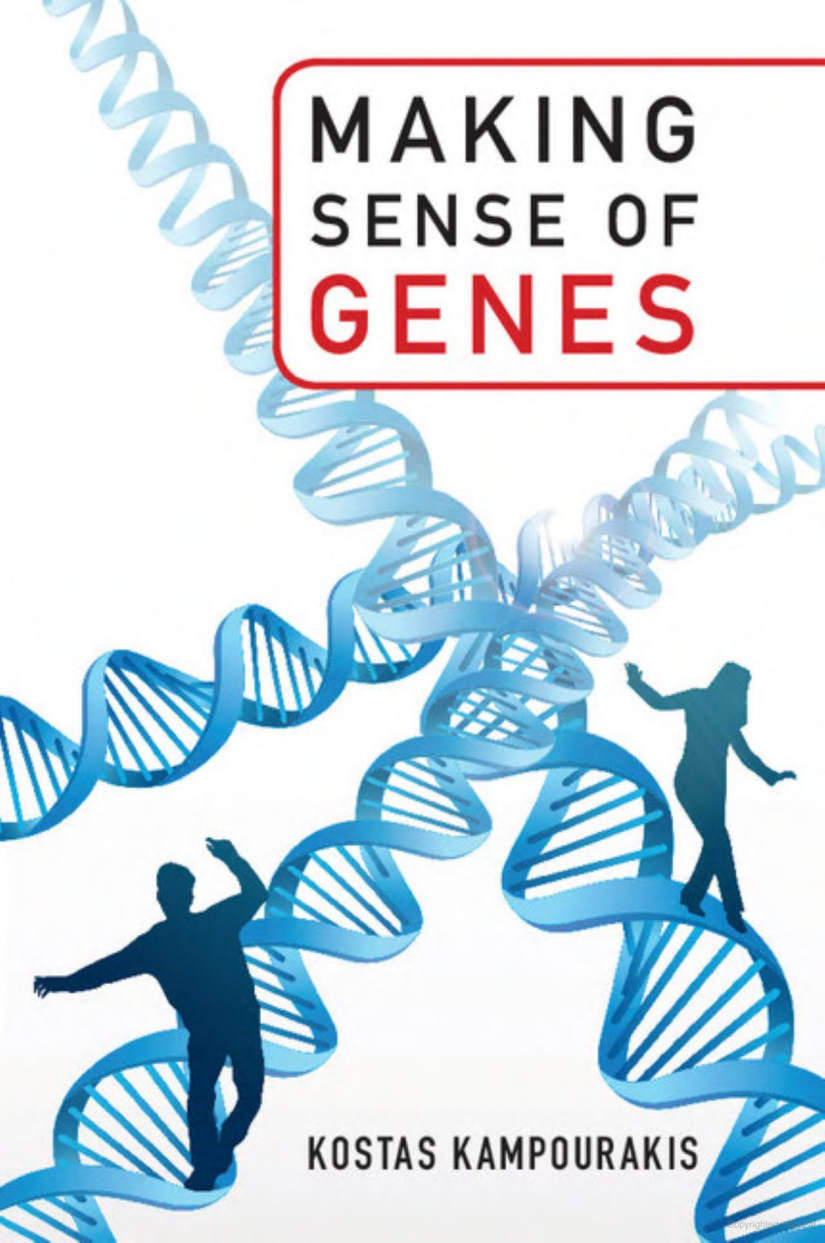
MAKING SENSE OF GENES



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Prolegomena: Genes, Science, and Science Fiction

If one looks at mass media headlines, one will find several accounts of how genes determine various aspects of our lives. Many of these claim to take into account conclusions from recent research in genetics. The general impression is that there exist "genes for" characters,[1] i.e. that single genes cause even complex characters. This view seems to be quite prevalent e.g. it is common to find teachers teaching that genes determine characters, media reports presenting studies that found associations between particular genes and particular diseases, and personal observations of the development of characters that do not seem to be affected by the environment (Moore, 2008). A quick search on the World Wide Web reveals several examples. For instance, a 2014 article in the *Guardian* was titled "Happy gene' may increase chances of romantic relationships."[2] The title of a 2015 article in the *New York Times* suggested that "Infidelity lurks in your genes."[3] A 2014 article in *Time* magazine was titled: "The genes responsible for deadly prostate cancer discovered."[4] And there are more. Several authors have argued that messages like these impose genetic determinist views on the public (e.g. Hubbard & Wald, 1997; Nelkin & Lindee, 2004). This certainly seems plausible, particularly as many people might just read the headlines such as those mentioned previously, without ever reading the full article that might suggest otherwise. Therefore, they might conclude that genes determine who we are.

The problem of making sense of genes, i.e. understanding what genes are and what they do, has concerned me a lot and for a long time. However,

[1] To avoid inconsistencies while referring to features, traits, characteristics, and so on interchangeably, I am using the term "character" throughout this book, which can be defined as any recognizable feature of an organism that can exist in a variety of character states, and at several levels from the molecular to the organismal (based on Arthur, 2004, p. 212). Disease conditions will be considered as character states that deviate from what we tend to consider as "normal."

[2] www.theguardian.com/science/2014/nov/20/happy-gene-romantic-relationship-serotonin-romance

[3] www.nytimes.com/2015/05/24/opinion/sunday/infidelity-lurks-in-your-genes.html?partner=rss&emc=rss

[4] http://time.com/96247/scientists-have-discovered-the-two-genes-responsible-for-aggressive-prostate-cancer/

in my previous book, *Understanding Evolution* (Kampourakis, 2014), I refrained from using the term gene at all. Instead, I referred to genetic material and DNA sequences that are implicated in biological phenomena. Eventually, it was possible to write a whole book without any reference to genes. Yet, ignoring the problem does not contribute anything to its solution, and so I decided to devote my second book to the gene concept that was put aside in my first one. There are two reasons for this. On the one hand, the term exists in the public discourse and so it is better to try to clarify it rather than just ignore it. On the other hand, scientists use the term in their work and in its public presentation. Therefore, I thought that I could make a minor contribution to countering the public distortions of the gene concept and help students in the life sciences, biologists, biology teachers, health professionals, and anyone else interested in acquiring a better understanding of it, as well as provide them with conceptual tools to explain genes to nonexperts.

