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### GENES

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In this chapter, we describe traditional historical accounts of the gene and gene concepts and raise some issues from recent revisionist historiography dealing with this topic. Histories of the gene and genetics are still in their infancy. Until the mid-1970s, most histories were written by scientists and reflected the viewpoints of the victors in scientific controversies.<sup>1</sup> Only recently have professional historians contested traditional accounts and probed deeply into lost aspects of the history of the gene.<sup>2</sup> Recent biological work has raised doubt whether there is such an entity as “the” gene. Historians now disagree about whether the gene should count as an invention or a discovery, whether the history involved is fundamentally continuous or discontinuous, and how technical and theoretical developments in genetics are connected to larger social issues, including eugenics, genetic medicine, and biotechnological “interference” with nature.

#### BEFORE MENDEL

From prehistoric times, people have recognized that like begets like and have believed in some form of inheritance of acquired characters, which was used

<sup>1</sup> One of the best of these is Elof A. Carlson, *The Gene: A Critical History* (Philadelphia: Saunders, 1966; repr. ed., Ames: Iowa State University Press, 1989). See also L. C. Dunn, *A Short History of Genetics* (New York: McGraw-Hill, 1965); L. C. Dunn, ed., *Genetics in the 20th Century: Essays on the Progress of Genetics during Its First 50 Years* (New York: Macmillan, 1951); Alfred Sturtevant, *A History of Genetics* (New York: Harper, 1965). On the origins of molecular biology, see John Cairns, Gunther S. Stent, and James D. Watson, eds., *Phage and the Origin of Molecular Biology* (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory of Quantitative Biology, 1966).

<sup>2</sup> See Jonathan Harwood, *Styles of Scientific Thought: The German Genetics Community, 1900–1933* (Chicago: University of Chicago Press, 1993); Robert C. Olby, *The Path to the Double Helix* (Seattle: University of Washington Press, 1974); Jan Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics* (New York: Oxford University Press, 1986).

to help explain familial inheritance of character traits and physique.<sup>3</sup> Later, it was used to explain susceptibility to particular diseases, such as syphilis and tuberculosis, and the adaptation of imported plants and domesticated animals to their new environments. The Hippocratics had already developed explicit theories in support of such inheritance,<sup>4</sup> but sustained efforts to develop particulate theories of heredity began with the introduction of the idea of evolution in the writings of such figures as Erasmus Darwin (1731–1802), Jean-Baptiste Lamarck (1744–1829), and, above all, Charles Darwin (1809–1882).<sup>5</sup> Around 1900, most biologists still thought that, whatever detailed principles or mechanisms were involved, a theory of heredity must find a way of explaining the inheritance of acquired characters.

Unlike most mid-nineteenth-century evolutionists, Charles Darwin drew deeply on breeding work. In the first chapter of *On the Origin of Species*, he used artificial selection as a model for natural selection. His later “provisional hypothesis of pangenesis” also drew on knowledge of breeding. According to that theory, each cell casts off minute particles (“gemmules”) that circulate to the gonads. The process of fertilization activates most of the gemmules, which, if adequately nourished, begin to form cells and organs like those from which they were derived. Others remain latent. This doctrine allowed Darwin to sketch hypothetical explanations of many phenomena, including inheritance of oversized biceps by blacksmiths’ sons, loss of eyes by cave animals, and (thanks to latent gemmules) atavisms or reversions to ancestral traits.<sup>6</sup>

#### FROM MENDEL TO THE TURN OF THE CENTURY

Gregor Johann Mendel (1822–1884) was a scientifically trained Moravian monk. His influence on genetics stems from work concerning hybridization of plant “species” (or varieties – the German word *Art* is ambiguous between the two) to produce stable new “species,” not work in genetics in *our* sense.<sup>7</sup> Mendel designed a powerful method for testing whether carefully

<sup>3</sup> For general background, see William Coleman, *Biology in the Nineteenth Century* (New York: Wiley, 1971); Ernst Mayr, *The Growth of Biological Thought: Diversity, Evolution, and Inheritance* (Cambridge, Mass.: Harvard University Press, 1982); Robert C. Olby, *Origins of Mendelism*, rev. ed. (Chicago: University of Chicago Press, 1985); Hans Stubbe, *History of Genetics, from Prehistoric Times to the Rediscovery of Mendel’s Laws*, trans. T. R. W. Waters (Cambridge, Mass.: MIT Press, 1965).

<sup>4</sup> Conway Zirkle, “The Early History of the Inheritance of Acquired Characters and of Pangenesis,” *Transactions of the American Philosophical Society*, n.s., 35 (1946), 91–151.

<sup>5</sup> See the biographies in the *Dictionary of Scientific Biography* for these and most individuals for whom we supply dates.

<sup>6</sup> Charles Darwin, *On the Origin of Species* (London: John Murray, 1859) and, for pangenesis, Charles Darwin, *The Variation of Animals and Plants under Domestication* (London: John Murray, 1868), chap. 27.

<sup>7</sup> Gregor Mendel, “Versuche über Pflanzen-Hybriden,” *Verhandlungen des naturforschenden Vereines in Bruenn*, 4 (1866), 3–47, Engl. trans. Eva Sherwood in *The Origin of Genetics: A Mendel Source Book*, ed. Curt Stern and Eva Sherwood (San Francisco: W. H. Freeman, 1966). See Viteslav Orel, *Mendel* (New York: Oxford University Press, 1984), and, for a contrasting account, Olby, *Origins*

chosen sharp differences between varieties of garden peas were inherited discretely and for examining the distribution of those differences in subsequent generations. In the seven cases he tested, the first hybrid generation was uniform for one of a pair of alternating traits (e.g., green or yellow seed coat color); he called that trait “dominant” and the other “recessive.” In the second generation, obtained by self-fertilizing plants from the first generation, one-quarter of the offspring had the dominant trait and, when self-fertilized, produced only the dominant trait, one-half had the dominant trait but produced recessives as well as dominants, and one-quarter had the recessive trait and produced only plants with that trait. Mendel theorized that the “elements” (later called “factors”) causing the particular traits are preserved unaltered in the gametes (egg and pollen cells), providing continuity from one generation to the next. On the basis of the distribution of multiple traits through a series of generations (and employing statistical tools he learned from physics), Mendel proposed the famous laws of segregation and independent assortment for these elements. This proposal, ahead of its time if ever any proposal was, fell on only a few ears, all of them effectively deaf to it.

