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ABSTRACT

This paper examines Richard Goldschmidt's opposition to the classical concept of the gene as a combined unit of structure, function, mutation, and recombination. To replace the classical gene Goldschmidt articulated a genetic hierarchy drawing on the diverse strands of genetic research that had been bound together previously in the classical gene concept. As such, Goldschmidt's genetic hierarchies represent the possibility of retheorizing genetics without a unifying gene concept.

INTRODUCTION

Throughout the 1930s and 1940s Richard Goldschmidt took great pleasure in announcing the demise of the corpuscular gene. The resulting controversy surrounding Goldschmidt's opposition to the corpuscular gene is well known (Allen 1974; Burian 1985; Carlson 1966; Dunn 1965; Gilbert 1991; Maienschein 1992; Richmond 1986). While Goldschmidt relished claiming that the corpuscular gene was dead, his opponents did not refrain from stating, often in his presence, that he had gone crazy (Goldschmidt 1960, 323; Stern 1967, [1980, 83]). The maelstrom of rhetoric surrounding Goldschmidt and the problem of the gene has, however, obscured the history of the development of alternatives to the corpuscular gene. Biologists, historians, and philosophers have characterized Goldschmidt's position as the chromosome-as-a-whole hypothesis. Such characterizations of Goldschmidt's views do not reflect the development of Goldschmidt's thought as much as the fact that most commentators have failed to come to terms with Goldschmidt's views after 1940.

Elof Carlson, for instance, conflates Goldschmidt's early views (late 1930s) of the chromosome-as-a-whole with his later views that Carlson characterized as view of "the genetic continuum of the chromosome" (Carlson 1966, 125, 126, 128). What Goldschmidt actually articulated in the passages that Carlson quoted was a notion of genetic hierarchy of which the chromosome-as-a-whole was merely a constituent. From the mid-1940s until his death in 1958, Richard Goldschmidt articulated and refined multi-leveled genetic hierarchies to replace the classical, corpuscular gene concept. This paper will examine, first, the development of Goldschmidt's opposition to the classical, corpuscular gene as a particulate entity, and second, his articulation of genetic hierarchies as an alternative.

Despite the diversity of genetic units that a genetic hierarchy introduces, Goldschmidt maintained a unified understanding of genetics by advocating a theoretical genetics in which results from cytogenetics, transmission genetics, and physiological genetics were integrated. Through at least 1940, the gene acted as a boundary object, drawing together diverse strands of genetic investigation (Star and Griesemer 1988; Rheinberger 1995). The loss of the gene as a powerful unifying entity created a need, in Goldschmidt's eyes, for a reconceptualization of genetics that would integrate and unify those diverse aspects previously associated with the corpuscular gene. As Pierre Duhem noted, when faced with negative results, a scientist can choose to tinker with the parts of his theoretical system or he or she can choose to question the very foundations of his or her thought (Duhem 1914, [1981, 217]). Goldschmidt sought to maintain a unified theory of genetics by rethinking its foundational entity, the gene. As such Goldschmidt's genetic hierarchies represent the possibility of retheorizing genetics without a unifying gene concept.

THE DEMISE OF THE PARTICULATE GENE

According to his own account of the development of his thought, Richard Goldschmidt began to question the existence of the particulate gene in 1932 when Theodosius Dobzhansky convinced him that position effects should be taken seriously (Goldschmidt 1944a, 185). A position effect occurs when the location of a gene alters the phenotypic effects of that gene. Position effects had been discovered in

1927 by A. H. Sturtevant in his now famous set of experiments on the Bar eye effect in *Drosophila*. Changing phenotypic effects with position raised questions of whether genes were functional units in the sense of whether or not they carried their function with them. The particulate theory of the gene represented genes as indivisible beads on a string, each a unitary structure and sufficient to fulfill its function. The particulate gene or the classical gene was a unifying entity in that it was simultaneously a unit of structure, a unit of function, a unit of mutation, and a unit of recombination. In the mid-1930s, however, the particulate gene was, in L. C. Dunn's words, showing "some signs of disappearing in a cloud of position effects" (Dunn 1937). Indeed, by 1934 with the first report of the results from H. J. Muller's group in the Soviet Union concerning mutation and rearrangements at the *scute* locus in *Drosophila*, Goldschmidt was ready to declare that the demise of the classical gene was at hand. Goldschmidt's conviction was bolstered by his own work on spontaneous mutation and chromosomal rearrangement, which was becoming his main line of experimental research in 1934 (Goldschmidt 1944a, 185). Goldschmidt's campaign against the gene was, thus, sustained by earlier work on position effects by Sturtevant and others, by Muller's work on X-ray induced mutations/rearrangements, and by his own work on spontaneous mutability.[2]

In his biographical memoir of Goldschmidt, Curt Stern remarks that Goldschmidt waited until he arrived in America, the birthplace of Thomas Hunt Morgan's theory of the gene, to announce in a funereal voice: "The theory of the gene is – dead!" (Stern 1967, 83). As Goldschmidt toured the United States in 1935, desperately trying to find a job and raise money with lecturing fees, he began to articulate his doubts about the particulate gene. At the time, his views drew heavily on the experiments of H. J. Muller's group on position effects and on the ability of X-rays to produce minute rearrangements in chromosomes.

Muller had pioneered the use of X-rays to induce mutations in *Drosophila* in the 1920s. The ability of X-rays to create mutations naturally raised questions about the action of radiation and the mechanisms of induced genetic changes. Muller and most notably Timofeéff-Ressovsky's group in Berlin were actively pursuing these concerns in the 1930s. By 1934, the results of X-ray radiation were

recognized visually as changes in the banding patterns of chromosomes in the salivary glands of *Drosophila*. The visual evidence of large chromosomal rearrangements and research on the ability of X-ray radiation to create breaks in the chromosomes led Muller to consider the possibility that some mutations were, in fact, the result of breaks and rearrangements.

