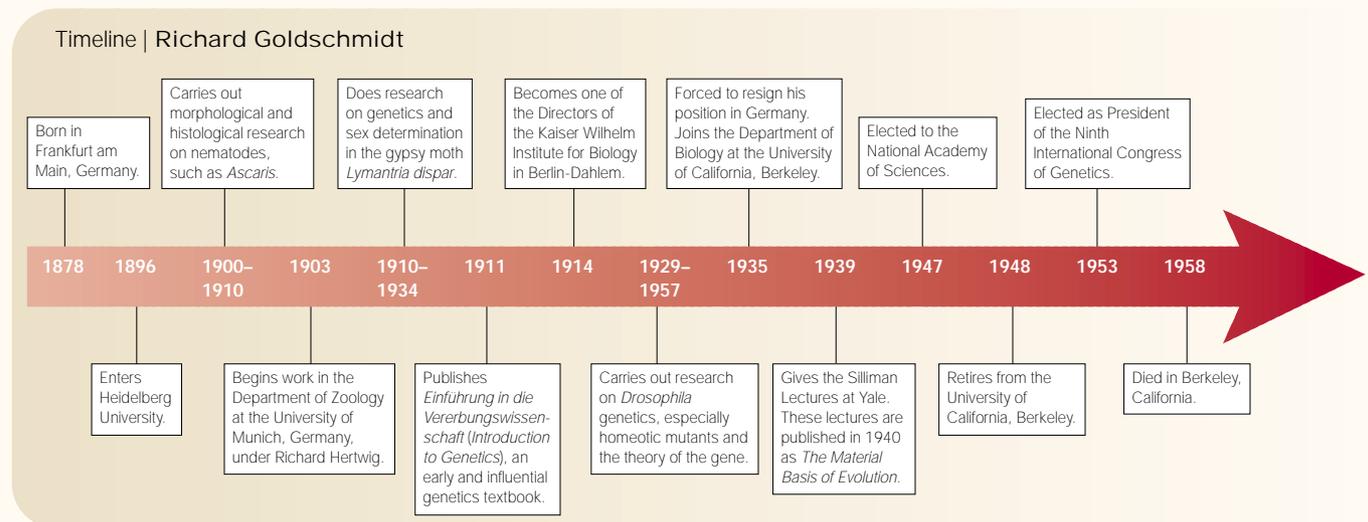

Timeline | **Richard Goldschmidt**

Born in Frankfurt am Main, Germany. — **1878**

Enters Heidelberg University. — **1896**

Carries out morphological and histological research on nematodes, such as *Ascaris*. — **1900–1910**

Begins work in the Department of Zoology at the University of Munich, Germany, under Richard Hertwig. — **1903**

Does research on genetics and sex determination in the gypsy moth *Lymantria dispar*. — **1910–1934**

Publishes *Einführung in die Vererbungswissenschaft* (*Introduction to Genetics*), an early and influential genetics textbook. — **1911**

Becomes one of the Directors of the Kaiser Wilhelm Institute for Biology in Berlin-Dahlem. — **1914**

Carries out research on *Drosophila* genetics, especially homeotic mutants and the theory of the gene. — **1929–1957**

Forced to resign his position in Germany. Joins the Department of Biology at the University of California, Berkeley. — **1935**

Gives the Silliman Lectures at Yale. These lectures are published in 1940 as *The Material Basis of Evolution*. — **1939**

Elected to the National Academy of Sciences. — **1947**

Retires from the University of California, Berkeley. — **1948**

Elected as President of the Ninth International Congress of Genetics. — **1953**

Died in Berkeley, California. — **1958**

the University of Heidelberg, where he took classes with the anatomist Karl Gegenbaur and the zoologist Otto Bütschli. Goldschmidt's education in the German morphological tradition was completed under Richard Hertwig at the University of Munich. Although he earned his doctoral dissertation under Bütschli, on the development of the trematode *Polystomum*, it was not until he began work as an assistant in Hertwig's laboratory that he began to move away from the histology of nematodes towards the nascent field of genetics. In Hertwig's laboratory, Goldschmidt spent the first years of his career painstakingly describing the development of nervous systems in *Ascaris* and the anatomy of *Amphioxus*; this careful work earned him accolades in the German scientific community. He was promoted in Hertwig's laboratory and founded the journal, *Archiv für Zellforschung* (*Archive for Cell Research*). At the same time, Hertwig's interest in chromatin sparked similar interests in Goldschmidt, and so he began to work on chromosome number and behaviour[2].

