KEYWORDS IN EVOLUTIONARY BIOLOGY

EDITED BY

Evelyn Fox Keller and
Elisabeth A. Lloyd

HARVARD UNIVERSITY PRESS
CAMBRIDGE, MASSACHUSETTS
LONDON, ENGLAND
1992

GENE: HISTORICAL PERSPECTIVES

Jane Maienschein

IN HIS CLASSIC paper of 1917, "The Theory of the Gene," Thomas Hunt Morgan sought to explain what the "genetic factor" meant for biologists. He also intended to lay to rest the various objections that had been leveled against the gene theory. In his discussion, he revealed the profusion of different ways in which different people had used the concept of the gene, and the different aspects of gene theory that were regarded as important—or as objectionable (cf. Burian et al., 1988; Mayr, 1982a).

Some critics objected, Morgan explained, to the apparently static nature of the gene; truly scientific explanations must be more physiological or dynamic. Others pointed to the theoretical or symbolic nature of the gene, which as yet had no solid chemical nature to give it reality. And the gene theory seemed to some to involve merely juggling numbers and pretending to explain something about heredity, when in reality nothing of importance had been accomplished. Still others insisted that something fundamental about the organization of whole organisms was necessarily lost when researchers focused on parts, especially hidden genetic parts. Another line of criticism objected that the genetic parts appeared to be "fixed and stable in the same sense that atoms are stable," although in both cases, the real natural world showed a lack of such solidity and fixity (Morgan, 1917, p. 514).

Clearly the gene had come a long way in the few years since Wilhelm Johannsen had coined the term in 1909. At that time, Johannsen had proposed the word "gene" as a replacement for Darwin's "pangen" but intended that it serve the same purpose. It was a unit of heredity. But just what its nature was or how it functioned remained open to question. "The word 'gene' is completely free from any hypotheses;" Johannsen had insisted, "it expresses only the evident fact that, in any case, many characteristics of the organism are specified in the gametes by means of special conditions, foundations, and determiners which are present in unique, separate, and thereby independent ways—in short, precisely what we wish to call genes" (quoted in Carlson, 1966, pp. 20, 22). This lack of hypotheses about form or function obviously left the way open to confusion and competing alternative theories.

By 1917 Morgan and his group at Columbia University had begun to provide the missing hypotheses and had, in fact, developed a theory of the gene (Morgan et al., 1915; Morgan, 1917). In their view, the statistical data gathered from hybridization or breeding experiments provided virtually definitive evidence that some independent hereditary elements *must* exist in the germ plasm and must serve as the units of heredity. These factors, or genes, remain independent of genes responsible for other characters and they assort independently of each other, as Mendel had said. The only exception came when sets of genes were linked together, a fact that the group turned to its further advantage in support of the chromosomal basis for the gene theory more generally.

So genes must exist, but the breeding studies alone tell nothing about their nature or functioning. Such information comes from further studies, specifically on mutant strains in *Drosophila*. Mutation, it seemed, was a normal process. Evidence accumulated that mutations occur regularly, and not so rarely as to be useless. Indeed, normal mutations might occur sufficiently often to provide useful variations and thereby the necessary differences for selection to act on and to choose among. When Hermann J. Muller succeeded in 1927 in generating mutations in the lab using x-rays, mutation became an important research tool (Muller, 1922, 1927).

Mutant strains of *Drosophila* provided information about the effects of genes in this fly. In particular, mutants such as the white-eyed fly differ from the wild type in more than one respect. White-eyedness is associated with yellow body pigment, a lower productivity, and lower viability, for example. As a result, Morgan argued that it made sense to conclude that the factor in the germ plasm that produced the one character also produced the others. An individual gene could apparently have more than one effect. Other studies showed that more than one gene could contribute to each character. To complicate the picture further, different genes might even produce indistinguishable characters in some cases. All such conclusions pointed to the existence of something like genes as the units of heredity and to their complex role in effecting development. Separate pairs of genes, one from each parent, must exist in some form and remain independent in the germ plasm. With this sort of evidential support, Morgan's group felt, the gene theory had established itself as a leading scientific theory, despite the hypothetical nature of its central units and despite lack of evidence about their functioning.