Generally speaking, our knowledge takes the form of concepts that are mental representations of the world. Concepts should be distinguished from conceptions, the latter being the different meanings of, or meanings associated with, particular concepts. This means that whereas we may generally agree on a general definition of a certain concept, e.g. "dog," people all over the world may hold different conceptions of what a dog is or looks like. In other words, even if a concept is well defined and even if it is clear to people to what this concept refers, individual conceptions may vary a lot if one takes the time to consider them. This is also the case for scientific concepts, such as the gene. Scientific concepts are systematic mental representations of the world through which explanations of and predictions about phenomena are possible (Nersessian, 2008, p. 186). In this case, the difference between concepts and conceptions becomes more striking; whereas scientists may agree on the definition of a certain concept, nonexperts may hold very different conceptions of it for various reasons. Such reasons may include the public distortions of the concept under discussion, or that people simply failed to understand it because of their own preconceptions. In the present book I focus on the gene concept that most people have heard of, but many fail to understand. My aim is to explain this concept and address certain prevalent but inaccurate conceptions. At the end of this book, the reader should have acquired a better understanding of what a gene is and is not, as well as what a gene can and cannot do.

but historical. By presenting how the gene concept was coined and has evolved over the past 100 years or so, during which time research on heredity has been conducted, I show that different gene concepts have dominated discourse on heredity over different periods and that, recently, more than one have co-existed.

The next question that arises is this: What is it that genes do? If you open a newspaper or a popular magazine it is very likely that you will read a report about a recent discovery of a "gene for" something. Genes have been reported to determine characters of all kinds, such as eye color and height. They have also been reported to determine well-studied diseases, such as thalassemia and phenylketonuria, but also more complex and less-well understood ones such as coronary heart disease and cancer. Most interestingly, genes are often reported in the popular press to determine all kinds of behaviors and psychological states. Thus, "genes for" depression, schizophrenia, intelligence, alcoholism, criminality, promiscuity, homosexuality, and more have been reported to exist. As a result, genes are perceived as determining everything. This is particularly evident in characters that run in families, which are, often without a second thought, attributed to genes inherited from parents to offspring, and not to other possible factors such as their shared environment.

I speculate that if there was a report that George H. W. Bush (1924–) and his son George W. Bush (1946–) were both elected presidents of the United States because of a particular gene they both had, perhaps a "gene for" US presidency, many people would not question such a conclusion. Similarly, many people might find reasonable that there exists a "gene for" becoming a Hollywood star in the case of Kirk Douglas (1916–) and his son Michael (1944–), or in the case of Judy Garland (1922–1969) and her daughter Liza Minelli (1946–). These same people might attribute to a "gene for" the Nobel Prize the fact that both Arthur Kornberg (1918–2007) and his son Roger (1947–) were awarded a Nobel Prize – but perhaps different versions of that gene could account for the fact that Arthur's prize was in physiology and medicine, whereas Roger's was in chemistry. These examples might sound exaggerated, but as I show later in this book, claims like these are quite common in the public sphere. For many people, the interesting question is not whether genes determine characters and behaviors; the common assumption is that they do. The interesting question is how they do it.

The metaphors currently used about genes present them as autonomous entities, which both contain all the necessary information to determine characters and are capable of making use of it. Therefore, both in research and in popular parlance, genes have been described as the "essences" of life, as the absolute "determinants" of characters and disease and therefore as providing the ultimate explanations for all biological phenomena because the latter can be "reduced" to the gene level and thus be explained. These views have been described as *genetic essentialism*, *genetic determinism*, and *genetic reductionism*, respectively. They are all related to one another, and they may even seem to overlap. However, they are distinct and should not be confused. In order to avoid confusion and overlaps in definitions, in this book I use the following definitions (based on Beckwith, 2002; Kitcher, 2003; Wilkins, 2013):

- *Genetic essentialism:* genes are fixed entities, which are transferred unchanged across generations and which are the essence of what we are by specifying characters from which their existence can be inferred.
- *Genetic determinism:* genes invariably determine characters, so that the outcomes are just a little, or not at all, affected by changes in the environment or by the different environments in which individuals live.
- *Genetic reductionism:* genes provide the ultimate explanation for characters, and so the best approach to explain these is by studying phenomena at the level of genes.

Most importantly, these are the onerous conceptions that the present book aims at addressing.

Whether or not these conceptions are distinct apparently depends on how one defines them. I use these definitions in order to distinguish between three important properties usually attributed to genes: (1) that they are fixed essences; (2) that they alone determine characters notwithstanding the environment; and (3) that they best explain the presence of characters. The power attributed to genes has often gone beyond the realm of science to reach that of science fiction. Genes have been described as autonomous, self-replicating entities capable of doing everything and of determining everything. There are "fat" genes, "smart" genes, "cancer" genes, "infidelity" genes, "aggression" genes, "happiness" genes, "God" genes, and more (a World Wide Web search of these terms is illuminating;

in some cases, even books with titles like these exist). The underlying assumption in most cases is that much of what we are or do is driven (if not dictated) by our genes. Perhaps we find attributing whatever happens to one's genes very intuitive, because it makes sense immediately? It is the supernatural powers attributed to genes that this book aims at addressing. Of course, I am not going to argue that genes are not important – they are! But it is one thing to say that genes are important for what we are or do, and another that they are the ultimate determinants of these. I hope that, at the end this book, I will have succeeded at clarifying what genes are and are not, as well as what they can and cannot do.