Inspired by Wilhelm Johannsen's *Elemente der exakten Erblichkeitslehre* (*Elements for the Exact Study of Heredity*), Goldschmidt turned his attention in 1909 to the experimental study of genetics. Guided by reports of the unusual sexual morphs produced by hybridization in the gypsy moth *Lymantria*, Goldschmidt decided to focus his attention on the problem of sex determination in this organism. Sex determination was an important scientific issue at the turn of the twentieth century as biologists such as Carl Correns and Edmund Beecher Wilson sought to ground it in Mendelian genetics[5,6]. Goldschmidt's approach to this topic was shaped by the particular dynamics of sex determination in the gypsy moth. Typically, gypsy moths are sexually dimorphic: females have white wings with dark bands, whereas males are smaller and have brown wings. When different geographical varieties of gypsy moth are mated, however, they produce a continuum of sexual types that range from female to male (BOX 1). Goldschmidt coined the term 'intersex' to describe these intermediate forms and proceeded to develop a genetic theory that could account for their phenotype[7].

Physiological genetics

As he tried to explain intersexuality in the gypsy moth, Goldschmidt articulated a dynamic and quantitative theory of genetics, which integrated heredity with developmental and physiological processes. Although many geneticists during this time period, especially *Drosophila* geneticists under the influence of Thomas Hunt Morgan, emphasized gene transmission, Goldschmidt focused on gene function or gene action. In other words, Goldschmidt thought that an important aspect of genetics was to integrate the gene with the physiological processes of development[8,9]. The key to explaining the range of intersexes produced in *Lymantria*, according to Goldschmidt, lay in the balance of the Mendelian factors that determine sex. Goldschmidt believed that each individual contained factors for both sexes; the sexual phenotype expressed depended on the relative strengths of the male and female factors, which were produced in varying quantities[10] (BOX 1).

From 1911 to 1931, Goldschmidt developed a theory of sex determination that would provide a unifying explanation of the phenomenon in all animals. Goldschmidt's solution was articulated as a principle of genetic action that he called the 'time law of intersexuality'[11], in which intersexes could be explained by the amount of time that they spent developing as one sex before switching to the other (BOX 1). Extending the scope of the time law to vertebrates forced Goldschmidt to distinguish between what he called zygotic intersexuality and hormonal intersexuality[10]. Zygotic intersexuality was grounded in genetic differences that were present in the zygote; by contrast, hormonal intersexuality included sexual differentiation later in life that was mediated by hormones and controlled by hormone-producing tissues. Vertebrates had hormonal intersexuality, whereas invertebrates had zygotic intersexuality. Although this distinction diminished the ubiquity of the time law for all animals, it revealed Goldschmidt's desire to understand a broad range of phenomena and to bring them under one or a few unifying

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Box 1 | **Goldschmidt's genetic theory of sex determination**

Goldschmidt's studies on the many intersex morphologies seen in hybrids of the gypsy moth *Lymantria* led him to formulate a general genetic theory for sex determination. The diagram shows some of the intersex morphologies in *Lymantria*: the five intersex morphs (I–V) contain decreasing amounts of 'maleness', as indicated by the reduced amount of brown, typically male, pigment compared with the white and striped features of the female morph (the butterfly shown at the top is a normal male). To explain the expression of these intersex morphologies, Goldschmidt proposed that all males and females contained two male and two female factors. Females were homozygous for the female factors (FF) and heterozygous for the male factors (Mm). Males were homozygous for both male and female factors. Females were therefore designated FFMm, and males were designated FFMM. In a genetic male, if both factors in the MM pair were weak and both FF were strong, the female factors would predominate and produce an intersex instead of a phenotypic male.

Fig. 12. Series of increasing male intersexuality; above normal ♂.