In the 1870s, developments in microscopy plus new dyes helped scientists visualize the internal parts of cells and improve cell theory. During the 1880s and 1890s, with great difficulty, microscopists worked out the dance of the chromosomes in mitosis (ordinary cell division) and meiosis (formation of gametes). By 1900, there was partial consensus that chromosomes divide longitudinally and that each gamete receives only one of each pair of chromosomes. These findings soon suggested a plausible mechanism that could yield Mendelian segregation of factors.<sup>8</sup> Shortly after the “rediscovery” of Mendel’s paper in 1900, Theodor Boveri (1862–1915), Walter Sutton (1877–1916), and others emphasized this connection between the new knowledge of chromosomes and Mendel’s theory, arguing that chromosomes are the bearers of Mendelian factors, with each gamete getting one of each pair of factors.<sup>9</sup>

Starting in 1883, August Weismann (1834–1914) argued strenuously that germ-line cells are segregated from somatic cells very early in development and thus cannot be altered by environmental changes that alter somatic

*of Mendelism*, especially “Mendel no Mendelian,” pp. 234–58. For general background, see Garland Allen, *Life Science in the Twentieth Century* (Cambridge: Cambridge University Press, 1975); Peter J. Bowler, *The Mendelian Revolution* (Baltimore: Johns Hopkins University Press, 1989).

<sup>8</sup> But there is considerable evidence that the cytological findings were stabilized in interaction with Mendelian findings after 1900. See Alice Baxter and John Farley, “Mendel and Meiosis,” *Journal of the History of Biology*, 12 (1979), 137–73.

<sup>9</sup> Boveri used experiments with sea urchins to argue that each chromosome is a distinct individual and that a full complement of chromosomes is required to produce viable offspring. See Theodor Boveri, “Über mehrpolige Mitosen als Mittel zur Analyse des Zellkerns,” *Verhandlungen der Physikalisch-medizinischen Gesellschaft zu Würzburg*, 35 (1902), 67–90. Sutton started from the cytological behavior of chromosomes. See Walter S. Sutton, “The Chromosomes in Heredity,” *Biological Bulletin*, 4 (1903), 231–51.

cells.<sup>10</sup> Accordingly, characteristics acquired during the organism's life cannot be inherited. This marks a key turning point; it made it conceptually possible to separate the transmission of determinants from an account of how they accomplished their functions and encouraged experiments aimed at learning how hereditary traits are transmitted. Weismann's doctrines became the focus of enormous public controversy, remaining influential even after many of his specific doctrines were discredited, and helped set the context in which Mendel's work was rediscovered.<sup>11</sup>

### THE DEVELOPMENT OF GENETICS AND THE GENE CONCEPT UP TO WORLD WAR II

In 1900, three botanists explicitly acknowledged the importance of Mendel's findings: Hugo De Vries, Carl Correns (1864–1933), and Erich von Tshermak-Seysenegg (1871–1962). All three discovered Mendelian ratios in their own experiments and subsequently found Mendel's text.<sup>12</sup>

The response to this "rediscovery" was very rapid. William Bateson (1861–1926), originally trained as a traditional British Darwinian, played the role of Mendel's bulldog. Early on, he employed embryology and morphology in order to understand the course of evolution and phylogenetic histories, but he became disillusioned in the 1890s and became an advocate of the importance of discontinuous variation. Bateson denied that Mendelian factors (his term) could be material particles or substances because they had to direct the development of the organism, something that he was convinced mere material particles could not do. Instead, he apparently thought of them as some sort of stable harmonic resonance.<sup>13</sup>

Mendelism quickly became a large-scale enterprise, thanks partly to the controversies it evoked and partly to support from plant and animal

<sup>10</sup> See, for example, August Weismann, *Die Continuität des Keimplasmas als Grundlage einer Theorie der Vererbung* (Jena: Gustav Fischer, 1885), translated as chap. 4 in *Essays upon Heredity and Kindred Biological Problems*, vol. 1, ed. Edward B. Poulton, Selmar Schoenland, and Arthur E. Shipley (Oxford: Clarendon Press, 1889).

<sup>11</sup> See, for example, Jane Maienschein, "Preformation or New Formation – or Neither or Both?" in *A History of Embryology*, ed. T. J. Horder, J. A. Witkowski, and C. C. Wylie (Cambridge: Cambridge University Press, 1986); Jane Maienschein, "Heredity/Development in the United States, circa 1900," *History and Philosophy of the Life Sciences*, 9 (1987), 79–93; Jane Maienschein, "Cell Theory and Development," in *Companion to the History of Modern Science*, ed. R. C. Olby, G. N. Cantor, J. R. R. Christie, and M. J. S. Hodge (London: Routledge, 1990), pp. 357–73.

<sup>12</sup> See Stern and Sherwood, *Origin of Genetics*, which contains English translations of the de Vries and Correns papers. Twenty-seven original papers (including Mendel's) are reprinted in Jaroslav Krizenecky, ed., *Fundamenta Genetica* (Prague: Publishing House of Czechoslovakia Academy of Science; Brno: Moravian Museum, 1965).

<sup>13</sup> See Alan G. Cock, "William Bateson, Mendelism, and Biometry," *Journal of the History of Biology*, 6 (1973), 1–36; William Coleman, "Bateson and Chromosomes: Conservative Thought in Science," *Centaurus*, 15 (1970), 228–314; William B. Provine, *The Origins of Theoretical Population Genetics* (Chicago: University of Chicago Press, 1971). Coleman discusses Bateson's arguments against interpreting factors as particles.

breeders<sup>14</sup> and from agricultural stations, especially in the United States. Much work went into delimiting traits inherited in Mendelian fashion, demonstrating that such “Mendelizing” traits are found in all sorts of plants and animals, and applying Mendelism to practical breeding. Much of the fundamental vocabulary of genetics was elaborated from 1900 to 1910, including such terms as “allele” (originally “allelomorph”), “homozygote” and “heterozygote,” “genetics,” “gene,” “genotype,” and “phenotype.” During the same period, numerous theoretical conceptions of Mendelian factors were put forward, many of them quite vague. Although these pointed in different directions, most of them sought to link factors to the development of organisms and formation of species and varieties. Because the developmental and evolutionary consequences of Mendelism were not readily tested, those issues were gradually dismissed as speculative and set aside. By 1910, younger Mendelians (especially in the United States) came to focus increasingly on the phenomenology and mechanics of trait transmission and to require that theories of genetic change be testable. The resultant successes narrowed the concept of the gene toward transmitted causal factors whose differences are reflected in phenotypic differences inherited in a Mendelian pattern. These successes reinforced the belief that doctrines of heredity were finally making genuine progress.