Together with Alexandra Prokofyeva and later Daniel Raffel, Muller began investigating the ability of X-rays to create single and double breaks in chromosomes that could result in cytologically visible differences (Carlson 1981, 193). Focusing on breaks in the *scute* region, Muller and Prokofyeva had found "definitive evidence . . . of the correctness of the 'position effect' interpretation of the action of chromosomal breaks" (Muller, Prokofyeva, and Raffel 1935, 253). Instead of claiming that the various *scute* effects were the results of gene mutations located near breakages, Muller and Prokofyeva claimed that the breaks themselves produced rearrangements that had position effects (Muller and Prokofyeva 1934; Muller, Prokofyeva, and Raffel 1935). This raised the question, in their words, "as to what proportion of 'natural mutations' in *Drosophila* may really be minute rearrangements." The only reason that Muller et al. gave for not making the inferential leap that most mutations were position effects was that "rearrangements alone must be far from adequate for any indefinitely continued evolution" (Muller, Prokofyeva, and Raffel 1935, 255).

Even armed with Muller's experimental results, the reaction to Goldschmidt's rejection of the gene was overwhelmingly negative (Goldschmidt 1960, 323). In the summer of 1936, however, new experimental evidence on the mutability of the *Drosophila* genome was introduced and brought to bear on the question of the gene. As the Goldschmidts sailed for Berkeley and a new life at the University of California, Milislav Demerec, Harold Plough, and C. Holthausen announced at the meetings of the Genetics Society of America their independent observations of a high frequency of spontaneous mutation in an inbred Florida stock of *Drosophila*. Just before his departure from Germany, Goldschmidt had also observed a higher than normal number of spontaneous mutations in the same Florida stock. Demerec and Plough and Holthausen and Goldschmidt all published accounts of their experiments in 1937 (Demerec 1937; Goldschmidt 1937a; Plough and Holthausen 1937). Goldschmidt's article was significantly different from the others, however (see Dietrich 1996).

In his short article published in the *Proceedings of the National Academy of Sciences*, Goldschmidt used his observations of increased spontaneous mutability to argue against the existence of the gene. Goldschmidt argued that the sudden appearance of many different kinds of mutations was the result of rearrangements affecting a number of different loci. Specifically, experiments involving crosses of a stock containing the *blistered* mutants would result in the next generation in the disappearance of blistered and the appearance in every individual of the brood of the mutants *plexus*, *dumpy vortex*, *thoraxate*, and *purple*. Goldschmidt interpreted these events as chromosomal rearrangements with an insertion or break in the *blistered* locus. (Goldschmidt 1937a, 622) From his brief and admittedly preliminary analysis, Goldschmidt concluded that all gene mutations were in fact rearrangements and that all mutations were in fact position effects. One could still localize the production of a phenotypic effect, but, according to Goldschmidt, it did not follow that there was a wild-type allele corresponding to the site of the mutation that produced the phenotypic effect. Instead, the "whole, wild type chromosome" was the "allele for all 'mutant genes' within this chromosome" (Goldschmidt 1937a, 622). Goldschmidt did promise further clarification of his ideas in a future publication, but it is important to note that while he did claim in 1937 that the chromosome was the "unit," he did recognize that it had to have some internal structure or "texture" in order to ensure normal development. As Goldschmidt's thinking advanced this "texture required for normal development," took form as a multi-level hierarchy of genetic units within the chromosome.

In a letter to L. C. Dunn, Goldschmidt admitted that the 1937 article would make him "an outcast in genetics," since he "now stated in writing, as before only orally, that there is no such thing as a gene. Horror!" (Goldschmidt 1937b). In 1938, Goldschmidt submitted the full report of his experiments to *Genetics* for consideration. In his accompanying letter, Goldschmidt admitted that the experiments were not yet completed, but that he wanted to publish in parts, starting with general comments followed by detailed analysis of

particular mutants. L. C. Dunn, acting as editor of *Genetics*, was not willing to go along with this plan. Dunn refused to publish Goldschmidt's results until he had provided the analysis of results from the study of the specific mutants and their representation on the salivary gland chromosomes.

Goldschmidt took Dunn's advice and stepped up research, but he also made his views known (Goldschmidt 1938a; Goldschmidt 1938b). The next year, 1939, Goldschmidt's article "Mass Mutation in the Florida Stock of *Drosophila melanogaster:* Details of an Old Experiment Reinterpreted" appeared in *The American Naturalist* (Goldschmidt 1939a). Dunn was not at all pleased (Dunn 1940). Despite his serious warnings, Goldschmidt had published something that was evidently very similar to the manuscript rejected by *Genetics*. Goldschmidt pleaded to Dunn that *The American Naturalist* article was not a report of his new experiments, but merely the interpretation of his old temperature shock experiments from 1929. Dunn felt that Goldschmidt was promoting useless controversy (Dietrich 1996).

From 1939 to 1945, Richard Goldschmidt's experimental program was devoted to analyzing the spontaneous mutations in *Drosophila* completely (Goldschmidt 1944b; Goldschmidt et al. 1945). Where Muller had been given to caution when interpreting the effects of rearrangements because of the implications for evolutionary biology, Goldschmidt was not. The differences between Muller and Goldschmidt are complex, but Goldschmidt himself summed up many of them in a letter to Muller in 1939. Goldschmidt wrote:

> I just read with great pleasure your admirable paper in *The Collecting Net.* But I was a little disappointed that you were so cautious about the gene. I had actually expected (without knowing your Paris paper, but on the basis of the one with Prokofiewa [sic]) that you would be the first to jump over the fence and to discard unequivocally the classic gene. I know of course that temperaments are different and that I may be less cautious than required. But in times of transition from one basic viewpoint to another – these times I think are at hand with the classic theory in its last convulsions – I prefer the analytic mind to be a small step ahead of the experimentation (Physics proceeds that way, but biologists consider it a crime). I know of course what our differences are. First the small regions of similar action and second evolution. Regarding the first point I shall explain my position soon on the basis of some new facts; and as for the evolution I shall show in a forthcoming book (Silliman Lectures) that it is better understood without genes. (Goldschmidt 1939b)

Goldschmidt's exhortations did not convince Muller to throw caution to the wind and leap ahead of his meticulously gathered experimental results. Goldschmidt's forthcoming views on evolution, published as *The Material Basis of Evolution*, did little to help his cause against the classical gene.