Factors did not produce traits in a direct fashion; instead, they did so by producing a substance, such as an enzyme or hormone. Because the quantity of substance and rate of its production could vary, the potency, or what Goldschmidt called the 'valence', of the factor was also said to vary — in a range from strong to weak. The production of male and female moths depended on the balance of male and female factors, and so Goldschmidt named his hypothesis "the balance theory of sex"[11]. Calvin Bridges would later introduce a different theory under the same name to explain intersexes in *Drosophila*.

In an attempt to account for sex determination in all animals, Goldschmidt charted the development of several distinguishing sexual characteristics in species other than *Lymantria*. He found that, even though all the cells of an organism had the same genetic components and so must have the same hereditary basis for sex characteristics, adult intersexual organisms frequently appeared as mosaics of different sexual characteristics, some male, some female, some intermediate. The absence of sex-specific traits that were uniformly expressed was a significant problem for a general genetic theory of sex determination.

His solution was formulated in the 'time law of intersexuality'. According to this law, rates of differentiation could explain the mosaic nature of sex-specific traits in all animals: intersexes could be explained by the relative time that was spent developing as one sex, before reaching a turning point at which they began to develop into the opposite sex[11,12]. Reproduced with permission from REF. 14 © (1934) Bibliographia Genetica.
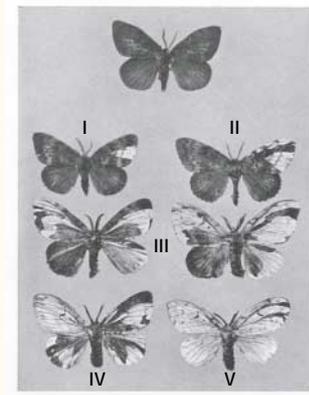
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principles. When he published *Die sexuellen Zwischenstufen* (*The Intersexes*) in 1931, it represented the culmination of his research on sex determination and his last attempt to generalize his findings from insects to humans[12]. This drive for unification was also characteristic of Goldschimdt's later research.

The demise of the classical gene

Shortly after beginning his work on sex determination in *Lymantria*, Goldschmidt was appointed to the Kaiser Wilhelm Institute for Biology in Berlin (FIG. 1). As Director of his own section of the Institute, Goldschmidt was free from teaching duties and could devote his full energy to research. Because the production of intersexes depended on the mating of different geographical varieties, Goldschmidt made three trips to Japan between 1914 and 1934 to collect Asian varieties to cross with European varieties. As a result of these trips, Goldschmidt developed a close relationship with several Japanese geneticists; he also trained several Japanese researchers in Berlin and taught at the Imperial Tokyo University for two years in the 1920s. Later he would sell his extensive personal library to the National Institute of Genetics in Mishima, where it became the foundation for their collection. Scientifically, Goldschmidt's trips to Japan enabled him to conduct one of the first geographical studies of genetic variation, as he mapped strong and weak varieties of gypsy moths from Korea to Okinawa[13].

Goldschmidt concluded his work on gypsy moths in 1934 with the publication of a monograph on *Lymantria*[14]. Only one year earlier, the purge of Jewish scientists had begun in Germany under the Nazis. Although Goldschmidt was not forced to resign until 1935, it was clear to him that he would have to leave. After many months of searching, Goldschmidt secured a new appointment at the University of California, Berkeley. On his arrival in the United States, however, Goldschmidt was rapidly immersed in controversy.

In the late 1920s, Curt Stern had brought *Drosophila* research to Goldschmidt's laboratory in Berlin. As his work on *Lymantria* wound down, Goldschmidt began to use *Drosophila* to study the effects of temperature shocks on development. To his surprise, temperature shocks seemed to produce a six-fold increase in the rate of mutation[15]. After some initial scepticism from his scientific peers, who were initially unable to repeat the results, Goldschmidt's experiments were soon vindicated. High rates of mutation were reported at the meeting of the Genetics Society of

Figure 1 | **Richard Goldschmidt at the Kaiser Wilhelm Institute, Berlin 1931**. Reproduced with permission from Curt Stern Papers, American Philosophical Society, Philadelphia, Pennsylvania, USA.