Starting in 1910, T. H. Morgan (1866–1945) and his students developed the theory that came to dominate the field from about 1915 on – the classical theory of genes as linearly arrayed particles on chromosomes. Although there had been intimations of such a theory since the 1890s (especially Sutton’s contributions), the Morgan group provided a detailed, closely reasoned, and testable way of combining cytological knowledge of the behavior of chromosomes and genetic knowledge of Mendelian factors. They worked with a very advantageous organism, the fruit fly *Drosophila melanogaster* – an insect with only four pairs of morphologically distinct chromosomes, easily raised in the laboratory, with a short generation time, high fecundity, and easily controlled crosses, allowing them to create and follow lineages.<sup>15</sup> In 1910, they found a white-eyed fly whose eye color was inherited in a sex-linked

<sup>14</sup> Jean Gayon and Doris Zallen, “The Role of the Vilmorin Company in the Promotion and Diffusion of the Experimental Science of Heredity in France, 1840–1920,” *Journal of the History of Biology*, 31 (1998), 241–62; Barbara A. Kimmelman, “The American Breeder’s Association: Genetics and Eugenics in an Agricultural Context, 1903–13,” *Social Studies of Science*, 13 (1983), 163–204; Diane B. Paul and Barbara A. Kimmelman, “Mendel in America: Theory and Practice, 1900–1919,” in *The American Development of Biology*, ed. Ronald Rainger, Keith R. Benson, and Jane Maienschein (Philadelphia: University of Pennsylvania Press, 1988), pp. 281–309; G. Olsson, ed., *Svalöf, 1886–1986, Research and Results in Plant Breeding* (Stockholm: LTS Förlag, 1986).

<sup>15</sup> See Carlson, *The Gene*; Garland E. Allen, *Thomas Hunt Morgan: The Man and His Science* (Princeton, N.J.: Princeton University Press, 1978). For the advantages and peculiarities of *Drosophila*, see Robert E. Kohler, *Lords of the Fly: Drosophila Genetics and the Experimental Life* (Chicago: University of Chicago Press, 1994). For the interplay between cytology and genetics in constructing and testing the chromosome theory of the gene, see Lindley Darden, *Theory Change in Science: Strategies from Mendelian Genetics* (New York: Oxford University Press, 1991).

pattern; that is, transmitted with the male-determining X chromosome. By 1912, they had found six different X-chromosome mutations. Some of these did not assort independently; they occurred together in specific frequencies greater than 50 percent. Given the pairwise combinations, the six formed a “linkage group” of factors that appeared together more often than expected.

In 1911, Morgan developed a key notion based on cytological findings by Frans Alfons Janssens (1863–1924), a Belgian cytologist. When the chromosomes twist around each other during meiosis, they sometimes break and rejoin, with a block of material “crossing over” from one chromosome to the other. If Mendelian factors occupied fixed places along the chromosome, as the Morgan group hypothesized, crossing over would allow testing of their relative locations. Using the hypotheses that factors are linearly arrayed on the chromosome and that the frequency of crossing over increases with distance along the chromosome, one of Morgan’s undergraduates, Alfred Sturtevant (1891–1970), used the statistics of linkage (co-occurrence) among the six X-linked factors to construct the first genetic map.<sup>16</sup>

The major features of the chromosomal theory of the gene were fixed by about 1915, although most of them were still controversial. Genetics, the science of the gene, developed rapidly into a major biological discipline located, conceptually, near the heart of biology because it claimed to specify how key features of organisms are determined. The key event was the publication in 1915 of *The Mechanism of Mendelian Heredity*, a textbook produced by Morgan’s group that covered many plants and animals, with special attention to examples from *Drosophila*.<sup>17</sup> This textbook synthesized findings from many sources, supporting the following claims, among others:

- Chromosomes are the bearers of the hereditary material.
- Genes (not “unit characters”) are the fundamental units of heredity.
- Genes are arrayed linearly on chromosomes.
- The number of linkage groups of genes (with overlapping nonindependent assortment) equals the number of chromosomes.
- Although each distinct gene may have many alleles, it remains unchanged except by mutation.
- Environmental factors (e.g., temperature and nutrition) can influence the effects of some genes.
- Some genes can modify the effects of other genes, sometimes quite specifically.
- Genes themselves are not altered when their effects are changed by modifier genes.

<sup>16</sup> F. A. Janssens, “La theorie de la chiasmotypie,” *La Cellule*, 25 (1909), 389; Thomas Hunt Morgan, “Random Segregation versus Coupling in Mendelian Inheritance,” *Science*, 34 (1911), 384; Alfred H. Sturtevant, “The Linear Arrangement of Six Sex-Linked Factors in *Drosophila*, as Shown by Their Mode of Association,” *Journal of Experimental Zoology*, 14 (1913), 43–59.

<sup>17</sup> Thomas Hunt Morgan, Alfred H. Sturtevant, Hermann J. Muller, and Calvin B. Bridges, *The Mechanism of Mendelian Heredity* (New York: Henry Holt, 1915, rev. ed., 1922). See also Thomas Hunt Morgan, *The Theory of the Gene* (New Haven, Conn.: Yale University Press, 1926).

- Genes must cooperate in large numbers to yield observable traits.
- Many mutations have large effects, but many more have small effects.
- Even though the pathways from genes to characters are wholly unknown, Mendel's principles, interpreted via the gene theory, provide "a scientific explanation of heredity [that] fulfills all the requirements of any causal explanation" (rev. ed., p. 281).

Morgan and his colleagues deemphasized hereditary phenomena that could not be explained by their theory. For example, in *Mechanism of Mendelian Heredity* they argued that the few known cases of cytoplasmic inheritance could be explained as inheritance of (potentially) self-reproducing particles (e.g., chloroplasts) in the cytoplasm or as the delayed effects of maternal genetic input into the egg (e.g., the color of egg membranes).

The consolidation of the chromosomal theory is marked by a terminological change. Morgan et al. still employed the term "factor" in *Mechanism of Mendelian Heredity*. By 1920, they had switched to "gene," emphasizing the specific commitments of the chromosomal theory. Although numerous hard-fought debates took place over refinements and specific issues, that theory dominated genetics until after World War II.

One other important development, initiated in 1927 by Herman J. Muller (1890–1967), was the discovery that x-rays could drastically alter the rate of mutation.<sup>18</sup> The interaction of x-rays with genes provided a way of interfering with genes that promised to be helpful in studying their structure. It also stimulated interest in genetics among physicists, some of whom made lasting contributions to genetics starting in the 1930s.

As of 1940, three long-standing problems remained to plague genetics and give opponents from other disciplines grounds for objecting to the insufficiency of the new science.

The first of these problems was the chemical composition of the gene. Once the gene was classed as a material entity, it became necessary to analyze its material and structural properties. The requirements to be met were spelled out by Muller. He emphasized three remarkable properties that must be explained by the composition or structure of the gene. First, genes are "autocatalytic" (i.e., they can duplicate or reproduce themselves). Second, they are "heterocatalytic" (i.e., they can catalyze, direct, or otherwise control the formation of substances different from those of which they are composed, including all the proteins, lipids, and carbohydrates in the bodies of all organisms). Finally, they retain both their autocatalytic and heterocatalytic powers even after mutation, so they must allow structural changes that do not remove these powers.<sup>19</sup> Proteins were the primary candidates for the

<sup>18</sup> Hermann J. Muller, "Artificial Transmutation of the Gene," *Science*, 66 (1927), 84–7.