The Material Basis of Evolution (Goldschmidt 1940a) was very hotly contested in its own right. Coming as it did in the middle of his campaign against the gene, Goldschmidt's evolutionary theory was an exploration of the phylogenetic consequences of his view of the demise of the gene. In his words, it would be "typical Goldschmidt with everything I like about him, and some others dislike" (Goldschmidt 1940b). I doubt Goldschmidt was prepared for how much his views would be disliked (Dietrich 1995).

The principal thesis of *The Material Basis of Evolution* is that microevolution and macroevolution are distinct phenomena and that the slow and gradual accumulation of micromutations was not a sufficient mechanism to bridge the gaps between species in an evolving lineage. In order for these bridgeless gaps between species to be crossed, Goldschmidt argued that large-scale systemic mutations were needed. Systemic mutations are complete changes of the primary pattern of the chromosome (the reaction system of the chromosome) into a new, well-integrated pattern (Goldschmidt 1940a).

A crucial part of Goldschmidt's argument was that changes in intrachromosomal structure or pattern are the basis for species level differences. In making this argument, Goldschmidt did not simply marshal his own evidence; he instead focused on the work of the influential neo-Darwinian, Theodosius Dobzhansky. The picture Goldschmidt painted of Dobzhansky was that of a man at a scientific impasse: He must decide whether species formation is a matter of genic differentiation or differentiation in chromosomal pattern. According to Goldschmidt, Dobzhansky knew a decision had to be made when he wrote in *Genetics and the Origin of Species:*

> To what extent the differences between such species as *Drosophila pseudoobscura* and *D. miranda* are due to position effects is also a matter of specula-

tion; the greatly different gene arrangements in these species may be responsible for many alterations in the morphological and physiological properties of their carriers. In any event, position effects show that gene mutations and chromosomal changes are not necessarily as fundamentally distinct phenomena as they at first appear. (Dobzhansky 1937, 117)

Dobzhansky's failure to take the next step and admit that chromosomal repatternings could be the decisive changes needed for speciation was, according to Goldschmidt, the result of "a dogmatic belief in the inflexibility of the classical theory of the gene" (Goldschmidt 1940a, 242). Unfettered by the dogma of the gene, Goldschmidt could promote a theory of evolution that was compatible with the "facts," meaning Dobzhansky's and Muller's own results on position effects and chromosomal differences.

It is not surprising that Dobzhansky became one of Goldschmidt's harshest critics and took him to task specifically on his attack on the gene in *The Material Basis of Evolution*. In the second edition of *Genetics and the Origin of Species* published in 1941, Dobzhansky made it clear that he was not about to give up genes in the face of Goldschmidt's attack, but neither was he willing to advocate the idea of genes as beads-on-a-string. In his words, "regardless of whether position effects are interpreted as due to interactions of chromosome products in development or to changes in these products themselves, the genes can no longer be thought of as absolutely discrete entities." Dobzhansky thought Goldschmidt had created a false dichotomy: "Genes must either be separated by impregnable walls, or else they do not exist at all." Dobzhansky preferred an intermediate position, where "the germ plasm may consist of genes and yet have a continuity of a higher order." Dobzhansky felt that his view was similar to that advocated by Muller and allowed him to consider genes as parts of functionally integrated systems, although the extent of the functional interaction of gene products was recognized to be an open question (Dobzhanksy 1941, 110; see also Dietrich 1995, 441–442, 445).

While Goldschmidt continued to articulate his views during the early 1940s, the Drosophilists lined up their evidence against him: Most notably at the 1941 Cold Spring Harbor Symposium where Plough and Demerec sought to set the record straight. As they saw it,

the spontaneous mutations they observed were not associated with any gross rearrangements.

Plough's paper summarized the work of his group at Amherst on the effects of temperature and temperature shock on spontaneous mutation. It was Plough's position that there were genuine gene mutations that could be affected by temperature in much the same way that enzyme reactions could and there were chromosome breaks that were not sensitive to temperature but could be affected still by temperature shocks (Plough 1941, 136). This distinction was based on two main lines of reasoning. First, it was argued that if there are genuine gene mutations responding to temperature, they ought to respond as chemical reaction systems and the mutation frequency ought to follow a Van't Hoff curve. Plough's experiments with different temperatures did follow a Van't Hoff curve and as a result the mutations induced were thought to be the result of biochemical reactions. Second, the experiments tested for large translocations resulting from development at high temperature and from temperature shock. A large translocation would require two breaks on two chromosomes. Plough found that large translocations were very rare. Moreover, the creation of these large translocations was not effected by temperature or temperature shock. This justified Plough's distinction between genic and intergenic substances. Mutations were chemical changes in genes or genic substance and were sensitive to temperature and temperature shock, whereas large translocations were created by breaks in intergenic substance. Plough thus concluded that "spontaneous mutability requires the classical gene-chromosome framework involving genes as entities separable from the inter-genic substance" (Plough 1941, 136).

Plough's paper is explicitly directed against Goldschmidt's interpretation of spontaneous mutation, but just to make sure that there was no room for confusion Demerec raised Goldschmidt's views in the discussion period. Demerec asked: "What evidence does the Amherst group have on Goldschmidt's theory that mutation is due to chromosomal rearrangement and not gene changes, and that high mutability lines carry aberrations?" (Plough 1941, 136–137). In response, Plough reaffirmed his opposition to Goldschmidt's interpretation and claimed that while they did in some cases find an inver-

sion on the second chromosome, it may have been there before the experiment began. Demerec continued: "Goldschmidt says that if mutants obtained from our high mutability stock were analyzed cytologically, they would prove to contain aberrations. Actually some of this analysis was done by Slizynski, who studied salivary gland chromosomes of induced and spontaneous lethals. The spontaneous lethals were all from the high mutability stock, and no aberrations except small deficiencies were found" (Plough 1941, 137). Because Plough had not done any cytological work, only analysis based on linkage and recombination, he could only claim that there were no "obvious chromosome rearrangements." The nonobvious rearrangements could still be undetectable deficiencies. The finer details that a cytological analysis could have yielded were missing and would become major issues later in the dispute.