America by Milislav Demerec, Harold Plough and C. F. Holthausen. For biologists such as Demerec, these increased mutation rates indicated the possible presence of loci that were prone to mutation. For Goldschmidt, however, the increased spontaneous mutability was a nail in the coffin of the classical gene[16], which, according to T. H. Morgan's theory, was represented as an indivisible particle or 'bead on a string'[17].

Goldschmidt began to question the existence of the particulate gene in 1932 when Theodosius Dobzhansky convinced him of the seriousness of POSITION EFFECTS[18]: discovered in 1927 by A. H. Sturtevant, in relation to the *BAR EYE* mutant in *Drosophila*, position effects raised questions about how best to ascribe functions to genes. The beads on a string theory proposed by Morgan also underlay concepts such as mutation and recombination: mutations altered the chemical nature of the gene, whereas recombination did not — it simply reordered the beads from different strings. Position effects called the classical gene concept into question by challenging the existence of independent particulate structural and functional units[17].

In 1934, H. J. Muller and his collaborators in the then Soviet Union furthered the case against the classical gene by questioning the nature of mutation. Muller suggested that *SCUTE* mutations in *Drosophila* could be caused by different chromosomal rearrangements[19]. This was not a typical case of position effect, however, because the locations of the breaks associated with the rearrangements were distributed over a much larger section of

the chromosome than had previously been thought possible[17]. For Goldschmidt, work on these types of rearrangement indicated that most mutations were probably rearrangements of different sizes, each having different phenotypic effects, and not chemical changes in a 'bead' as predicted from the classical gene theory. Moreover, these results showed that, even if mutations could be localized as breaks created by rearrangements, the function of producing a phenotype was extended over a much larger segment of chromosome than a single bead.

The increases in spontaneous mutability that were seen in Goldschmidt's heat-shock experiments contributed to his argument against the classical gene by allowing him to claim that the sudden appearance of many kinds of mutation was the result of rearrangements that affect several loci. Goldschmidt's mutability experiments involved crossing a fly stock of *BLISTERED* mutants with wild-type flies. Progeny from the crosses did not show the *blistered* phenotype; instead, each individual showed the *PLEXUS, DUMPY VORTEX THORAXATE* and *PURPLE* phenotypes. Goldschmidt interpreted these results as being the consequence of chromosomal rearrangements with an insertion or break in the blistered *locus*[20]. From his brief and admittedly preliminary analysis in 1937, Goldschmidt concluded that all gene mutations were in fact rearrangements and that all mutations were position effects. Although mutations could be localized, the region responsible for producing a wild-type phenotype was considered to be much larger than the location indicated by noting mutational differences[21].

Goldschmidt never shied away from confrontation. In Germany, he was known for his bold claims and impassioned defence of his theories. His deliberate provocation on arriving in the United States was probably the result of his radical change in status. In Germany, Goldschmidt enjoyed a prestigious position devoted solely to research. At Berkeley, he had to teach introductory biology to students that he often considered ill prepared. Seeking controversy might have been a way for Goldschmidt to restore some of the renown he had lost when he was forced to leave Germany. Or it might have been, as he suggested, a matter of "genetic makeup", which encouraged him to "run ahead of the facts with conclusions" and immediately assign new facts "their place within the whole"[22]. An even more controversial treatise on evolution — *The Material Basis of Evolution*[23] — was soon to appear. This was considered by Goldschmidt to be an explication of the

phylogenetic consequences of his view on the gene. In Goldschmidt's words, *The Material Basis of Evolution* would be "typical Goldschmidt with everything I like about him, and some others dislike"[22]. I do not think that even Goldschmidt was prepared for how much some people would dislike this part of his work[24].

The case for saltation

Goldschmidt's research on evolution was rooted primarily in his study of the geographical variation of *Lymantria*. His groundbreaking work on the genetic basis of geographical differences led him to propose a fundamental difference between the processes of microevolution, which concerned the production of intra-species varieties, and the processes of macroevolution, which concerned the production of new species and higher taxa. Goldschmidt claimed that the gradual accumulation of small mutations advocated by neo-Darwinians, such as Dobzhansky, was sufficient for microevolution, but could not cross the bridgeless gap between species. To explain speciation (macroevolution), a different mechanism was required. In *The Material Basis of Evolution*, Goldschmidt proposed two mechanisms for macroevolution: systemic mutation and developmental macromutations[23].