<sup>19</sup> Hermann J. Muller, "Variation Due to Change in the Individual Gene," *American Naturalist*, 56 (1922), 32–50. See also Hermann J. Muller, "The Gene," *Proceedings of the Royal Society B*, 134 (1947), 1–37.

gene material because they were diverse enough in composition and structure, stable enough, and present in sufficient quantity on chromosomes to be able to provide the necessary specificity, stability, and structural variety. The only other component of chromosomes plentiful enough to be considered was nucleic acid. But DNA, long known to be present in chromosomes, seemed highly unsuitable. It had only four variable parts (the nucleotide bases adenine, guanine, cytosine, and thymine, abbreviated A, G, C, and T) and was thought to be structurally uniform, with a “boring” series of repeated nucleotides in a fixed order. Such a molecule could not serve a genetic role.<sup>20</sup>

The second problem that plagued genetics concerned the connections between genetics and evolution. Although R. A. Fisher (1890–1962), J. B. S. Haldane (1892–1964), and Sewall Wright (1889–1988) elaborated the mathematical foundations of theoretical population genetics in the 1920s and 1930s, it remained unclear whether the theory of the gene could be adequately reconciled with naturalists’ theories of evolution. The so-called evolutionary synthesis, begun in the late 1930s, did not really take hold until the 1940s and 1950s (see Hodge, Chapter 14, this volume).

The final problem that raised objections to genetics was the relationship between genetics and embryology. Genetics still did not explain the development of the organism from fertilization through all the stages of its life history to the end of its life. The Morgan school by and large set this problem aside as intractable. Among the founders of genetics, Bateson and Wilhelm Johannsen (1857–1927) had been skeptical of the ability of the chromosomal theory of the gene to accomplish this task. Most embryologists and many European geneticists shared this skepticism. They maintained that an adequate theory of heredity had to explain how genetic factors guided or determined development, much of which was (or seemed to be) controlled by events in the cytoplasm, not the nucleus.

From the beginning, there was considerable tension between two philosophical poles in the interpretation of the gene. Some theorists held that the gene is a formal device for representing breeding results. If there was an entity, the gene, behind those representations, it was not yet adequately characterized. Johannsen, in 1909, intended the very term “gene” to capture this view. He meant the term to be theoretically uncommitted as a label for whatever was transmitted in the pattern characteristic of Mendelian factors. One could entertain hypotheses, but one had to remain agnostic, for example between a materialist view such as Morgan’s and a dynamicist view such as Bateson’s. L. J. Stadler (1896–1954), a major plant geneticist, propounded a similar view from his deathbed in 1954.<sup>21</sup> He distinguished between the “operational gene,” which could be delimited by breeding criteria, and the “hypothetical

<sup>20</sup> Olby, *Path to the Double Helix*; Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, expanded ed. (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 1996).

<sup>21</sup> Lewis John Stadler, “The Gene,” *Science*, 120 (1954), 811–19.

gene,” which required intrinsic characterization. Agreement about the “operational gene” could be achieved straightforwardly by applying a clear-cut calculational system to actual experimental results, but Stadler did not expect agreement on the “hypothetical gene” until the distant future at best.

#### POSTWAR NOVELTIES: THE MATERIAL OF THE GENE AND GENE ACTION

At least two sorts of knowledge, neither available in 1940, were required to resolve the foundational problems of genetics: What are genes made of and how do they act? These questions were addressed during World War II as well as after, when large numbers of scientists, many trained in other disciplines (especially biochemistry and physics), entered the field, bringing new techniques and approaches with them.<sup>22</sup> By war’s end, new approaches, findings, and tools made it possible to pursue genetics at the molecular level, thereby transforming the discipline. There were two major sorts of changes in tools and techniques. One was the utilization of radioactive tracers, electron microscopes, ultracentrifuges, and other tools that allowed geneticists to follow cellular organelles and molecular components through various reactions and processes. The second was the use of microorganisms. Most microorganisms had been unanalyzable via Mendelian techniques because they do not exhibit regular sexual crossing and because those that do were too small and hard to handle for analysis of their lineages. Until the late 1940s, most geneticists and bacteriologists thought that bacteria (which do not have a true nucleus) did not have a system of genes like those of higher organisms. The groundwork for removing this obstacle was laid during World War II.<sup>23</sup>

Oswald Avery (1877–1955) and his colleagues pursued a line of work with a bacterium unfamiliar to geneticists. They showed that transfer of a substance identified as deoxyribonucleic acid (DNA) could transform *Pneumococcus pneumoniae* from one antigenic structure to another – and from nonvirulence to virulence.<sup>24</sup> Work on the nutrition of bacteria and microorganisms with nuclei (e.g., yeasts, fungi, and protozoa), begun in the 1930s, showed that basic nutritional requirements are universal. During World War II, George Beadle (1903–1989) and his colleagues employed the bread mold *Neurospora* to screen for and study mutations affecting nutritional needs. By 1945 they had

<sup>22</sup> The most important general histories covering this period are Judson, *Eighth Day of Creation*, and Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Cambridge, Mass.: Harvard University Press, 1998).

<sup>23</sup> Thomas D. Brock, *The Emergence of Bacterial Genetics* (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 1990).

<sup>24</sup> Oswald T. Avery, Colin M. MacLeod, and MacLyn McCarty, “Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types. I. Induction of Transformation by a Deoxyribonucleic Acid Fraction Isolated from *Pneumococcus* type III,” *Journal of Experimental Biology and Medicine*, 79 (1944), 137–58.

shown that each of the *Neurospora* genes affecting nutrition are responsible for directing the formation of a single enzyme that enters into the metabolism of the organism. This claim was soon generalized to yield the hypothesis that one gene produces one enzyme.<sup>25</sup> In France, Jacques Monod (1910–1976) showed how to separate the genetic capacity of certain bacteria to digest certain sugars from the actual presence of the enzymes required to do the digestion. Some bacteria have the ability to control the production of enzymes to digest particular sugars. For example, some bacteria do not produce enzymes to digest lactose when glucose is present or lactose is absent but, as Monod showed, have the genetically determined ability to switch by producing the enzymes necessary to digest lactose when it is present but glucose is not.<sup>26</sup> In retrospect, though it was not obvious at the time, this was a first step toward understanding the regulation of gene action. Max Delbrück (1906–1981) and Salvador Luria (1912–1991) began working with viruses that attack bacteria (“bacteriophages” or just “phages”) and were able to show that a few bacteria in a large culture have preexisting genes that enable them to resist phages.<sup>27</sup>