Demerec's own work tried to address this situation, but was still geared toward large scale changes. Demerec's contribution was a review of his work on unstable genes in *Drosophila* and their bearing on questions of spontaneous mutability and the nature of the gene. Demerec made it very clear at the end of his paper that the unstable genes he had been studying were not associated with visible chromosomal aberrations. He had confirmed this with linkage studies and with analysis of the salivary chromosomes by himself and Dr. Eileen Sutton. However, he did note that the "closest known parallel" to unstable genes found in *Drosophila melanogaster* were mottled characters that were "connected with chromosomal aberrations involving heterochromatin" (Demerec 1941a, 149). Perhaps as a result, Demerec refrained from the type of ringing endorsement for the gene that Plough had given earlier.

Immediately following Plough and Demerec at the Cold Spring Harbor Symposium in 1941, was H. J. Muller. Muller had the task of summarizing the current state of work on induced mutations. On this topic, Muller could speak with unrivaled authority and his comments were often at odds with those of Plough and Demerec. Plough's argument was predicated on a simple division between gene mutation and gross rearrangement such that if gross rearrangement was eliminated the best explanation was gene mutation. Muller diversified the range of explanatory options to include the possibility of minute rearrangements detectable by cytological analysis and

even minute rearrangements too fine to be cytologically detected. What enabled this diversification was Muller's interpretation of the molecular action of radiation on the chromosome. Muller accepted that a "single atom change" induced by radiation could create, via a chain of reactions, a single break in a chromosome. Two such changes far apart could create two breaks and possibly a gross rearrangement. A minute rearrangement, however, could be produced by a single atom change that initiates "a chain of reactions in two or more directions, so that two or more different but nearby breaks in the chromonema are induced . . . " (Muller 1941, 163). This possibility suggested that mutations may be minute rearrangements. Moreover, it had the consequence that "the concept of the individual gene" may be "only an approximate one, roughly describing, for our convenience, certain chromosome regions having to do with certain functions" (Muller 1941, 161).

Muller's only hesitancy about equating mutations and minute rearrangements had to do with the chemical nature of the chromonema, the fibrous portion of the chromosome capable of coiling and uncoiling. Muller reasoned that the chromonema was a nucleoprotein and so was composed of amino acid units that were "grouped into higher units, in a kind of ascending hierarchy" (Muller 1941, 161). If breaks occur, Muller argued, they were not likely to occur between amino acids since that would require the breaking of a peptide bond with the resulting fragments having opposite charge. In order for a peptide bond to be reformed, fragments with opposite charge must reunite. Yet, Muller argued, this was not what occurred in chromosomes where "two fragments that unite may have the same sign [or charge]" (Muller 1941, 161). Chromosome breaks were, thus, not breaks within protein molecules. Instead they must be breaks between the protein molecules that make up the chromonema. As a consequence, Muller believed that "there must be larger groupings in the chromonema than the amino acid units" (Muller 1941, 161). Muller never came right out and claimed that these larger groupings were in fact genes. Although he did not call for a return to the old corpuscular gene, Muller was not willing to get rid of it entirely. As a result he concluded his survey by claiming that "the underlying facts may be more complicated than we have imagined" (Muller 1941, 162).

By the 1940s, Muller, Dobzhansky, L. C. Dunn, and many others were willing to accept that genes were not the discrete entities that they were represented to be by the classical beads-on-a-string metaphor (Dobzhanksy 1937, 117; Raffel and Muller 1940). They were not willing to give up, however, that there were no mutations, only rearrangements of different sizes. Nor were they willing to give up that there were units that corresponded to specific functions. It was not clear that these functional units corresponded to discrete or discontinuous structures, nor was it clear what kinds of structures were manifest in the chromosome.

GENETIC HIERARCHIES

From 1944 until his death in 1958, Goldschmidt articulated and elaborated a hierarchy of genetic units. Goldschmidt's position was based on the argument that the unit of mutation did not necessarily provide any insight into the wild-type or what he called the hereditary unit. Mutations were detected differences and could be localized; hereditary units were units with structures and functions that need not be localized in the same way mutations were (Goldschmidt 1946, 250–251). Hereditary units were the units necessary for the process of normal development (Goldschmidt 1944a, 197).

Goldschmidt first presented a fully articulated genetic hierarchy in 1944. This hierarchy of hereditary units was summarized in a table based on five levels of visible structures (see Table 5-1). Because this table was constructed as part of an argument against the classical gene, it contrasts the classical interpretation with the cytological data and with Goldschmidt's own interpretation. This table started with the smallest structures and proceeded up to extremely large structural divisions, thereby creating an inclusive structural hierarchy. The higher levels were composed of well-recognized cytological structures. The lowest level was more controversial.

The smallest units in Goldschmidt's 1944 hierarchy corresponded to visible structures that he and his student Masuo Kodani had been able to detect in salivary gland chromosomes after treatment at very high pH (Calvin, Kodani, and Goldschmidt 1940). Structures resembling lamp brushes were produced after treatment in high pH solutions of NaCl and staining with acetocarmine solution. The salivary

Table 5-1 *Goldschmidt's Genetic Hierarchy as of 1944 (after Goldschmidt 1944 a, 206, table 2)*

Level	Lowest	Next Higher	Next Higher	Next Higher	Next Higher
Visible Structure	Goldschmidt Kodani penultimate chromomeres	Salivary band	Belling's ultimate chromomeres	Wenrich's pachytene and diplotene chromomeres	Heitz's chromosomal segments of euchromatin
Approximate Numbers	5,000	1,000	100	6 10	1–6
Units of Genetic Action	Not yet known rearrangement changes of penultimate chromomeres	Mutants without visible rearrangements	Sections of localized action like y- or sc- segment	Segments of identical action in special circumstances	Situation as found in homeotic mutants
Within Classic Theory	Subgenes	Gene	Muller's redefined gene	Genes influencing each other	Numerous independent genes

gland chromosomes appeared after treatment as irregular cylinders marked by dark staining lateral threads with transverse bristles or loops. These loops were assembled in a rosette structure around a centromere. The interpretation of these structures was controversial (Metz 1941; Goldschmidt 1955, 19). Goldschmidt seemed to favor Koltzoff's interpretation of the loops as individual protein molecules, but in the end left the question open and referred to them as penultimate chromomeres.