Chapters 1–4 provide a brief account of how the initially "empty," or, to be more precise, referentially indefinite (i.e. that did not refer to a particular entity), gene concept came to have two distinct meanings during the twentieth century: that of a hypothetical inherited factor, the changes in which were somehow related to changes in characters, and that of a DNA sequence that encoded the information for a protein. Whereas it may have initially seemed self-evident that these two gene concepts might overlap and that they would converge to the same segments of DNA, by the 1970s it became quite evident that this is not the case. More recent research has shown that it is impossible to structurally individuate genes, and that the best we can do is to identify them on the basis of their functional products. I must note that in these chapters I do not intend to provide a detailed and complete history of the "gene" concept (for such histories see Beurton et al., 2000; Falk 2009; Rheinberger et al., 2015; Rheinberger & Müller-Wille, in press). Rather, these chapters aim at providing an idea of the complexities of precisely defining what a gene is.

Then, in Chapters 5–8, I describe the presentations of genes in the media and on the websites of companies selling genetic tests. I show that the underlying message in many cases is that there are genes that determine characters and disease. I also present research on the conceptions that students and the public hold about genes and the difficulties they face in understanding what genes are and do. Then, I show that simple, causal connections between genes and characters or genes and disease are not adequate to accurately represent the actual phenomena. Research in genetics shows that these are actually very complicated. In many cases, single genes cannot explain the variation observed not only for complex characters and disease but also for simple monogenic ones. On the basis of these, I conclude by explaining that genes do not actually

do anything on their own. I also explain why the notion of "genes for," in the vernacular sense, is not only misleading but also entirely inaccurate and scientifically illegitimate.

Finally, in Chapters 9–12, I come to some major conclusions from the research presented in the previous chapters. First, I show that genes "operate" in the context of developmental processes only. This means that genes are implicated in the development of characters but do not determine them. Second, I explain why single genes do not alone produce characters or disease but contribute to their variation. This means that genes can account for variation in characters but cannot alone explain their origin. Third, I show that genes are not the masters of the game but are subject to complex regulatory processes. There seem to exist many regulatory sequences in what until recently has been called "junk" DNA. As a result, the genome of an organism is more than the sum of its genes. Finally, I discuss in some detail the limitations of genetic testing that are not often taken into account in public discourse, in order to show what is and what is not currently possible to achieve from DNA analyses, and to debunk the myth of their infallibility. I also show how misleading information about genes can be when it comes to probabilistic thinking.

The chapters of this book could be read independently from one another; however, in many cases individual chapters build on knowledge and understanding of concepts that have been presented in previous ones. Therefore, I recommend that you read this book from beginning to end, without skipping any chapters – unless you are very well familiar with the respective topics. However, for those readers who decide not to do so, the book includes a glossary with the definitions of the most important concepts. Next to that, there is also a guide to further reading that includes relevant books that treat in more detail many of the topics presented in this book. In most cases, I have read and cited the original research articles. However, in several cases I found the accounts given in certain books useful or the ideas illuminating, and so I am citing these. Many of the topics I present are discussed in several books, but I am only citing them wherever it is really useful. The *Further Reading* section provides information about the books one should read after reading the present one.

A central feature of the present book is that it is mostly about human characters and disease. When this is not the case, it is usually about phenomena of relevance to human life. I must note that this is not due to any anthropocentricism on my part. Quite the contrary, I believe that we are not anything special in this world, or at least that we are not any

more special than any other organism that lives in it. Nevertheless, I thought that the book would be more interesting to readers if I discussed phenomena about, or relevant to, human life. I made the decision to focus on human genes because my experience as a teacher and an educator was that students' interest was aroused whenever a topic about human life or health came up. Pragmatically thinking, making sense of genes also has an important medical interest; therefore, I wanted this book to be useful not only for biologists but also for physicians and other health professionals. This approach is biased, of course, because it overlooks important aspects of life on Earth. But it is also more interesting for humans. I do hope that readers will appreciate both this decision and the outcome. I hope that they will find this biased-toward-humans book interesting and didactic. But they should also keep its bias in mind and avoid unwarranted generalizations from the mostly medical-centered and human-focused research presented in this book.

I must also note that the term "genetics" is used throughout the book in a very broad sense to refer to any research about genes. Therefore, the term "genetics" encompasses research in classical genetics of the first half of the twentieth century, molecular biology and genetics of the latter half of the twentieth century, and genomics of the past twenty-five years or so, despite the important differences among these research approaches. Conceptually, "genetics" could be perceived to refer to genes only, whereas "genomics" could be perceived to refer to the genome as a whole, including genes and everything else in DNA. Therefore, "genomics" could be considered as a broader term than "genetics," as the genome is a broader concept than the gene (see Annas & Elias, 2015, p. 3). Nevertheless, as genes have been the main focus of research so far, it is conceptually sound and certainly simple for the purpose of the present book to use the term "genetics" to refer to all research about, or relevant to, genes – no matter how these are defined – also encompassing genomics research.

The present book is intended primarily for non-experts, i.e. people not working on genetics, who want an introduction to genes. The intended audience includes undergraduate students in biology, medicine, and pharmacy, as well as biology teachers and educators. The book provides an overview of the core concepts and issues in genetics, and it can also serve as an introduction to more detailed and advanced forays in the literature. Physicians and other healthcare professionals who are interested in getting a concise overview of contemporary genetics research and

FIGURE 1.1 Gregor Mendel (© Time Life Pictures).

2011, p. 86). Note the common assumption in all textbooks: Mendel was doing genetics. In several cases, Mendel is described as the person who discovered that heredity is particulate in nature, and that the factors controlling it are those we now call genes.