The identification of the genetic material was the first major problem to fall. After World War II, work that built on the results of Avery et al. and many others made it clear that both DNA and RNA are more intimately involved in gene physiology than had previously been recognized<sup>28</sup> and that the DNA molecule was massively larger than had been anticipated. By 1952, a small group of geneticists and biochemists were convinced that DNA is the genetic material; they analyzed its chemistry, its roles in the cell, and its structure in every possible way. The most famous biological discovery of the era is James Watson (b. 1928) and Francis Crick’s (1916–2004) discovery of the double-helical structure of DNA in 1953, which they accomplished by means of x-ray crystallography and model building.<sup>29</sup> A key aspect of this structure was the complementary pairing of A with T and G with C in the interior of the helix. The structure suggested a solution for the problem of gene replication (autocatalysis). All that was needed to copy the double helix

<sup>25</sup> George W. Beadle and Edward L. Tatum, “Genetic Control of Biochemical Reactions in *Neurospora*,” *Proceedings of the National Academy of Sciences USA*, 27 (1941), 499–506; George W. Beadle, “The Genetic Control of Biochemical Reactions,” *Harvey Lectures*, 40 (1945), 179–94. See also Norman H. Horowitz, “Fifty Years Ago: The *Neurospora* Revolution,” *Genetics*, 127 (1991), 631–5; Lily Kay, “Selling Pure Science in Wartime: The Biochemical Genetics of G. W. Beadle,” *Journal of the History of Biology*, 22 (1989), 73–101.

<sup>26</sup> Jacques L. Monod, “The Phenomenon of Enzymatic Adaptation and Its Bearing on Problems of Genetics and Cellular Differentiation,” *Growth Symposium*, 11 (1947), 223–89.

<sup>27</sup> Salvador E. Luria and Max Delbrück, “Mutations of Bacteria from Virus Sensitivity to Virus Resistance,” *Genetics*, 28 (1943), 491–511.

<sup>28</sup> Alfred D. Hershey and Martha Chase, “Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage,” *Journal of General Physiology*, 36 (1952), 39–56. Other work pointed in the same direction, such as Jean Brachet, “The Localization and the Role of Ribonucleic Acid in the Cell,” *New York Academy of Sciences*, 50 (1950), 861–9. See Olby, *Path of the Double Helix*; Franklin H. Portugal and Jack S. Cohen, *A Century of DNA* (Cambridge, Mass.: MIT Press, 1979).

<sup>29</sup> James D. Watson, *The Double Helix* (New York: Atheneum, 1968), or the Norton Critical Edition, ed. G. Stent (New York: Norton, 1980).

was to open up the original double helix and use each of the complementary strands as a template for making a new strand.

The problem of how DNA specifies a product, however, remained unsolved. Crick was perhaps the most important theoretician to attack this problem. He and various colleagues showed that a genetic code would probably employ a sequence of three nucleotides (a “codon”) to specify one amino acid, with the sequence of codons specifying the sequence of amino acids needed to yield a protein. But in the end the detailed solution of the code was found by the techniques of wet biochemistry. Those details depended on the mechanism of protein synthesis (a long-standing biochemical problem) and required two major intermediate steps.<sup>30</sup>

One of these was the discovery of small RNA molecules that link specific codons to specific amino acids. They were discovered biochemically by the combined work of many groups, especially that of Paul Zamecnik.<sup>31</sup> He and his colleagues discovered “soluble RNAs” required to “activate” amino acids—that is, provide them with the energy to be added to a protein. These molecules, now called transfer RNAs (tRNAs), are intermediary molecules that link codons and amino acids. Crick had predicted the existence of such intermediaries, calling them “adaptors.”

The second step concerned the way the information contained in the sequence of DNA nucleotides is brought to ribosomes, the units in the cytoplasm where proteins are assembled. François Jacob (b. 1920) and Monod produced the key findings between 1958 and 1961. In brief, a “messenger RNA” (mRNA) is “transcribed” from the DNA and “read” in the cytoplasm by the ribosomes. As a ribosome proceeds along a strand of mRNA, it “translates” the mRNA nucleotide acid sequence into an amino acid sequence by moving along the mRNA one codon at a time, picking off the amino acid on a transfer RNA linked to that codon and adding it to the growing protein chain.<sup>32</sup>

Once the differences between mRNA and tRNA were understood and techniques for making proteins in vitro were developed, it was possible to solve the genetic code. This was done, between 1961 and 1966, by difficult biochemical experiments performed in many laboratories. In essence, these workers made highly repetitious synthetic mRNAs and analyzed the resulting protein chains. By matching each RNA codon to an amino acid, they slowly filled in the conversion table from nucleic acid to protein.<sup>33</sup>

<sup>30</sup> Judson, *Eighth Day of Creation*, chap. 8.

<sup>31</sup> Hans-Jörg Rheinberger, *Towards a History of Epistemic Things: Synthesizing Proteins in the Test Tube* (Stanford, Calif.: Stanford University Press, 1997).

<sup>32</sup> See Judson, *Eighth Day of Creation*, chap. 7; Morange, *History of Molecular Biology*, chap. 13.

<sup>33</sup> The breakthrough was the first production of a protein from an artificial mRNA; see Marshall W. Nirenberg and J. Heinrich Matthaei, “The Dependence of Cell-Free Protein Synthesis in *E. coli* upon Naturally Occurring or Synthetic Polyribonucleotides,” *Proceedings of the National Academy of Sciences USA*, 47 (1961), 1588–1602. See also Judson, *Eighth Day of Creation*, chap. 8, Morange, *History of Molecular Biology*, chap. 12.

In related experiments from 1958 to 1961, Jacob and Monod solved another major problem – describing a key mechanism by means of which gene action is regulated. They constructed the “operon” model, according to which a gene called the operator, which works like a switch that is opened and closed by environmental signals, determines whether a sequence of genes is transcribed to mRNA or not. Such a group of genes typically controls a significant trait (e.g., the ability to digest a particular sugar). Jacob and Monod divided genes into different classes – some that produce enzymes and others that regulate the expression of other genes. Their model thus provided a clear understanding, for bacteria at least, of the difference between genetic potential (what protein-producing genes are present) and the regulation of genes and gene action (how the control system determines which genes are expressed and when).<sup>34</sup>

Starting about 1975, new findings concerning the control of gene expression in eukaryotes (organisms with true nuclei) complicated this picture considerably. The correspondence between the nucleotide sequence in DNA (or the RNA of RNA viruses) and the eventual product is subject to enormous physiological modulation. A few examples illustrate these new complexities.