Systemic mutations. For Goldschmidt, systemic mutations were large rearrangements of the chromosome. A successful systemic mutation would constitute a shift from one well-integrated chromosomal arrangement to another. According to this view, the linear arrangement of the genetic material had a marked impact on the set of reactions created by its immediate products; a new linear arrangement of the genetic material would therefore produce a new set of subsequent reactions. A new phenotype would suddenly appear when a stable genotypic arrangement was sufficiently coordinated to have a reaction system able to produce enough product to cross a certain threshold[23]. Gene expression was understood as a matter of producing sufficient substance. If too little product was created by a set of reactions, the threshold would not be reached and the phenotype would not be expressed. The genotypic changes associated with a systemic mutation could be extended over a long period of time, but their phenotypes appeared suddenly. Moreover, unlike micromutations, the phenotypic effects of systemic mutations were large enough to create a new species.

Because they were thought to correspond to chromosomal rearrangements, systemic mutations were an extension of Goldschmidt's rejection of the classical gene. Their dependence on reaction thresholds also grounded them in Goldschmidt's physiological genetics. Goldschmidt proposed a theory to explain gene action based on rates of reaction, which he derived from his work on sex determination. In his 1927 book *Physiologische Theorie der Vererbung* (*Physiological Theory of Genetics*) and his 1938 book *Physiological Genetics*, Goldschmidt showed that variable PENETRANCE and expression of a gene variant could be explained in terms of rates and thresholds[25,26]. Coordination of different reactions to produce a phenotype in an integrated developmental system required that reactions cross their threshold for expression within certain critical periods. If a reaction proceeded too slowly, it would not produce enough substance during the critical period. If a reaction proceeded too quickly, it would produce too much substance too early. In either case, rates regulated the expression and integration of phenotypes.

Developmental macromutations. The second mechanism that Goldschmidt proposed to explain macroevolution did not depend on the rejection of the classical gene. Drawing once again on his theories of physiological genetics, Goldschmidt proposed that mutations in developmentally important genes could produce large phenotypic effects. He called the results of these developmental macromutations "hopeful monsters" because they were the embodiment of large phenotypic changes that had the potential to succeed as new species. It is important to note that Goldschmidt's idea of a hopeful monster was not tied to his idea of systemic mutation. In fact, Goldschmidt used hopeful monsters to argue, by analogy, for evolution by systemic mutations. The possibility of mutations in developmentally important genes was intended to make the genetic mechanism of systemic mutation more plausible[23,24].

The developmental macromutations discussed in *The Material Basis of Evolution* were the foundation of Goldschmidt's thoughts on evolution in 1940. Bringing together his views on genetics, development and evolution, Goldschmidt firmly believed that

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Glossary

ARISTAPEDIA
A *Drosophila* homeotic mutant first described by Elizaveta Balkaschine in 1929 in which aristae (bristle-like structures at the tip of the antenna) are replaced by legs.

BAR EYE
A *Drosophila* mutant in which the eye is reduced to a narrow bar owing to a reduction in the normal number of eye facets.

BITHORAX
A *Drosophila* homeotic mutant first described by Calvin Bridges in 1915 in which the anterior part of the third thoracic segment is replaced by the anterior part of the second thoracic segment.

BLISTERED
A *Drosophila* mutant first described by Calvin Bridges and T. H. Morgan in 1919 in which the wings appear blistered, small and pointed.

DUMPY VORTEX THORAXATE
A *Drosophila* mutant first decribed by Calvin Bridges and T. H. Morgan in 1919 in which wings appear truncated, and altered wing-vein vortices and pits are present on the wing cuticle.

HALTERES
Small wing-like appendages that are located on the third thoracic segment of *Drosophila* and act as balancing organs.

HOMEOTIC MUTATION
A mutation that causes one structure to develop in a place where another structure would normally develop.

IMAGINAL DISC
A group of embryonic cells that differentiate and develop into adult structures such as legs and wings in *Drosophila*.