The same story is also found on the World Wide Web. For instance, the Wikipedia entry about Mendel goes like this:[1] "He [Mendel] published his work in 1866, demonstrating the actions of invisible 'factors' – now called genes – in providing for visible traits in predictable ways. The profound significance of Mendel's work was not recognized until the turn of the 20th century." The relevant entry in *Encyclopedia Britannica* provides the following account of Mendel's life and work: "From the precise mathematical 3:1 ratio ... he deduced not only the existence of discrete hereditary units (genes) but also that the units were present in pairs in the pea plant and that the pairs separated during gamete formation" (Winchester, 2013). A similar account is given in the education website of the prestigious scientific journal *Nature*: "Mendel's insight

[1] http://en.wikipedia.org/wiki/GregorMendel.

greatly expanded the understanding of genetic inheritance … Mendel … hypothesized that each parent contributes some particulate matter to the offspring. He called this heritable substance 'elementen' … Indeed, for each of the traits he examined, Mendel focused on how the elementen that determined that trait was distributed among progeny" (Miko, 2008).

Mendel, the story continues, discovered that characters are controlled by hereditary factors, the inheritance of which follows two laws: the law of segregation and the law of independent assortment. In the first case, when two plants that differ in one character, e.g. plants having seeds that are either round or wrinkled, are crossed, their offspring (generation 1) resemble one of the two parents (in this case they have round seeds). In generation 2 (the offspring of the offspring) there is a constant ratio 3:1 between the round and the wrinkled character (Figure 1.2). Round shape is controlled by factor *R* that is dominant, whereas wrinkled shape is controlled by factor *r* that is recessive. Dominant and recessive practically means that when *R* and *r* are together, it is *R* that dominates over *r* and so the respective "*R*" phenotype is produced as if *r* was not even there. This means that plants with factors *RR* or *Rr* will have round seeds, whereas plants with *rr* will have wrinkled seeds. The explanation of these results is that the factors (*R*/*r*) controlling the different characters (round/wrinkled) are separated (segregated) during fertilization and recombined in the offspring. This is described as Mendel's law of segregation.

When Mendel simultaneously studied the inheritance of two characters, e.g. both the shape of the seed and its color, he observed a similar but more complicated picture. When he crossed plants with yellow/round seeds and plants with green/wrinkled seeds, in generation 1, all offspring had yellow/round seeds. However, when those plants were crossed with each other, a constant ratio of 9 yellow/round: 3 yellow/wrinkled: 3 green/round: 1 green/wrinkled emerged in generation 2. This is actually the result of the combination of the probabilities to have all possible combinations of two characters, e.g. the one described earlier and a similar one regarding color.[2] Plants with factors *YY* or *Yy* have yellow seeds, whereas plants with *yy* have green seeds. The results

[2] This means that the ratio 9:3:3:1 for two characters results from the combination of the 3:1 ratio for each character (¾ x ¾ = 9/16; ¾ x ¼ = 3/16; ¼ x ¼ = 1/16).

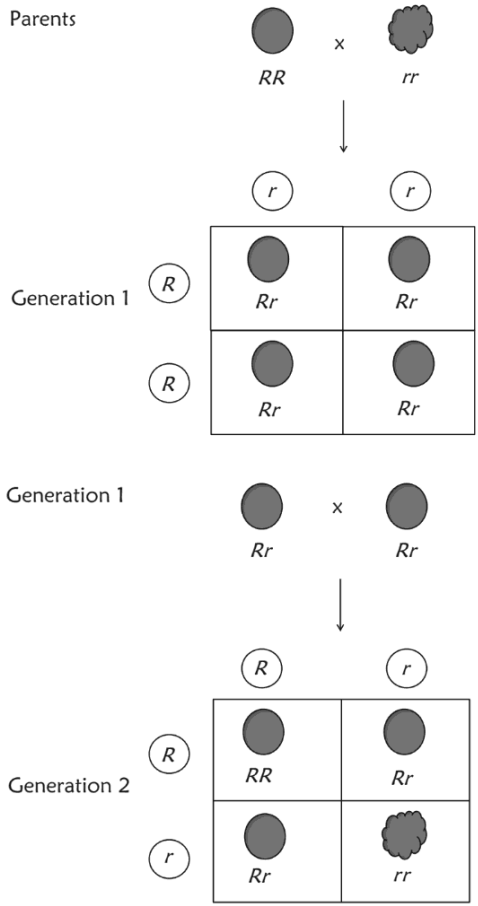

FIGURE 1.2 A cross between two plants that differ in the shape of seeds (round or wrinkled). Plants with round seeds have factors *RR* or *Rr*, whereas plants with wrinkled seeds have factors *rr*. The "wrinkled" character "disappears" in generation 1 and "reappears" in generation 2 (green peas appear here as having a darker color than yellow peas; note also that all possible combinations of gametes are made).

suggested that the factors (*R*/*r* and *Y*/*y*) controlling the different characters (seed shape and seed color, respectively) were assorted independently during fertilization. As a result, all possible combinations were obtained (yellow/round, yellow/wrinkled, green/round, green/wrinkled), and this is why these are observed in generation 2 (see Figure 1.3). This is described as Mendel's law of independent assortment.