- *Variations in the genetic code.* The genetic code depends on the pairing of nucleotide triplets on mRNA with amino acids on tRNAs. A few organisms and the mitochondria of many organisms have tRNAs with nonstandard pairings. For example, in *Drosophila*, whether the codon AGA is translated as the amino acid serine or the amino acid arginine depends on whether it is translated inside a mitochondrion or in the cytoplasm of the cell. Thus, the protein product made from a given nucleotide sequence is context dependent.
- *Genes in pieces.* Typical eukaryotic genes that encode proteins have many more nucleotides than are expressed in the protein product. Noncoding segments (“introns”) interrupt the coding material. To get from the DNA nucleotide sequence to the protein, one must understand the regulatory apparatus that excises the introns from the mRNA transcript. Many factors, including cell type, environmental conditions, and developmental stage, can influence the pattern of excisions.
- *Shuffling of parts of genes.* Both in organismal development (e.g., in immune system genes) and on an evolutionary timescale, parts of genes are moved around as units and recombined to yield novel products. On an organismal scale, this means that the DNA of a fertilized egg does not contain the entire structure of the adult genome. On an evolutionary scale, it means that the units of evolutionary change include parts of genes (sometimes corresponding to functional protein domains) and factors that control gene organization and expression.
- *Processing of mRNA transcripts.* In many circumstances, after mRNA reaches the cytoplasm, it is altered in ways that change its message. The alterations are

<sup>34</sup> François Jacob and Jacques L. Monod, “Genetic Regulatory Mechanisms in the Synthesis of Proteins,” *Journal of Molecular Biology*, 3 (1961), 318–56; François Jacob and Jacques L. Monod, “On the Regulation of Gene Activity:  $\beta$ -galactosidase Formation in *E. coli*,” *Cold Spring Harbor Symposia on Quantitative Biology*, 26 (1961), 193–211. See also Judson *Eighth Day of Creation*, chap. 7.

often significant – in different organs, the same mRNA transcript yields *different* proteins. The reason is that a specific change in the transcript, made after the transcript has reached the cytoplasm of the relevant cells, alters the protein. For example, in the intestines and liver of mammals, a T is substituted for a C in the transcript coding for a protein called apolipoprotein-B, with the result that the protein is truncated earlier (and works differently) in the intestine than in the liver.<sup>35</sup>

These illustrations support a straightforward point. If a gene is identified by reference to its product or to what it does, it cannot be identified simply by its nucleotide sequence. On the other hand, if a gene is identified by a nucleotide sequence, more is required to infer what it makes or what it does. Because the genome is dynamic, because the correspondence between structure and function depends on context, and because genes are identified by mixed structural and functional criteria, there is no single correct way to delimit them. But this means that scientists who delimit genes in different ways will not agree about which changes to the genetic material should count as gene mutations. This complication of going from a description of the genetic material to an account of the behavior of genes appears to be unavoidable.

#### THE GENE IN THE LIGHT OF RECENT HISTORIOGRAPHY

Most traditional histories of the gene emphasize two striking characteristics: homogeneity and linearity. That is, the historical development of the field is represented as if there were a single mainstream tradition. It thus seems that, thanks to a reductionist agenda, research moved in a relatively straight intellectual line from the rediscovery of Mendel's work to the current detailed understanding of the precise chemical nature of the genetic material and of how genes function. In general, according to such accounts, the study of the gene proceeded in a reasonably uniform manner wherever it was an object of study.

Newer historical studies of genetic research differ sharply from this picture. They emphasize the importance of conflicting traditions in the scientific literature and challenges to conceptions of the gene that were previously overlooked or dismissed as "dead ends" by historians and scientists. Recent accounts of the era after World War II also emphasize interactions among workers from many disciplines, each tugging genetics in different ways. Much work has gone into understanding the various factors involved in re-forming genetic research.

It is now clear that genetic research moved in different directions in different places. Comparative studies have shown that genetics in one country

<sup>35</sup> An early textbook description of this result is provided by Benjamin Lewin, *Genes IV* (Oxford: Oxford University Press, 1990), pp. 606–7.

is not, as L. C. Dunn thought it was after World War I, “virtually indistinguishable from genetics in any other country.”<sup>36</sup> In general, geneticists in different countries focus on different problems and utilize different concepts and techniques. These differences depend on such factors as the problems investigated and the organisms employed.<sup>37</sup> These are influenced, in turn, by the intellectual roots established by the founders of research traditions, the educational systems that celebrate national accomplishments or promote distinctive styles of investigation,<sup>38</sup> and the long-term commitments of key research institutions. Together, these factors have created different standards of legitimacy for research questions and for answers to those questions.

Among the national traditions whose patterns of research differ distinctly from those of the United States, the example of France is striking.<sup>39</sup> Except in a few practically oriented agronomic institutions, research programs in France were not built on Mendelian concepts and did not rely on standard Mendelian research practices. French biologists were well aware of Mendelian contributions and were not reluctant to exploit new experimental systems. Nonetheless, the dominant research traditions in France undercut acceptance of Mendelism as a major key to understanding heredity. Research traditions that eventually contributed to the development of genetics in France included physiology (from Claude Bernard), causal embryology (linked to Yves Delage and Emmanuel Fauré-Frémiet), and microbiology (begun by Louis Pasteur). These traditions led French biologists to emphasize the importance of understanding the development of the whole organism from a single fertilized egg and the maintenance of harmonious functioning (which Mendelism could not explain) rather than the inheritance of individual traits. They also fostered acceptance of the standards of French positivism, particularly the insistence that theories had to follow behind the step-by-step acquisition of “positive knowledge” of the relevant empirical facts. Consequently, Mendelian genetics barely entered French university curricula until after World War II. At the same time, such French research institutions as the Pasteur Institute fostered long-term commitments to investigations in the dominant research traditions. Against this background, it is not surprising that, when French researchers entered molecular genetics after World War II, they played a leading role in the analysis of gene regulation.

<sup>36</sup> Leslie Clarence Dunn, “The Reminiscences of L. C. Dunn,” typescript from the Columbia University Oral History Project (1960), p. 935, distributed by Microfilming Corp. of America, Glen Rock, N.J., 1975.

<sup>37</sup> Adele E. Clarke and Joan H. Fujimura, eds., *The Right Tools for the Job: At Work in 20th Century Life Sciences* (Princeton, N.J.: Princeton University Press, 1991).

<sup>38</sup> See, for example, Harwood, *Styles of Scientific Thought*.

<sup>39</sup> For French genetics and further references, see Richard M. Burian, Jean Gayon, and Doris Zallen, “The Singular Fate of Genetics in the History of French Biology, 1900–1940,” *Journal of the History of Biology*, 21 (1988), 357–402; Richard M. Burian and Jean Gayon, “The French School of Genetics: From Physiological and Population Genetics to Regulatory Molecular Genetics,” *Annual Review of Genetics*, 33 (1999), 313–49; Sapp, *Beyond the Gene*.