PENETRANCE
A term introduced by Oscar Vogt to describe the degree of expression of a trait.

PHENOGENETIC
An explanation of the relationships between phenotype and genotype.

PLEXUS
A *Drosophila* mutant first described by Calvin Bridges and T. H. Morgan in 1919 in which wings have extra veins, especially at their tips and margins.

POSITION EFFECT
A change in phenotype caused by a change in the location of a gene.

PURPLE
A *Drosophila* mutant first described by Calvin Bridges in 1919 in which the adult eye colour appears to be purple.

SCUTE
A *Drosophila* mutant first described by Calvin Bridges in 1919 in which the differentiation of bristles on the head and thorax are altered.

SHIFTING BALANCE THEORY
A theory of evolution in which random genetic drift and different forms of selection are integrated to explain evolving populations.

"a single mutational step affecting the right process at the right moment can accomplish everything, providing that it is able to set in motion the ever-present potentialities of embryonic regulation"[23]. Significantly, Goldschmidt's idea of developmentally important mutations with large effects was widely recognized and accepted. Biologists, such as Stern, W. Dwight Davis, George Gaylord Simpson and Sewall Wright recognized the importance of developmental macromutations. This support did not extend, however, to Goldschmidt's theory of systemic mutations[24]. In general, Goldschmidt's theory of speciation through systemic mutation had no support among geneticists or evolutionary biologists. On the one hand, its emphasis on chromosome rearrangement mired the mechanisms of evolutionary change in an unresolved controversy concerning the nature of the gene. On the other hand, by placing so much importance on genetic structure and developmental processes, it neglected the role of the dynamics of evolving populations. As his critics were happy to point out, a single hopeful monster did not constitute evolution[27]. Goldschmidt's immediate response to these charges was to appeal to the physiological dynamics of gene expression rather than the dynamics of evolving populations. Understanding how a mutation with a large phenotypic effect could spread through a population was addressed later by Wright as he grappled with Goldschmidt's views. Indeed, Wright eventually incorporated macromutations into his SHIFTING BALANCE THEORY as one possible mode of evolutionary change[28].

Hopeful monsters to homeotic mutation

Goldschmidt spent the final years of his life researching HOMEOTIC MUTANTS in *Drosophila*. He saw homeotic mutants such as ARISTAPEDIA as hopeful monsters. As such, they revealed the evolutionary potential of genetic alterations in developmental processes[28].

Drawing once again on his theory of physiological genetics, Goldschmidt sought to understand homeotic mutants in their developmental context. Whereas geneticists such as E. B. Lewis chose to work on mutants such as BITHORAX, Goldschmidt chose *podoptera* and *tetraltera* because they had variable penetrance and so were more amenable to his interpretation of gene action. In *D. melanogaster*, *podoptera* was marked by the "transformation of wings into leg-like structures", whereas *tetraltera* was distinguished by the "transformation of wings into HALTERES"[29].

Homeotic mutants were thought to be caused by alterations in genes. However, in Goldschmidt's view, they were part of a genetic hierarchy of structural and functional units. Beginning in 1944, he articulated a hierarchy of genetic structures, which extended from what were then barely visible structures to large segments of the chromosome, such as heterochromatic blocks[18,21]. Structures at each of these levels were thought to have different functions. For instance, some developmental processes seemed to require the integration of many genes, so Goldschmidt proposed that this integrated function probably corresponded to a larger chromosomal structure that would

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Box 2 | **Phenogenetic interpretation of homeosis**