The account that presents Mendel as the founding father of genetics, who understood that inheritance was particulate in nature, who

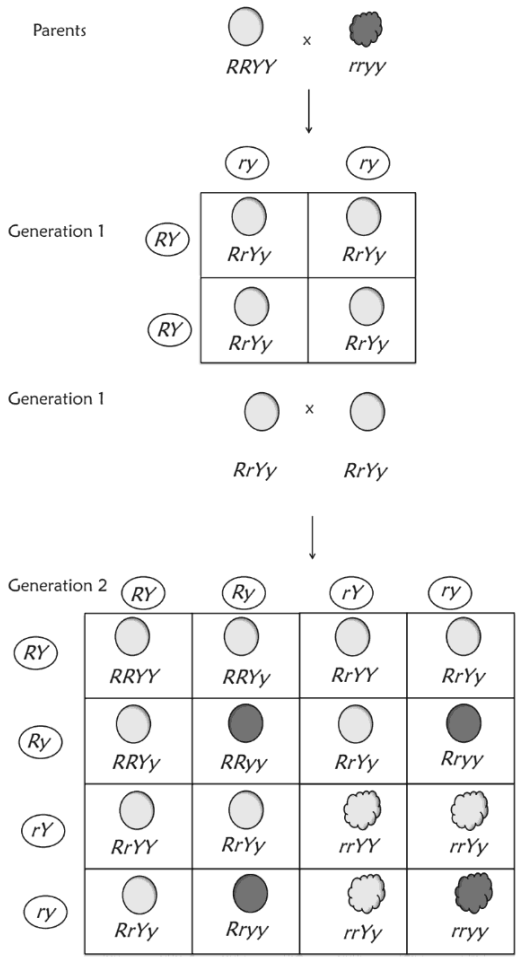

FIGURE 1.3 A cross between two plants that differ in the shape of seeds (round/wrinkled) and the color of seeds (yellow/green). In the second generation we find the characteristic ratio 9:3:3:1 (green peas appear here as having a darker color than yellow peas; note also that all possible combinations of gametes are made).

discovered the laws of heredity, who was ignored by his contemporaries, and whose reputation was established posthumously, in 1900, with the rediscovery of his pioneering paper, is quite prevalent, although it has been critically questioned since at least 1979 (Brannigan, 1979; Olby, 1979). If one looks closer into the historical details, it becomes clear that Mendel intended to study hybridization in particular and not heredity in general, whereas his 1866 paper,

FIGURE 1.4 The stereotypical image of Mendel, working alone in his garden (© Bettmann).

titled "Versuche über Pflanzen-Hybriden" [Experiments on Plant Hybrids], does not clearly indicate that he was thinking in terms of hereditary particles. Furthermore, the laws of segregation and of independent assortment, which are attributed to him, certainly do not appear in his paper in the way biology textbooks currently describe them. In fact, many of the accounts presented in textbooks are distortions of history. In order to understand Mendel's work and contribution, we should consider it in its actual historical context. Paying attention to the details of history is important because stories about "fathers" of disciplines, such as Mendel, give the false impression that a discipline may emerge from nothing and develop independently of the surrounding context. This is most exemplarily portrayed by the usual illustration of Mendel working alone in his garden (Figure 1.4).

However, it seems that stories like these have an appeal. A recent book that is intended to provide a historical account of the development of the gene concept and that became a best seller as soon as it

that Mendel began his hybridization experiments in 1856. He selected thirty-four distinct varieties of the edible pea (*Pisum sativum*) for his experiments, and subjected them to a two-year trial for purity, in order to obtain varieties that when self-reproduced always produced plants with the same characters. Then he performed crosses between different varieties, focusing on seven characters: the shape of the seed (round or wrinkled); the color of the seed (yellow or green); the color of the seed coat (white or gray-brown); the shape of the ripe pod (smoothly arched or deeply ridged between seeds); the color of the unripe pod (green or yellow); the position of flowers (axillary or terminal); and the length of the stem (1.9–2.2m or 0.24–0.46m) (Orel, 1984, p. 44). Mendel concluded his experiments with *Pisum* in 1863 (see Orel, 1984; Olby, 1985; Allen, 2003; Gliboff, 2013, for more details on Mendel's work).[5]

Mendel's results were presented in the meetings of the Brno Natural Science Society on February 8 and March 8, 1865, and were published in the society's journal in 1866. In the beginning of his paper Mendel expressed his aim to "to follow the development of hybrids in their descendants". He also noted that, until that time "a universally valid law describing the formation and development of hybrids has not yet been established".[6] It is important to note that Mendel was interested in studying the transmission of characters over generations bred from hybrids, and to better understand how this happened. In his paper Mendel described the transmission of characters rather than that of hereditary particles like genes. In particular, Mendel observed that the hybrids obtained from the various crosses between different varieties were not always intermediate between the parental forms. In contrast, some hybrids exhibited certain characters exactly as they appeared in the parental plants. Mendel called dominant the parental characters that appeared in the hybrids, and recessive the parental characters that did not appear in the hybrids but that reappeared fully formed in the next generation. Thus, Mendel studied and wrote about characters and not about hereditary particles, and so did not discover that heredity was particulate in nature. More generally, he studied hybridization and not

[5] Mendel studied intraspecific hybrids, i.e. hybrids stemming from crosses between varieties of the same species, not between different species.

[6] All quotations from Mendel's paper are from a new translation by Kersten Hall and Staffan Müller-Wille, titled "Experiments on Plant Hybrids" and available at http://centimedia.org/bshs-translations/mendel/. I am very grateful to both of them for granting me access to it before its publication.

heredity, and it should therefore be no surprise that the term "heredity" does not appear in his paper.[7] A careful study of his paper also shows that, strictly speaking, Mendel did not discover the two laws commonly attributed to him; rather, he observed their consequences under the particular experimental conditions. Statements that look like the laws of segregation and independent assortment can be found in his paper, but they are not explicitly described as such; they are also quite different from the way they are currently described in textbooks and elsewhere (see Kampourakis, 2015, for a more detailed account).[8]

The term "heredity" in the modern, biological sense, i.e. with reference to the transmission of some substance across generations, does not appear in writings on the generation of organisms until the mid-eighteenth century. The systematic use of this term was initially done in medical contexts around 1800 by French physicians, and was soon introduced to other European languages (López Beltrán, 2004, 2007; Cobb, 2006). The term "heredity" derives from the Latin *hereditas*, which means inheritance of succession. The biological concept of heredity resulted from the metaphorical use of a juridical concept, which referred to the distribution of status, property, and other goods, according to a system of rules about how these should be passed on to other people once the proprietor passed away (Müller-Wille & Rheinberger, 2012, pp. 5–6). In other words, heredity, in the modern biological sense, is a rather "recent" concept. However, it is in this sense that this term is mostly used today, whereas the term "inheritance" is used both in biological and nonbiological contexts. Therefore, in the present book, "genetic inheritance" will refer to the process of transmission of genetic material across generations, whereas "heredity" will refer to the broader phenomenon of which this process is part. In this sense, "heredity" is considered as an exclusively biological concept, whereas "inheritance" is not.