What was significant about this structural hierarchy was that Goldschmidt could attribute genetic action to each of the units at the salivary gland chromosome band level and higher. Mutations were regularly attributed to the salivary gland chromosome bands, even though rearrangements were not visible at that level. Localizable genetic action, however, was usually attributed to the next higher level. It was at this level, which Goldschmidt associated with Belling's 1928 description of chromomeres in leptotene chromosomes (Belling 1928), that he put the important results concerning Muller's *scute* mutants and his own *yellow* mutants. In both of these cases, breaks over as much as a five band section of chromosome produced very similar phenotypic effects (Goldschmidt 1944a, 191). To Goldschmidt, this argued strongly for his position that regions of normal action were larger than those associated with mutation and the particulate gene.

The two highest levels of structures were the chromomeres identified by Wenrich in the diplotene stage of meiosis and the alternating blocks of euchromatin and heterochromatin identified by Heitz (Heitz 1929; Wenrich 1916). These structures were associated with position effects and homeotic mutants. It was known that rearrangements with one break in heterochromatin and the other in euchromatin behaved differently from those with both breaks in euchromatin. In particular, rearrangements involving the placement of the heterochromatin next to euchromatin seemed to have position effects that stretched over long distances (Goldschmidt 1946, 255). The grouping of many homeotic mutants within a short segment of the third chromosome of *Drosophila* was similarly suggestive of larger functional units. In general, however, the actions both of heterochromatin and of homeotic mutants were poorly understood in 1944. As a result, Goldschmidt dedicated the final years of his experimental career to researching these two higher levels in his genetic hierarchy. The culmination of these efforts to articulate a genetic hierarchy came in Goldschmidt's 1955 book *Theoretical Genetics*. In many ways this book is Goldschmidt's last word on many of the diverse lines of research he had pursued during his lifetime, including physiological genetics, evolution, and sex determination. For present purposes, what is most significant is the lengthy section on the nature of the genetic material.

As he had years earlier, Goldschmidt's arguments in *Theoretical Genetics* began with position effects and moved to now familiar arguments against the particulate gene. The possible sources of position effects were expanded from the 1940s to include visible and invisible deficiencies as well as inversions ranging from large to so small as to be cytologically invisible (see Figure 5-1). The diversity of position effects and their role in the case against the particulate gene justified the concentration of Goldschmidt's efforts on chromosome segments. Given that there were no discrete genes *identifiable by muta-*

Normal	a b c d e f
Deficiency visible	a b d e f
Deficiency invisible	a b $\underline{c}$ d e f 2
Deficiency invisible	a b c $\underline{d}$ e f 2
Large inversion or translocation	a b c x y z
or	a b c d e x y z
Microinversion (visible or not)	a b c d **e** f
or	a **b** c d e f

Figure 5-1 Possible types of position effects. Possible changes in the serial order of the structural elements of a section of a chromosome. c/2 represents that only c^1c^2 is present, instead of a submicroscopic series of $c^1c^2c^3c^4$. **b** (or **e**) represents that the order $b^1b^3b^2b^4$ ($c^1e^3e^2e^4$) is present, instead of submicroscopic series $b^1b^2b^3b^4$ ($e^1e^2e^3e^4$). (Goldschmidt 1955, 161)

tion, Goldschmidt wanted to know if there were nonetheless discrete "well-defined morphological structures." The diagrammatic representation of possible position effects (see Figure 5-1) suggested that there were discrete structures. Indeed Goldschmidt's 1944 hierarchy had been based on well-defined differences in the morphology of the chromosome. In *Theoretical Genetics,* however, Goldschmidt cites two phenomena that bring into question the possibility of morphologically distinct segments and consequently any hierarchy based on sharply defined morphological differences in chromosome structure: the overlap between neighboring segments and position effects with heterochromatic breaks.

Based on his own study of *yellow* mutants, Muller's study of *scute* mutants, and Demerec's study of other mutants, such as *white* and *Notch* in *Drosophila,* Goldschmidt argued that the ability to produce these phenotypes was spread over segments of chromosome and that these segments could overlap. In the case of *yellow* and *scute,* for instance, breaks between the 1B1 and 1B3 bands on the X-chromosome produce *yellow* and *scute,* whereas breaks farther to the left will produce only *yellow* and breaks farther to the right will produce only *scute* (see Figure 5-2). This phenomenon with the *yellow* and *scute* segments led Goldschmidt to conclude that "it cannot be the morphological segment which counts [as the hereditary unit], but a field-like function of the segment which under certain conditions . . . reaches from the center of the segment to different distances" (Goldschmidt 1955, 162). This interpretation in terms of fields required that a segment be thought of in terms of a "definite polarized order on a molecular level" with a specific range of action associated with a specific function.

The same interpretation was offered for position effects produced by breaks in heterochromatin. Rearrangements with one break in heterochromatin (and the other in the euchromatin) were known to have a greater effect than rearrangements with both breaks in euchromatin. In 1941, Demerec had explained this difference in terms of what he called sensitive regions.

According to Demerec, when a rearrangement occurred new parts of the chromosome were brought into contact with each other resulting in a position effect. The sensitive region was the region surrounding the place where this new contact occurred and in which position