Richard Goldschmidt sought to explain the range of forms that are expressed in the homeotic *podoptera* mutants by proposing a physiological scheme that links genotype and phenotype[27]. The *podoptera* mutants were sorted into six classes ranging from one in which the wings are spread out at a right angle to the body of the adult fly (class I) to one in which the wings resemble a set of four irregular knobs (class VI)[28]. These classes presumably reflect the degree of transformation of wings into leg-like structures (increasing in severity from class I to class VI). Because homeotic mutations were thought to act on the imaginal dics, Goldschmidt explained the classes of *podoptera* mutants as being the result of differences in the concentration of a putative leg inducer that was affecting the imaginal discs at different times during development. The observed classes of *podoptera* mutants represented the different times at which growth was stopped. Goldschmidt represented this situation by plotting the phenotypic differences realized during the determination of the wing imaginal disc against the concentration of leg-inducing substance (see diagram). In the wild-type fly, the imaginal disc continues to grow in the presence of a certain amount of inducer. The phenotype that is expressed depends on how much inducer is present during the crucial labile period of development (between the vertical lines, *a* and *n*) before differentiation into a wing disc becomes irreversible (at the vertical line, *n*). If the amount of inducer is above the threshold (horizontal dashed line) during this period, normal wing development occurs. In *podoptera* mutants, normal growth of the wing disc stops before the threshold, and the classes of mutant phenotypes are explained in terms of the point at which the wing disc stopped growing (indicated by stages a–a^4). Variations in stopping points would also produce variations in the expression of the phenotype in each class of *podoptera* mutant (not shown)[29]. Reproduced with permission from REF. 29 © (1951) University of California Press.

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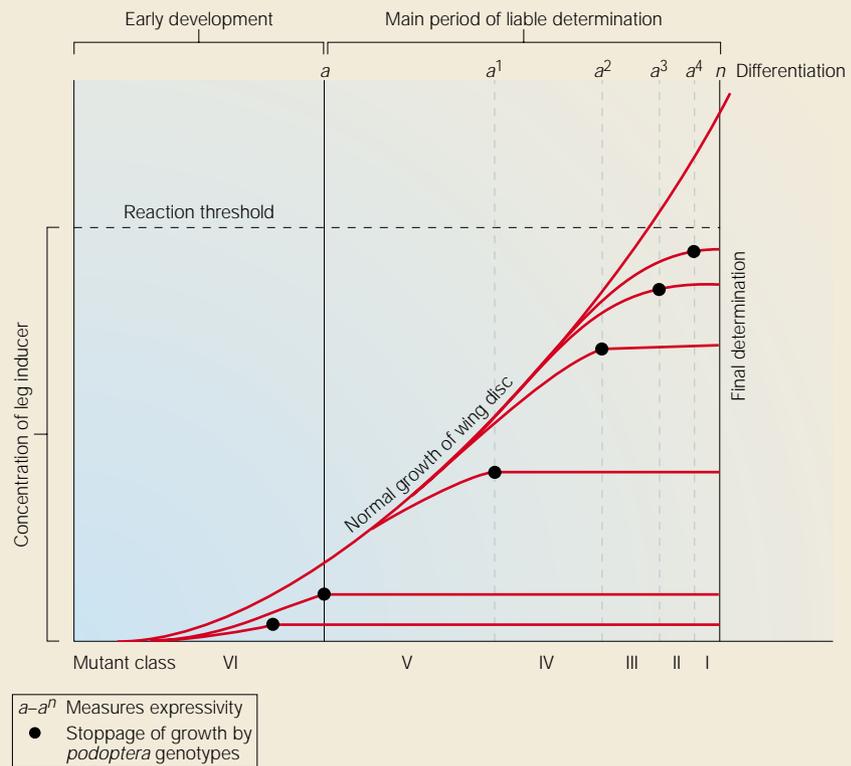
allow such integration. Goldschmidt thought that homeotic mutations belonged to a fairly large structure in his hierarchy because they seemed to be well integrated and, in *Drosophila*, homeotic mutations seemed to be grouped in a region of the third chromosome[18,29]. Because these mutations affected the determination of segmental appendages, Goldschmidt interpreted this segment of the third chromosome as a field that was "vitally concerned with the processes of segmental determination"[30]. With IMAGINAL DISCS posited as the location of gene action in this case, Goldschmidt claimed that "the whole intact section [of the third chromosome] controls certain parts of the process of normal development of the discs"[30]. Goldschmidt's analysis of homeotic mutations, therefore, suggested a means of understanding the developmental role of large sections of genetic material.