The earliest references to heredity can be found in Herbert Spencer's (1820–1903) *Principles of Biology* (1864), just a year before Mendel's paper was presented. At that time, the mechanism of heredity was

[7] Even though the noun *heredity* (*Vererbung*) does not exist in Mendel's paper, the verb *inherit* (*vererben*) does. Mendel also used quite frequently verbs that could be translated as "transmit" (übergehen … auf; übertragen) and are also used in the context of inheritance (Müller-Wille, personal communication).

[8] Interestingly, Jonathan Marks (2008) has argued that Mendel's two laws were invented in the form that they are widely known by Thomas Hunt Morgan (1866–1945) in 1916.

at the center of biological thought, in part because Charles Darwin's (1809–1882) theory of descent with modification through natural selection (published in 1859 in the *Origin of Species*) lacked a complementary theory that could explain the origin and inheritance of new variations that were so central to it.[9] Darwin wrote: "The laws governing inheritance are quite unknown; no one can say why the same peculiarity in different individuals of the same species, and in individuals of different species, is sometimes inherited and sometimes not so" (Darwin, 1859, p. 13). In response to this problem, Darwin proposed in 1868 his *Provisional Hypothesis of Pangenesis*, a term that he attributed to Hippocrates (460 BCE–370 BCE), which literally means "origin from everywhere" (*pan*: all; *genesis*: origin). According to this hypothesis, all parts of the body participated in the formation of the offspring by producing microscopic entities, the gemmules, which somehow carried the organismal properties from generation to generation. Herbert Spencer had also proposed in 1864 a theory of heredity based on minute hereditary determinants, as did Ernst Haeckel (1834–1919) in 1876. Both Spencer and Haeckel accepted that the inheritance of acquired characters was possible, and this idea was also central in Darwin's *Pangenesis* (Kampourakis, 2013; Allen, 2014).

In 1871, Francis Galton (1822–1911) tried to test experimentally the hypothesis of *Pangenesis* and practically disconfirmed it (Galton, 1871a).[10] In 1876, he proposed his own theory of heredity, suggesting that hereditary factors did not arise from the various body tissues. He also proposed the term "stirp" that accounted for the total of the hereditary elements or germs at the fertilized ovum, thus postulating a form of a germline theory, i.e. that reproductive cells existed separately from body (somatic) cells. Galton also suggested that evolutionary change might take place in a discontinuous manner and not gradually. William Keith Brooks (1848–1908) took this idea further in 1883 to suggest that evolution proceeded with extensive modifications, and not gradually as Darwin had suggested. Carl von Nägeli (1817–1891) proposed a theory that combined older views (spontaneous generation) and modern views

[9] It should be noted that in the nineteenth century heredity was strongly associated with variation and was largely discussed as hereditary variation (see Müller-Wille & Rheinberger, 2012, chapter 5).

[10] There is an interesting exchange on this topic between Darwin and Galton in *Nature* (see Darwin, 1871; Galton, 1871b).

(the existence of hereditary factors). Hugo de Vries (1848–1935) retained some of Darwin's ideas, and by combining breeding experiments with Galton's statistical methods he suggested in 1889 a modified theory of pangenesis. In the meantime, during the 1880s, vital dyes and improved microscopes made possible the visualization of cellular structures and processes. In this way it was also shown that reproductive cells existed independently of the rest of the body tissues. August Weismann (1834–1914) drew on these new findings to propose the shift from "pangenesis" to "blastogenesis": the idea that characters were inherited only from the germline and not from the whole body.[11] This led to the abandonment of some of Darwin's ideas, including the inheritance of acquired characters that Weismann strongly rejected (Kampourakis, 2013). Some central features of these theories are presented in Table 1.1, and the respective scholars are presented in Figure 1.5.

All these people were aware of one another's work and practically formed a scientific community, actively and interactively working to develop a theory of heredity. Mendel is nowhere in this picture. Only Nägeli came to know of Mendel's experimental work, through their correspondence from 1866 until 1873. Following Nägeli's advice, Mendel worked on *Hieracium* (hawkweed, a genus of the sunflower family) from 1866 to 1871, which gave different results from those of *Pisum*. Nägeli did not seem to pay much attention to Mendel's work, yet on at least one occasion he cited Mendel's 1866 paper. Most importantly, the Brno Natural Science Society sent more than 100 copies of the journal that included Mendel's paper to scientific centers around the world. At least ten references to Mendel's paper appeared in the scientific literature before 1900, some of them in books that were widely read by naturalists. Therefore, it was possible for Mendel's work to become more widely known during his lifetime. Why did it not? Probably because it was not an explicit attempt to develop a theory of heredity that was of interest to naturalists at that time (Olby, 1985; Kampourakis, 2013). Mendel was rather interested in understanding hybridization and its

[11] See Weismann (1893/1892, p. xiii). Weismann's account of inheritance also gave rise to neo-Darwinism in the original sense of the term. Neo-Darwinians were "neo" because they explained adaptation exclusively on the basis of the elimination of unfit and preservation of fit variants in germline factors by natural selection, and not like Darwin himself who relied on use and disuse as an explanation of some adaptations and assumed that acquired characters could be passed on to descendants (Depew & Weber, 1995, pp. 187–191).