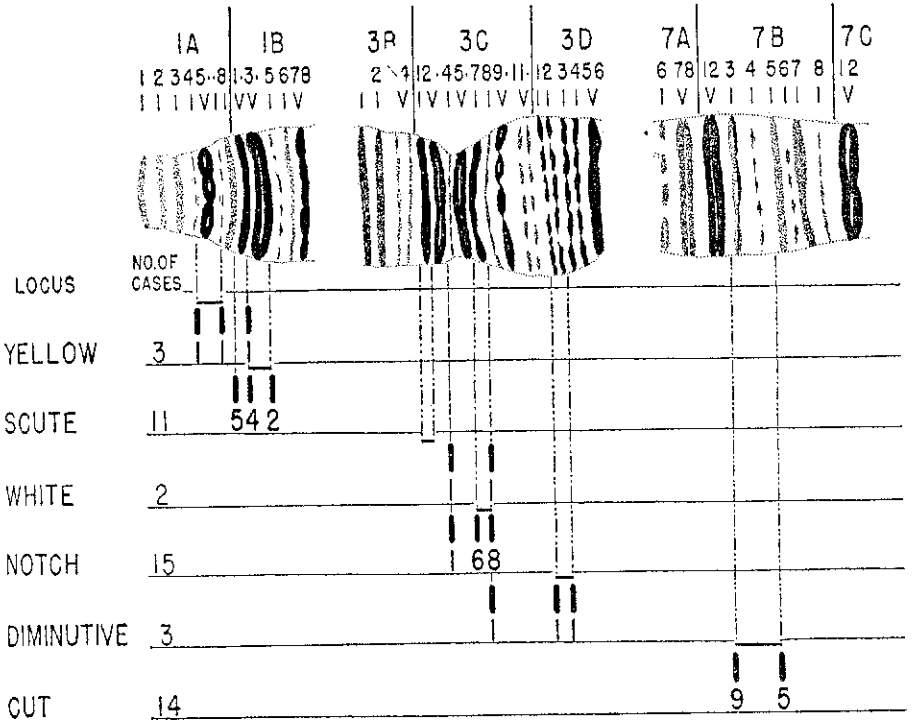

Figure 5-2 Locations of breaks associated with rearrangements in the X-chromosome of *Drosophila.* Vertical bars represent the location of breaks, the numbers below indicate the numbers of breaks per location. According to Demerec's interpretation, the horizontal bars represent the position of loci. Goldschmidt interprets the same data on the location of breaks as evidence that genic segments overlap. (After Demerec 1941b, 4, figure 1.)

effects could be detected. Using his research on *Notch* and *white* mutants, Demerec concluded that rearrangements involving placement of euchromatin next to heterochromatin resulted in a sensitive region that was five to ten times bigger than a similar rearrangement involving only euchromatin (Demerec 1941b, 6). Demerec explained this effect as a change in either the gene or in gene activity. Goldschmidt thought that explanations that appealed to heterochromatin's action on distant genes provided no insight and were "devoid of meaning" (Goldschmidt 1955, 162). Instead, Goldschmidt preferred to think of heterochromatin as stretching the fields of adja-

cent segments to produce what he thought of as a case of "an extreme type of overlapping." This stretching effect, like overlapping, convinced Goldschmidt that chromosomes had to be understood in terms of segments with associated fields of action.

As he had done in 1944 for genetic structures, Goldschmidt ordered these segments and their fields into a genetic hierarchy. These fields would range from those associated with submicroscopic segments of the chromosome to larger fields covering possibly the entire chromosome (Goldschmidt 1955, 180). The action of genic material at any time could be the result of a field at any one of these levels.[3] Goldschmidt represented these fields in a diagram where a series of numbers represented the molecular structure of a chromosome from the centromere to its end and possible fields at different levels were represented as corresponding to different segments of the number series (see Figure 5-3). Goldschmidt based this type of representation on Kenneth Mather's analysis of what he called fields of coordination or integration (Mather 1946, 1948).

In arguing against the bead-on-a-string view of the gene, Mather claimed that the gene should be delimited as a physiological unit. Using Goldschmidt's results on the *yellow-scute* region of the X-chromosome in *Drosophila* from 1944, Mather reasoned that the chromosome produced a number of major products. Each product was produced by a specific region of the chromosome that was independent of the others, to the extent that its limits could be determined. "Within one such region," Mather continued, "we must suppose that the parts act together to give a single major product in a way depending on their arrangement with relation to each other. Such a region would be the ultimate genetical unit. In this way we can arrive at the idea of a gene as a field of coordinated activity, the property of full activity being conditioned by internal arrangement, but, within limits, independent of external relations" (Mather 1946, 67–68). Moreover, the more complex the system of coordination the greater the likelihood that there were also lesser fields of coordination. Mather's purely physiological interpretation of the gene as fields of co-ordination thus suggested a functional hierarchy. Goldschmidt effectively extended this hierarchy above the level of Mather's gene.

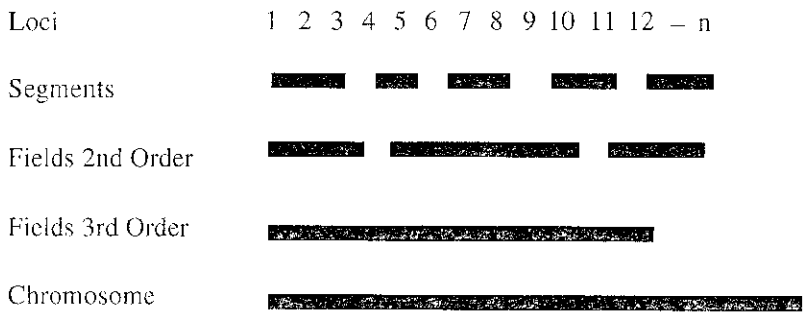

Figure 5-3 Goldschmidt's genetic hierarchy as of 1955. (After Goldschmidt 1955, 180.)

That there could be large fields of action associated with extended segments of the chromosome was a far cry from the localized action associated with a mutant locus. Goldschmidt bolstered his case for higher fields with his analysis of homeotic mutants in *Drosophila*. Homeotic mutants were understood as mutants that produced the substitution of one homologous part for another, e.g., an antenna for a leg. What struck Goldschmidt about homeotic mutants in *Drosophila* was the high concentration of related mutants in a region of the third chromosome. All of these mutants affected the determination of segmental appendages, which led Goldschmidt to interpret this segment of the third chromosome as a field "vitally concerned with the processes of segmental determination" (Goldschmidt 1955, 182). Because homeotic mutants were understood to alter the development of the imaginal discs, Goldschmidt claimed that "the whole intact section [of the chromosome] controls certain parts of the process of normal development of the discs; but a disturbance of this action at individual points inside this field or inside another similar field (in the 2d chromosome) leads to upsets of development in the discs . . . " (Goldschmidt 1955, 182). As he had done earlier with the *yellow* and *scute* regions, Goldschmidt disassociated mutation from normal gene action. The homeotic mutants of the third chromosome, however, were spread over a much larger section of chromosome. This distance between mutants, together with the similarity of their effects and their association with specific developmental processes, allowed Goldschmidt to claim that the homeotic mutants should be understood as affecting a much higher

level field than the mutants in the *yellow scute* region. A major result of this difference was the claim that "larger fields act upon more basic (i.e., earlier) developmental processes, while the smaller segments are concerned with the control of late, more or less superficial features of development" (Goldschmidt 1955, 183). Goldschmidt's hierarchy of fields was thus translated into a hierarchy of sequential developmental processes.