This interpretation of the structure and function of homeotic mutations allowed them to act as a bridge between systemic mutations and developmental macromutations. On the one hand, homeotic mutations were recognized as having large phenotypic effects that involved key developmental processes: they were excellent candidates for hopeful monsters. On the other hand, interpreting homeotic mutations in terms of the arrangement of fairly large sections of the chromosome was, for Goldschmidt, further evidence of the plausibility of systemic mutations.

Although many biologists recognized the potential importance of mutations in developmentally important genes, several resisted Goldschmidt's claim that developmental macromutations were the key to speciation. For biologists such as Simpson, developmental macromutations and homeotic mutants, in particular, were insufficient to explain the distinction between microevolution and macroevolution[31]. Simpson preferred to explain variability in terms of the selection of many, small modifying genes. Goldschmidt thought that Simpson's approach left no role for development and argued that Simpson was in danger of "forgetting that evolution is to a large extent also a problem of development". In 1946, Goldschmidt responded to Simpson's criticisms with a PHENOGENETIC analysis that explained the high variability of homeotic mutations and thereby argued that a single mutant could express all of the variability described by Simpson[31].

Goldschmidt's case for a single homeotic mutant and a dynamic developmental system, as opposed to fixed developmental reactions altered only by changes in their determining genes, was based on a phenogenetic interpretation of *podoptera* and *tetraltera*. Goldschmidt used phenogenetics to show that threshold effects, reaction rates and developmental timing could explain the low penetrance, high variability and asymmetry of actual homeotic mutants, such as *podoptera*. As he had since 1920, Goldschmidt represented his phenogenetic explanation effect graphically (BOX 2). As in his case of systemic mutations, Goldschmidt realized that he did not have direct evidence that would resolve his dispute with Simpson about homeotic mutants. Goldschmidt was not arguing that his interpretation was the only correct interpretation; rather, he was arguing for a broader vision of biology that allowed for a range of alternatives. In *The Material Basis of Evolution*, and later, Goldschmidt was clear that what he was offering was a theory that agreed equally well with the facts. This caution, however, was easily overlooked due to his confrontational rhetoric and faith in eventual vindication.

Conclusion

Goldschmidt clearly created the foundation for his reputation as a heretic by deliberately framing arguments that were designed to undercut the classical gene and the emerging neo-Darwinian synthesis. His support for alternative theories that agreed with the evidence was important in two respects. First, the alternatives proposed by Goldschmidt sought an integrated or unified understanding of genetics, development and evolution; however, unlike the unifying interpretations offered by Dobzhansky, Ernst Mayr and Simpson, Goldschmidt placed a great deal of emphasis on the place of development. Second, for Goldschmidt, developmental processes were active — they were not passive background conditions mediating genotype and phenotype. In this sense, Goldschmidt was attempting a synthesis of evolutionary and developmental biology similar to the synthesis that has been emerging during the past 15 years (known as evolutionary developmental biology, or evo–devo). This is not to say that current efforts share an affinity with the specific mechanisms that Goldschmidt proposed, but that they both seek to integrate genetics, evolution and development in a way that makes development an equal partner[32]. This emphasis was both Goldschmidt's strength and weakness. By focusing so much of his attention on development, he failed to grasp the importance of populations and population dynamics. Indeed, explaining population dynamics for evolutionarily important developmental processes remains a challenge.

Goldschmidt's controversial views are also historically significant because they highlight the tremendous breadth of his knowledge. Goldschmidt was a comprehensive biologist whose range of knowledge in biology was acknowledged by friend and foe alike[2]. This desire for a unified understanding drove him to collect and assimilate vast amounts of information. Goldschmidt's grasp of the field made his books valuable even if the reader did not agree with his interpretation of the assembled evidence. Much of Goldschmidt's positive reputation depended on this synthetic ability. Even as a 76-year-old man, he drew on more than 50 years of biological experience to write his last book, *Theoretical Genetics*[30]. In presenting an overview of the chemical nature of the gene, it incorporated the latest findings concerning the structure of DNA. In presenting an overview of gene action, it took the one-gene–one-enzyme hypothesis to task as simplistic. Like Goldschmidt himself, *Theoretical Genetics* is idiosyncratic and, of course, now seems dated; however, it represents all of those qualities that made Goldschmidt both revered and reviled as a scientist.

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