TABLE 1.1 *Theories of Heredity of the Latter Half of the Nineteenth Century*

Author (Publication Year)	Hereditary Factors	Mechanism for Variation	Acquired Characters Inherited
Herbert Spencer (1864)	Physiological units contained in cells	Physiological units were remolded	Yes
Charles Darwin (1868)	Gemmules thrown off from every unit of the body	Deficient amount of gemmules or modification of gemmules	Yes
Ernst Haeckel (1876)	Plastidules with a frequency and amplitude of vibration	The frequency and amplitude of the vibration of plastidules could change due to the influence of external conditions	Yes
Francis Galton (1876 & 1889)	Stirp (sum total of developed and latent germs) existing in the body	Germs were not identical and might be modified if remained latent for long	No
William Keith Brooks (1883)	Gemmules present in all cells	Gemmules, thrown off by affected cells, transmitted the change to the ovum	No
Carl von Nägeli (1884)	Determinants contained in the idioplasm	Internal perfecting forces, external stimuli causing changes to the idioplasm, and sexual reproduction could give rise to intermediate characteristics	No
Hugo de Vries (1889)	Pangens existing in cell nucleus into two groups (active and inactive)	Pangens of the same kind but of different origin might be activated or pangens might be slightly dissimilar to the original ones after cell division	No
August Weismann (1880s & 1892)	Biophors existing in the cell nucleus and forming units of higher order (determinants, ids, idants)	Modification of certain germ-plasm determinants and differential combination of parental ids during fertilization	No

Source: Based on Kampourakis (2013), except for Haeckel's theory that is described in Allen (2014).

long aware of Mendel's work, insisted on Mendel's priority over both de Vries and himself, perhaps in an attempt to resolve a potential priority dispute. However, it seems that de Vries did not intend to overlook Mendel's work in order to claim priority. Rather, it seems that he did not really think that Mendel's work was that important (see Brannigan, 1981, pp. 90–96; Olby, 1985, pp. 109–133). Nevertheless, this simultaneous "rediscovery" brought Mendel back to the scene. Read in a new context, his paper was considered as bringing together the findings of breeding experiments and cytology, showing that particulate determinants existing in the nucleus of the cell were segregated and independently assorted. But this happened in 1900. Mendel was an outsider to the community that developed theories of heredity based on invisible hereditary factors during the latter half of the nineteenth century (summarized in Table 1.1 and presented in Figure 1.5) from which the discipline of genetics actually emerged.

Two important points should be emphasized here. The first point is that the usual presentation of Mendel as a heroic, lonely pioneer of genetics distorts the actual history of genetics and also conveys an inauthentic image of how science is actually done. The portrayal of a whole discipline emerging from the work of an isolated individual is one of the most widespread myths about science (Olesko, 2015), which masks the fact that science is a human activity, done within scientific communities, in particular, social, cultural, religious, and political contexts. The second point is that scientific questions usually arise out of economic or technological ones, rather than from human curiosity alone. Mendel carried out his experiments in the context of a series of practical questions related to agriculture. This is why he was studying hybridization and why he was not trying to develop a theory of heredity. Contrary to what many textbooks still claim, Mendel contributed virtually nothing to the development of a theory of heredity during the latter half of the nineteenth century. This does not undermine the importance of Mendel's experimental approach for genetics. But one should clearly distinguish between the impact of Mendel's experiments in the context in which he conducted them in the 1850s–1860s, and their impact in the new context in which they were reconsidered and reinterpreted in the 1900s.

2 The Genes of Classical Genetics

After 1900, the work of Mendel guided the development of the new science of "genetics," a term coined by William Bateson (1861–1926) (Figure 2.1a). Bateson first mentioned the term "genetics" in a 1905 letter to a friend, noting that for "a professorship relating to Heredity and Variation … No single word in common use quite gives this meaning. Such a word is badly wanted and if it were desirable to coin one, 'Genetics' might do" (quoted in Dunn, 1991/1965, p. 69). The term appeared in print the next year, in a book review that Bateson wrote. He also proposed the term in 1906, during his inaugural address to the Third Conference on Hybridization and Plant Breeding of the Royal Horticultural Society. The term was adopted for the published proceedings the next year, describing the event as the Third International Conference on Genetics (Dunn, 1991/1965, pp. 68–69; Olby, 2000). So the stage for the new science was set.

Bateson's book *Mendel's Principles of Heredity: A Defence* contains the first English translation of Mendel's paper (Bateson, 1902, pp. 40–95). In this book, Bateson presented Mendel's work as providing the solutions for various problems relevant to heredity. He also introduced new terms such as "allelomorph," "heterozygote," and "homozygote." Allelomorph referred to the different versions of the same character and to the respective factors. In 1927, George Shull (1874–1954) introduced the shorter term, "allele" (Shull, 1935), which became the common term that refers to the alternative versions of the same gene. Currently, humans and other organisms are considered to carry pairs of alleles; an individual carrying the same allele twice is described as a homozygote, whereas another carrying two different alleles is described as a heterozygote. In that book Bateson also provided his own explanation for the neglect of Mendel's work: "It may seem surprising that a work of such importance should so long have failed to find recognition and to become current in the world of science. It is true that the journal in which it appeared is scarce, but this circumstance has seldom long delayed general recognition. The cause is unquestionably to be found in that neglect of the experimental study of the problem of Species which supervened on the general acceptance of the Darwinian doctrines" (p. 37).

FIGURE 2.1 (a) William Bateson, who coined the term "genetics" (© Universal Images Group); (b) Wilhelm Johannsen, who coined the term "gene" (© Paul Popper/ Popperfoto).