CONCLUSION

Richard Goldschmidt valued unification. As a biologist trained in turn-of-the-century Germany, Goldschmidt had what historian Jonathan Harwood calls a comprehensive style of scientific thought. Comprehensive geneticists are characterized by "their broad approach to the problems of genetics, their attitudes toward breadth of biological knowledge, and their cultivation of artistic sensibility, the recurring theme of striving for an all-embracing conceptual synthesis, occasionally manifest in sympathies for holism" (Harwood 1993, 270). Goldschmidt is a clear exemplar of this comprehensive style of thought. Throughout all of his work, Goldschmidt consistently strove to build a unified understanding of vast arrays of biological phenomena. In his work on sex determination, for instance, Goldschmidt produced a vast number of technical articles on the evidence and mechanisms of sex determination in *Lymantria*, but at the same time strove to generalize his findings as laws of nature. As a result, the book marking the culmination of Goldschmidt's research on sex determination, *Die sexuellen Zwischenstufen* (Goldschmidt 1931), attempted to use the regularities discovered for *Lymantria* to explain sex determination in higher orders of animals ranging from amphibians to humans.

Goldschmidt approached genetics in a similar fashion. *Theoretical Genetics* was his last grand synthesis for genetic phenomena, taking into account everything from Weismann to Watson and Crick. In terms of the gene, *Theoretical Genetics* contained Goldschmidt's final repudiation of the corpuscular gene as well as his most complete articulation of its alternative in genetic hierarchies. Rather than try to maintain that there was a new single entity to unify genetics, Goldschmidt articulated a hierarchy of fields of genetic action. This hierarchy of fields allowed Goldschmidt to maintain a unified understanding of genetic structure and function by making crossing-over and mutation secondary considerations when it came to the normal operation of the gene. Because crossing-over and mutation had been traditional tools for delimiting genetic structures, Goldschmidt's fields shift the emphasis in genetics toward function in general and developmental processes in particular. From one of the world's foremost champions of physiological genetics, this emphasis on function should not be surprising.

Richard Goldschmidt's proposal of genetic hierarchies represents an attempt to provide a unified theoretical foundation for genetics without a single unifying object, namely the classical gene. In terms of Petter Portin's (1993) history of gene concepts, Goldschmidt was clearly reacting against the classical gene but was not advocating a neoclassical gene to take its place. Where Portin's neoclassical gene narrowed the meaning of the term "gene" to emphasize structure–function relationships identified by the classical gene, Goldschmidt embraced the diversity of structures and functions known even then. In this sense, Goldschmidt's approach seems to resonate with the sentiment of molecular geneticists who continue to broaden the range of known genetic structures and functions (see review in Portin 1993). As such, the case of Goldschmidt's hierarchies illuminates the possibilities for producing a unified theory of genetics given a vast and diverse array of genetic phenomena. Indeed as the diversity of genetic structures and functions increases proponents of a unifying gene concept are faced with an ever increasing challenge, certainly one that would have continued to reinforce Richard Goldschmidt's belief that the classical gene is dead.

NOTES

1. Research for this paper was supported by a grant from the National Science Foundation (SBER94-12384).
2. See Dietrich 1996 for more on the history of Goldschmidt's early experimental work on *Drosophila*.
3. This genetic hierarchy was meant to be a hierarchy of structures (fields), but was not necessarily a hierarchy of functions since the function of

larger fields was not necessarily a product of the functions of lower level fields. I thank Sara Schwartz for drawing my attention to this ambiguity.

REFERENCES

Allen, G. E. 1974. Opposition to the Mendelian-chromosome theory: The physiological and developmental genetics of Richard Goldschmidt. *Journal of the History of Biology* 7: 49–92.

Belling, J. 1928. The ultimate chromomeres in Lilium and Aloé with regard to the numbers of genes. *University of California Publications in Botany* 14: 307–318.

Burian, R. M. 1985. The 'internal politics' of biology and the justification of biological theories. In *Human Nature and Natural Knowledge: Essays Presented to Marjorie Grene on the Occasion of Her Seventy-Fifth Birthday*, edited by A. Donagan, A. N. Petrovich and M. V. Wedin. Dordrecht: D. Reidel, pp. 3–21.

Calvin, M., M. Kodani, and R. Goldschmidt. 1940. Effects of certain chemical treatments on the morphology of the salivary gland chromosomes and their interpretation. *Proceedings of the National Academy of Sciences USA* 26: 299–301.

Carlson, E. A. 1966. *The Gene: A Critical History.* Philadelphia: Saunders.

Carlson, E. A. 1981. *Genes, Radiation, and Society.* Ithaca: Cornell University Press.

Demerec, M. 1937. Frequency of spontaneous mutations in certain stocks of *Drosophila melanogaster. Genetics* 22: 469–478.

Demerec, M. 1941a. Unstable genes in *Drosophila. Cold Spring Harbor Symposia on Quantitative Biology* 9: 145–150.

Demerec, M. 1941b. The nature of the gene. In *Cytology, Genetics, and Evolution.* Philadelphia: University of Pennsylvania Press, pp. 1–11.

Dietrich, M. R. 1995. Richard Goldschmidt's "heresies" and the evolutionary synthesis. *Journal of the History of Biology* 28: 431–461.

Dietrich, M. R. 1996. On the mutability of genes and geneticists: The "Americanization" of Richard Goldschmidt and Victor Jollos. *Perspectives on Science* 4: 321–345.

Dobzhansky, T. 1937. *Genetics and the Origin of Species.* New York: Columbia University Press.