German genetics also yielded a distinctive national tradition, far more oriented to grand synthetic theories, which provided the touchstone for the elaboration of unique research programs. Research programs established by such figures as Erwin Baur, Carl Correns, Richard Goldschmidt, Valentin Haecker, Alfred Kühn, and Fritz von Wettstein led to an intermediate role for Mendelian genetics in comparison with France and the United States. Most of these founders sought to incorporate Mendelian genetics into an overarching theory of the organism and evolution. Thus, those who taught genetics sought – far more strongly than their U.S. colleagues – to integrate it with embryology and developmental processes. Partly because of this, there was considerable interest in determining the contribution of the cytoplasm to heredity and development. As a result, recognition of cytoplasmic inheritance and the role of the cytoplasm in establishing templates for development first emerged from German laboratories.<sup>40</sup> During that same period, geneticists working in some other countries, such as England and the United States, generally frowned on such investigations.

Many factors other than national traditions have contributed to the remarkable diversity of approaches to genetics. These include the influence of research funding, choice of experimental organisms and investigative tools, and focal problems to investigate.

In order for scientific work to proceed, support is required to pay for equipment, facilities, reagents, salaries, and the like. Recently, historians have argued that patrons – who typically bring their own agendas to scientific work – have pushed genetics in specific directions. There have been many different types of patrons. Among them are universities,<sup>41</sup> government agencies (such as the U.S. Department of Agriculture, National Science Foundation, and National Institutes of Health; the Centre National de la Recherche Scientifique in France;<sup>42</sup> and the Medical Research Council in the United Kingdom), government-supported independent agencies (such as the Kaiser Wilhelm and Max Planck Institutes in Germany), professional associations,<sup>43</sup> foundations<sup>44</sup> (e.g., the Rockefeller Foundation and the Wellcome Trust), private research organizations (e.g., the Pasteur Institute and the Cold Spring Harbor Laboratory), consumer groups for the study of human disorders (such as the National Foundation for Infantile Paralysis and the Huntington Disease Foundation),<sup>45</sup> and private companies (such as breweries, seed companies, pharmaceutical companies, and biotechnology firms). The bonds

<sup>40</sup> Harwood, *Styles of Scientific Thought*; Sapp, *Beyond the Gene*.

<sup>41</sup> For the contributions of just one university, see Lily Kay, *The Molecular Vision of Life: Caltech, The Rockefeller Foundation, and the Rise of the New Biology* (New York: Oxford University Press, 1992).

<sup>42</sup> Jean-François Picard, *La République de Savants: La recherche française et le CNRS* (Paris: Flammarion, 1990).

<sup>43</sup> Kimmelman, “The American Breeder’s Association.”

<sup>44</sup> Robert E. Kohler, *Partners in Science: Foundations and Natural Scientists, 1900–1945* (Chicago: University of Chicago Press, 1991).

<sup>45</sup> Doris T. Zallen, *Does It Run in the Family?* (New Brunswick, N.J.: Rutgers University Press, 1997).

between patrons and researchers are strong and have encouraged different approaches to the study of the gene in the recipient research laboratories. In the 1930s and 1940s, the Rockefeller Foundation invested aggressively in research that incorporated the tools of the physical sciences into biology. It provided researchers with powerful investigative tools, promoted the development of a molecular mind-set, and fostered a view of the gene as a discrete molecule whose nature could be determined in isolation from the organism itself. Pharmaceutical and biotechnology patrons tend to treat the gene as a structural unit for producing a protein product.<sup>46</sup> In contrast, much of the support for agricultural research emphasized the genetics of complex features such as milk production, disease and pest resistance, muscle density, and nutritional quality. Many of these traits are quantitative and depend directly on very many (sometimes indeterminately many) genes. Thus, work of this sort favored a view of a gene as just one somewhat indeterminate entity in a complex array.

The type of organism studied also turns out to be crucial.<sup>47</sup> Ever since the rediscovery of Mendel's work, certain organisms have become – and remain to this day – the workhorses of genetic research. The originators of genetics worked mainly with plants. Morgan and his coworkers chose *Drosophila*. Others, such as Leonard Darbishire in the United Kingdom, William Ernest Castle in the United States, and Lucien Cuénot in France, used mammals such as mice.<sup>48</sup> As genetic studies took hold, a variety of other organisms were selected. With each new experimental organism, opportunities arose to pursue some new questions, while others were closed off. Some organisms possessed properties that helped draw genetics in new directions and provided insights that would not have been possible otherwise. To recognize the importance of choice of organisms is to challenge the traditional lock-step linear view of genetic study. For example, certain unicellular organisms with true nuclei, such as the yeast *Saccharomyces cerevisiae* and the green alga *Chlamydomonas reinhardtii*, helped reveal the existence of *non*-nuclear genes – genes residing in the mitochondria and the chloroplast – and the roles such genes play in the functioning of the cell and organism. The maize genetics work of Barbara McClintock (1902–1992) revealed the existence of movable genetic elements and opened up the possibility that the genetic material contains dynamic components active in the regulation of the development of the organism.<sup>49</sup> Studies of bacteria permitted the recognition of

<sup>46</sup> Morange, *History of Molecular Biology*; Arthur Kornberg, *Golden Helix: Inside Biotech Ventures* (Sausalito, Calif.: University Science Books, 1995).

<sup>47</sup> Muriel Lederman and Richard M. Burian, eds., "The Right Organism for the Job," a special section of the *Journal of the History of Biology*, 26, no. 2 (Summer 1993), 235–367.

<sup>48</sup> Some workers, including Bateson, Castle, and Morgan, used many organisms, but most specialized on one organism. The specialized knowledge and practices required to profit from a particular organism generally kept individuals from working with multiple organisms.

<sup>49</sup> See Evelyn Fox Keller, *A Feeling for the Organism: The Life and Work of Barbara McClintock* (San Francisco: W. H. Freeman, 1983); Nathaniel Comfort, *The Tangled Field: Barbara McClintock's Search for the Patterns of Genetic Control* (Cambridge, Mass.: Harvard University Press, 2001).

mechanisms that turn genes off and on, thereby regulating their expression. Butterflies, moths, and snails helped reveal evolutionary effects and the role of the natural environment in enhancing or diminishing gene function as well as the role of the egg cytoplasm, which contains genetic signals from the mother that determine patterns of development but do not correspond with the genetic makeup of the fertilized egg itself.<sup>50</sup>

Thanks to detailed family studies, human geneticists have been able to recognize small variations in phenotype (often connected with a health problem) and to trace the inheritance of those variations in greater detail than was feasible in other organisms. Nonetheless, human genetics developed slowly because human generation times are so long that even “natural experiments” – crosses between individuals with particular traits – are extremely hard to evaluate and because geneticists were practically and morally unable to employ traditional crossing techniques with (or to construct) defined genetic stocks.<sup>51</sup> Thus, until recently, the primary tool of geneticists studying humans was pedigree analysis based on detailed family studies. In some special cases, the availability of extensive pedigree data permitted specific variations in phenotype – often small or health related – to be followed in greater detail than is feasible in other organisms. With the development of tools of biochemical and molecular analysis, DNA could be isolated and studied independently of any requirement for sexual reproduction. Over the last two decades, new technologies have made it possible to trace genetic disorders, previously known only from pedigree studies, to mutations in specific genes. This has been done, for example, for genes leading to sickle-cell anemia, cystic fibrosis, Huntingdon disease, and breast-cancer susceptibility. As a result, humans have been brought from the periphery to the center of research programs. Since 1990, there has been an international, thirteen-year human genome project to map and sequence all human genes;<sup>52</sup> its findings are leading to significant revisions in our understanding of gene action and the interaction of the genetic material with its molecular and larger-scale environments.