Chromosome studies and linkage demonstrations lent further support and gave the gene theory a physical basis. William Bateson, Edmund B.

Wilson, Nettie Stevens, and others had begun to show the linkage of characters such as sex and eye color. Calvin Bridges (1916) had also demonstrated nondisjunction of the chromosomes, in which flies had one extra chromosome that presumably did not pair with any other in cell division; this also implied some sort of linkage of genes along the chromosome. Evidence of chromosomal crossing over and recombination during cell division added to this other work to support the idea of genes lined up like beads along a string. As Morgan put it, "While the linkage relations of genes do not *at present* have any immediate bearing on our conception of the nature of genes, they have a very important bearing on the problem of localization of genes in the germ plasm" (1917, p. 520). Because the Columbia group's gene theory encompassed more than the genes themselves, the questions of localization and function remained central. Though the distribution of genes during heredity remained a separate problem from the embryological questions about the genes' action during development, ultimately both were seen to form proper subjects for a full theory of the gene. Even in his role as geneticist, Morgan remained at least loyal in principle, if not in practice, to his embryological roots.

With the further elaboration of the theory by other members of the Columbia group, especially Muller, Morgan's theory of the gene achieved a quite obvious hegemony. Considerable resources, the Nobel Prize, admiring graduate students, and a host of other benefits accrued to the research program. And yet the theory underwent modification and refinement. The term "gene" had initially served for the (hypothetical) location in the germ plasm of the (hypothetical) hereditary unit. But it also referred to the specific occupant of the genetic locus. Not surprisingly, this caused confusion. Thus Morgan's group referred to the gene to indicate the relevant sort of hereditary unit. But each gene could have many alleles, or the specific genetic material that accounted for one version of a characteristic or another. There might, for example, be a gene for eye color with several alternative alleles—red, white, and whatever. Other modifications (e.g., crossing over) also called into question the static beads-on-a-string model of the genes-on-a-chromosome.

In addition, other views of "the" gene not only existed but represented reasonable lines of research responding to other basic commitments and other sets of concerns. In particular, William Castle's (1906, 1914) attempts to establish an alternative theory gained considerable notice. For Castle, unlike for the Morgan group, the gene was not inviolable and sacrosanct. Mendelian factors that determine characteristics could vary, Castle said. Furthermore, they were subject to the action of numerous "modifiers" as well. Castle rejected the position of the Morgan group, especially as put forth by Muller, that multiple genes may contribute to an individual character in the interest of simplicity. One variable gene made

more sense to him than a host of cooperating genes. It provided more variation on which selection could act, for example. Citing the lack of any actual sighting of any gene, and to the very theoretical nature of such units, Castle pointed to the advantages of not rushing to judgment in favor of the Columbia group's theory. Persisting in his use of the term "unit character" as well as "gene" to refer to the hereditary unit, Castle showed his resistance to making the sort of genotype-phenotype distinction that the Morgan group felt was essential in order to make progress in understanding either heredity or development.

Castle felt that a return to Johannsen's more neutral view of the gene was more appropriate: he implied that the gene was a sort of black box or place holder, the "something" in the germ cell that gives rise to characteristics. To hypothesize that the gene must be stable and invariant, the assumption that formed the very basis of the Morgan group's theory of the gene, was to Castle unjustified speculation. Of course, Johannsen had not said anything to preclude further hypothesizing about the gene's nature and/or action, whenever relevant information came to light. And with time, evidence accumulated in favor of the Morgan group and against Castle.

Another critical attack came from the German biologist Richard Goldschmidt, who did not at all agree with the particular theory Morgan's group had put forth. In particular, he objected to the static nature of their gene. The organism as a whole is clearly dynamic and interactive, he insisted, and the attempt to explain its complexities in terms of stable hereditary units must fail. At first he suggested a model according to which the chromosomes are more or less hereditary place holders, with physiologically active genetic units moving in and out of the places along the chromosomes during cell division. Because he was primarily concerned with the way the genes act to effect proper development, he focused on the way that varying quantities of the gene elements act to produce characteristics.