Dobzhansky, T. 1941. *Genetics and the Origin of Species.* 2nd ed. New York: Columbia University Press.

Duhem, P. 1981. *The Aim and Structure of Physical Theory.* New York: Atheneum.

Dunn, L. C. 1937. To R. Goldschmidt; November 15: L. C. Dunn Papers, American Philosophical Society Library, Philadelphia, PA.

Dunn, L. C. 1940. To R. Goldschmidt; May 27: L. C. Dunn Papers, American Philosophical Society Library, Philadelphia, PA.

Dunn, L. C. 1965. *A Short History of Genetics.* Ames, Iowa: Iowa State University Press.

Gilbert, S. F. 1991. Cellular politics: Ernest Everett Just, Richard B. Goldschmidt and the attempt to reconcile embryology and genetics. In *The American Development of Biology*, edited by R. Rainger, K. Benson and J. Maienschein. New Brunswick: Rutgers University Press, pp. 311–346.

Goldschmidt, R. 1931. *Die sexuellen Zwischenstufen.* Berlin: Julius Springer.

Goldschmidt, R. 1937a. Spontaneous chromatin rearrangements and the theory of the gene. *Proceedings of the National Academy of Sciences USA* 23: 621–623.

Goldschmidt, R. 1937b. To L. C. Dunn; November 3: L. C. Dunn Papers, American Philosophical Society Library, Philadelphia, PA.

Goldschmidt, R. 1938a. *Physiological Genetics.* New York: McGraw-Hill.

Goldschmidt, R. 1938b. The Theory of the Gene. *Science Monthly* 46: 268–273.

Goldschmidt, R. 1939a. Mass mutation in the Florida stock of *Drosophila melanogaster*: Details of an old experiment reinterpreted. *American Naturalist* 73: 547–559.

Goldschmidt, R. 1939b. To H. J. Muller; May 11: H. J. Muller Papers, Lilly Library, Indiana University, Bloomington, IN.

Goldschmidt, R. 1940a. *The Material Basis of Evolution.* New Haven: Yale University Press.

Goldschmidt, R. 1940b. To L. C. Dunn; May 27: L. C. Dunn Papers, American Philosophical Society Library, Philadelphia, PA.

Goldschmidt, R. 1944a. On some facts pertinent to the theory of the gene. In *Science in the University.* Berkeley: University of California Press, pp. 183–210.

Goldschmidt, R. 1944b. On spontaneous mutation. *Proceedings of the National Academy of Sciences USA* 30: 297–299.

Goldschmidt, R. 1946. Position effect and the theory of the corpuscular gene. *Experientia* 2: 197–230, 250–256.

Goldschmidt, R. 1955. *Theoretical Genetics.* Berkeley, CA: University of California Press.

Goldschmidt, R. 1960. *In and Out of the Ivory Tower.* Seattle: University of Washington Press.

Goldschmidt, R., R. Blanc, W. Braun, M. Eakin, R. Fields, A. Hannah, L. Kellen, M. Kodani, and C. Villee. 1945. A study of spontaneous mutation. *University of California Publications Zoology* 49: 291–500.

Harwood, J. 1993. *Styles of Scientific Thought: The German Genetics Community. 1900–1933.* Chicago: University of Chicago Press.

Heitz, E. 1929. Heterochromatin, Chromocentren, Chromomeren. *Deutsche Botanische Gesellschaft, Berlin* 47: 274–284.

Maienschein, J. 1992. Gene: Historical perspectives. In *Keywords in Evolutionary Biology*, edited by E. F. Keller and E. A. Lloyd. Cambridge, Mass.: Harvard University Press, pp. 122–127.

Mather, K. 1946. Genes. *Scientific Journal of the Royal College of the Sciences* 16: 64–71.

Mather, K. 1948. Nucleus and cytoplasm in differentiation. *Symposia of the Society for Experimental Biology* 2: 196–216.

Metz, C. 1941. The structure of salivary gland chromosomes. *Cold Spring Harbor Symposia on Quantitative Biology* 9: 23–36.

Muller, H. J. 1941. Induced mutations in *Drosophila*. *Cold Spring Harbor Symposia on Quantitative Biology* 9: 151–167.

Muller, H. J., and A. Prokofyeva. 1934. Continuity and discontinuity of the hereditary material. *Dokladi; Academy of Science of the USSR* 4: 74–83.

Muller, H. J., A. Prokofyeva, and D. Raffel. 1935. Minute intergenic rearrangement as a cause of apparent "gene mutation." *Nature* 135: 253–255.

Plough, H. H. 1941. Spontaneous mutability in Drosophila. *Cold Spring Harbor Symposia on Quantitative Biology* 9: 127–137.

Plough, H. H., and C. Holthausen. 1937. A case of high mutational frequency without environmental change. *American Naturalist* 71: 185–187.

Portin, P. 1993. The concept of the gene: Short history and present status. *The Quarterly Review of Biology* 68: 173–223.

Raffel, D., and H. J. Muller. 1940. Position effect and gene divisibility considered in connection with three strikingly similar scute mutations. *Genetics* 25: 541–583.

Rheinberger, H.-J. 1995. Genes: A disunified view from the perspective of molecular biology. In *Gene Concepts and Evolution (Workshop)*. Preprint no. 18. Berlin: Max Planck Institute for the History of Science, pp. 7–13.

Richmond, M. 1986. Richard Goldschmidt and sex determination: The growth of German genetics, 1900–1935. Ph.D. dissertation. Indiana University.

Star, S. L., and J. R. Griesemer. 1988. Institutional ecology, "translations" and boundary objects: Amateurs and professionals in Berkeley's Museum of Vertebrate Zoology 1907–1939. *Social Studies of Science* 19: 387–420.

Stern, C. 1980 (1967). Richard Benedict Goldschmidt (1878–1958): A biographical memoir. In *Richard Goldschmidt: Controversial Geneticist and Creative Biologist*, edited by L. Piternick. *Experientia Supplementum* 35: 68–99.

Wenrich, D. 1916. The spermatogenesis of *Phrynotettix magnus* with special reference to synapsis and the individuality of chromosomes. *Bulletin of the Museum of Comparative Zoology* 60: 57–133.

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