Even here, in spite of international cooperation, national differences remain.<sup>53</sup> In the United States, the emphasis has been on the study of individual genes. In the United Kingdom, where historical connections to ecological

<sup>50</sup> For butterflies, see Doris T. Zallen, “From Butterflies to Blood: Human Genetics in the United Kingdom,” in *The Practices of Human Genetics*, ed. Michael Fortun and Everett Mendelsohn (Dordrecht: Kluwer, 1999), pp. 197–216.

<sup>51</sup> Victor A. McKusick, “History of Medical Genetics,” in *Emery-Rimoin Principles and Practices of Medical Genetics*, 3rd ed., ed. D. L. Rimoin, J. M. Connor, and R. E. Pyeritz (Edinburgh: Churchill Livingstone, 1996), pp. 1–30. See also Arno G. Moulsky, “Presidential Address: Human and Medical Genetics, Past, Present and Future,” in *Human Genetics*, ed. R. Vogel and K. Sperling (Berlin: Springer, 1987), pp. 3–13.

<sup>52</sup> Daniel J. Kevles and Leroy Hood, eds., *The Code of Codes: Scientific and Social Issues in the Human Genome Project* (Cambridge, Mass.: Harvard University Press, 1992); Robert M. Cook-Deegan, *The Gene Wars: Science, Politics and the Human Genome* (New York: Norton, 1994).

<sup>53</sup> Krishna Dronamraju, ed., *History and Development of Human Genetics* (London: World Scientific, 1992).

genetics are strong, there has been a greater emphasis on complex diseases such as cancer and on the interaction of genes with environmental factors. In France, cytogenetic and immunological studies have predominated, and in Germany, the horrors of the Nazi period have created barriers to any type of human genetic research.

Historians have recently emphasized the strong influence that instruments and techniques used in the laboratory have had in shifting genetic research in new directions. This is especially clear in the early stages of the development of research tools, when instruments are not commercially available and procedures have not yet stabilized. Many of the pioneers who developed new research tools created the instruments themselves and painstakingly perfected the relevant procedures. Other tools of analysis required training in mathematics, chemistry, or physics and were not readily employed by most geneticists. Thus, local zones of expertise, often tied to particular theoretical perspectives, were created. It often took considerable time before such tools became widely dispersed in the genetics community and an even longer time before the results they yielded could be fully reconciled with preexisting perspectives and the results obtained by other techniques.<sup>54</sup>

The combination of differences in research organisms and research tools precipitated a wide variety of research practices. This is reflected in the appearance of many different subdisciplines within the field. Cytogenetics, for example, was founded by researchers who investigated details of the structure of the genetic material while relying on the microscope and associated staining techniques. For these investigators, the genetic material was divided into regions identifiable by bands of greater and lesser staining. For organisms such as sea urchins and humans, with many small chromosomes, these techniques were not sufficient to distinguish one chromosome from another. In contrast, they worked very well for *Drosophila*, lilies,<sup>55</sup> and maize. Until more precise staining procedures, based on gene biochemistry, emerged in the 1980s, individual genes could not be visualized. Meanwhile, investigators who relied on chemical approaches or used chromatography and radioisotope labels coalesced into communities of biochemical and physiological geneticists. Those who applied mathematical and statistical tools to study the features of groups of organisms formed distinct communities of population and quantitative geneticists. These differed over the number of genes in concrete cases, partly because their calculations had different starting points – gene up for population geneticists and phenotype down for quantitative geneticists. As the subdisciplines proliferated, so did the accounts of the gene. Developmental geneticists count genes in terms of units that affect development, cytogeneticists in terms of regions of chromosomes, physiological geneticists in terms

<sup>54</sup> Clarke and Fujimura, *Right Tools for the Job*.

<sup>55</sup> For example, the cytogeneticist John Belling believed he could see discrete genes on the chromosomes of certain lilies. See John Belling, "The Ultimate Chromomeres in *Lilium* and *Aloe* with Regard to the Numbers of Genes," *University of California Publications in Botany*, 14 (1928), 307–18.

of regulatory units that interact with others and with environmental cues to produce stable function, population geneticists in terms of units in the genome with long-term stability, and so on. In this respect, there are many irretrievably distinct criteria for identifying and individuating genes.<sup>56</sup> These disciplinary differences created barriers that distanced researchers from one another, so that, even within a single country, the genetics community often was not homogeneous.

## CONCLUSION

Standard histories of genetics have often served to provide “myths of discovery.” This role is worrisome to historians because it often results in misportrayals of the positions taken by pioneers in a discipline and the interpretations they put forward of their experiments and theories. There were always tensions in genetics between those who focused on the functions that genes were supposed to play and those who thought of them as material structures, between those who treated genes as units of calculation and those who believed that Mendelian analysis had discovered fundamental units, delimited as firmly as electrons and nuclei were in physics. The various traditions and disciplines surveyed in this chapter show that the notion of a gene was always open, at least to some extent, reflecting the tension between the approaches taken in different disciplines and contexts. Recent work in genetics has cast doubt on the idea that there is a unique resolution, dictated by scientific findings, of the proper delimitation of genes and gene concepts. We believe that it is important to keep alive the rich history of disagreements over the concept of the gene and its proper application – not only to keep alive some of the issues raised by outstanding scientists through the history of genetics but also to remind ourselves of the rich field of alternative interpretations of that history, which is in need of continuing analysis, debate, and (re)interpretation. An appreciation of the struggles over the concept of the gene and the interpretation of patterns of inheritance will yield an appreciation of the multiple strands of work and the victories and defeats that went into the formation of current genetics. It will also remind us forcefully of the open-ended character of our current knowledge of genetics.

<sup>56</sup> See Section 3 of Hans-Jörg Rheinberger, “Experimental Complexity in Biology: Some Epistemological and Historical Remarks,” *Philosophy of Science*, 64 (suppl.) (1997), S279–S291. See also Sahotra Sarkar, ed., *Foundations of Evolutionary Genetics: A Centenary Reappraisal* (Dordrecht: Kluwer, 1996).