Though sometimes modifying his views in light of new evidence, Goldschmidt (1928, 1938b) nonetheless consistently rejected the idea of the gene as a stable unit. The Morgan-Muller gene could not actually, physically exist, he felt, and it must remain a mere hypothetical construct with no reality and no function. Instead, the chromosome as a unit was what effects heredity and controls development for Goldschmidt. Rejected for his abstract "philosophical" position by the Morgan group, Goldschmidt attracted the attention of many others who developed their own rejections of the static gene and emphases on the functioning of genes within the whole, continually interactive, and dynamic organism.

Still another line of criticism came from those who advocated the importance of cytoplasmic inheritance. The Morgan group had stressed the chro-

mosomal locations of genes, which therefore must reside in the nucleus. But as the historian Jan Sapp (1987) has explained, some researchers felt they had considerable evidence in favor of the role of cytoplasm in inheritance. Whether through cytoplasmic genes or through some other hereditary vehicle, these critics held that inheritance demanded more than nuclear lines of genes strung along a chromosomal string.

The 1940s brought modifications and additional views of the gene as geneticists moved beyond statistical breeding studies to embrace molecular biological and biochemical studies as well (Olby, 1974). Whereas initially the gene had remained a theoretical unit, with only indirect evidence even for its existence, by the 1940s a variety of studies had emerged to ground various more definite theories about the chemical nature of the gene. In particular, researchers had begun to make progress on understanding its physiological functioning. George Beadle, trained in the Morgan tradition by Morgan's student Alfred Henry Sturtevant, led one such effort. He had also worked with the French geneticist Boris Ephrussi, whose interest in showing how differentiation occurs in response to genetic action evidently influenced Beadle in his physiological emphasis. Beadle's evidence supported a theory that saw one gene correlated with one "primary" character and with one enzyme. Beadle and Edward Tatum (1941) developed such a theory, which they then continued to refine.

By that time, a host of researchers had entered the game of identifying the precise biochemical nature of the gene and its action. As a result, the 1940s and 1950s brought a host of alternative hypotheses. These culminated in the accepted structural model of the genetic material as a double helix of DNA, with various related functional theories.

While some gathered increasing support for the DNA nature and the double helical structure of the chromosomal material, others pursued work on the morphological nature of the gene. Seymour Benzer, for example, used new mapping techniques to suggest that research could soon come to recognize the units of recombination, of mutation, and of hereditary action. These might, in fact, not all be the same. The apparently simple gene might actually have several parts, or might operate in different ways for different purposes. Perhaps the gene locus actually contains more than one chemical part, each of which can nonetheless act separately for some purposes. In 1957, Benzer introduced the terms "recon," "muton," and "cistron" to correspond to his three different roles for the gene. Others have continued along such lines and have broken down gene action in other alternative ways, each of which has moved away from the simple concept of the gene as the straightforward hereditary unit. Different theories of the gene have emerged and have found support for one purpose or another.

The gene as a location along a chromosome, the gene as a particular type of biochemical material, the gene as a physiological unit directing development: are these all the same gene? At root, the dominant lines of research since the Morgan group's rise to power have assumed that there is one hereditary unit, the gene. That this unit has a location on the chromosome, has a particular biochemical nature, and acts in certain eventually specifiable ways has been the implicit assumption. Despite lack of direct evidence and despite Johannsen's emphasis on the lack of hypotheses concerning the nature and action of the gene, the dominant research groups have operated on the conviction that there is some underlying unit of heredity, recombination, mutation, and physiological action.

Others, for a wide range of epistemological and metaphysical reasons, have rejected that basic assumption. In the long run, however, no one of these alternatives has succeeded in establishing itself on equal ground with some version of gene theory. Yet at any given time, diverse alternatives have existed and have quite reasonably vied for attention. Some have called into question the continued value of using the term "gene" at all, because it has played so many different roles and has undergone such modification since its introduction. Others point out that, as with so many other basic concepts from "atom" to "species," the meaning may change but such change may form a continuous tradition. Through the changes the evolving concept plays an enduring and useful role, and the basic concept may remain useful and may provide a constant substratum to which to attach different interpretations. To date, biologists have found it useful to persist in the idea that there exists some underlying hereditary unit. Whatever its nature, structure, location, and action, they generally find it useful to persist in calling it the "gene" even while recognizing that the concept of the gene continues to undergo considerable revision and even fragmentation.