Bateson had been influenced by Galton and Brooks, and considered discontinuous variation as having enormous importance, certainly being more important than continuous variation that Darwin favored. For this reason, he was in debate with the biometricians Karl Pearson (1857–1936) and Raphael Weldon (1860–1906) who considered themselves as Galton's followers. Bateson criticized them in his 1902 book for resisting the importance of Mendel's work in understanding heredity. In the heart of the debate was the relative importance of continuous and discontinuous variation for evolution (see Gillham, 2001, pp. 303–323). But in the same year, Weldon showed that Mendel's "laws" might not actually work even for peas. Weldon's studies of varieties of pea hybrids led him to conclude that there was a continuum of colors from greenish yellow to yellowish green, as well as a continuum of shapes from smooth to wrinkled. It thus appeared that in obtaining purebred plants for his experiments, Mendel had actually eliminated all natural variations in peas, and that characters were not as discontinuous as he had assumed (Weldon, 1902; Jamieson & Radick, 2013). So, less than two years after the rediscovery of Mendel's work, it was questionable how generalizable his conclusions were.

William Castle (1867–1962) also reported several exceptions to Mendel's ratios in 1903. Between 1904 and 1908, Bateson and his colleagues also reported deviations from these ratios and realized that these were not universal. According to the reinterpretation of Mendel's paper, when two heterozygotes for two characters were crossed (AaBb x AaBb), the phenotypic ratio in the offspring would be 9:3:3:1. In particular, 9 out of 16 offspring would exhibit the two dominant characters, 3 out of 16 one dominant and one recessive character, 3 out of 16 the other dominant and the other recessive characters, and 1 out of 16 would bear the two recessive characters (Bateson, 1902, p. 11; see also Figure 1.3). But Bateson and his colleagues soon observed other ratios, such as 15:1 and 9:7. These were explained as the result of epistasis; some characters were produced from the contribution of two distinct factors of which one affected the other (Carlson, 2004, pp. 122–124). These new epistatic phenomena did not lead to a reconsideration of mendelism, but rather to its modification in order to accommodate the new findings. Mendel's work looked too good to be abandoned.

One reason for this was that Mendel's work helped new observations make sense, as well as produce new observations in the first place. Perhaps the most interesting immediate implication was the understanding of the role of chromosomes in heredity. In 1903, Walter Sutton (1877–1916) provided cytological evidence that explained Mendel's ratios, based on the understanding of meiosis of that time. Sutton was concerned about recent observations indicating that the maternal and the paternal chromosomes remained independent. This implied that reproductive cells should contain either the maternal or the paternal chromosomes. Sutton performed a careful study of the process of cell division and concluded that a large number of different combinations of maternal and paternal chromosomes were possible in the mature reproductive cells of an individual. After a detailed analysis, Sutton concluded: "the phenomena of germ-cell division and of heredity are seen to have the same essential features, viz., purity of units (chromosomes, characters) and the independent transmission of the same" (Sutton, 1903, p. 237). Despite a critical flaw (Hegreness & Meselson, 2007), Sutton's insight brought cytology and genetics even closer together, putting the foundations for explaining the physical basis of Mendel's ratios and for understanding the chromosomal nature of heredity.

In 1909, Wilhelm Johannsen (1857–1927) (Figure 2.1b) proposed the term "gene" to refer to the hereditary factors. Etymologically, the term derives from the hereditary factors of de Vries' (Intracellular) Pangenesis, which were called "Pangens" and were occasionally transcribed as "Pangenes," whereas the idea goes back to Darwin's *Pangenesis*. Johannsen suggested that it was only the second part of this term that should be retained.[1] He also noted that: "The word gene is completely free from any hypothesis; it only expresses the established fact, that at least many properties of an organism are conditioned by special, separable and thus independent 'conditions', 'foundations', 'dispositions'" (translated in Roll-Hansen, 2014, p. 4). For Johannsen, the gene concept was practically undefined, and free from any assumption about its localization in the cell and its material constitution. However, he considered genes as real entities and contrasted them to the speculative hereditary particles proposed in earlier theories during the previous fifty years (see Table 1.1): "The genes are realities, not hypothetical conceptions, like so many entities that have previously been presented in a purely speculative manner like Darwin's gemmules, Weismann's biophores, de Vries' pangenes, (first time 1889) etc." (translated in Roll-Hansen, 2014, p. 5). So, the first conceptualization of the gene was not accompanied by a specific hypothesis about its nature. For Johannsen the gene was "nothing but a very applicable little word" that might be "useful as an expression of the 'unit factors', 'elements' or 'allelomorphs' in the gametes, demonstrated by modern Mendelian researchers" (Johannsen, 1911, p. 132).[2] There was thus no need to be more specific about the nature of the hereditary factors.[3]

[1] As Moss (2003, p. 2) correctly points out, the etymology of the term "gene" highlights the significance of the concept: it is something out of which other things arise.

[2] Johannsen was also the one to coin the terms "genotype" and "phenotype": "A 'genotype' is the sum total of all the 'genes' in a gamete or zygote… All 'types' of organisms, distinguishable by direct inspection or only by finer methods of measuring or description, may be characterized as 'phenotypes'" (Johannsen, 1911, pp. 133–134).

[3] One reason that the idea of hereditary factors became widely accepted among biologists seems to have been the dominance of a mechanistic-materialist philosophy in the beginning of the twentieth century. According to this philosophy, each organism was composed by distinct parts to which it should be broken down in order to be studied, and experimentation was the best way to do this. It was under the influence of this philosophy that genes were conceived as the "atoms" of biology, which was thus no longer different from chemistry and physics. Furthermore, the initial applications of this new mendelian genetics were quite successful, and almost all phenomena could

genes that produce changes in characters totally ignores environmental influences. The reason for this is that the research by Morgan and his colleagues was conducted in controlled laboratory conditions, where environmental changes did not take place and could thus be ignored. This is why the different characters that the same gene could produce in different environments were not considered until much later (Schwartz, 2000; see also Chapters 9 and 10).

Although Morgan and his colleagues considered the relationship between gene and characters as many-to-many one, one can find in the very same book the idea of a "gene for" a character. For instance, we read (Morgan et al., 1915, p. 11):

> As shown in this diagram, a spermatozoon bearing *the factor for long wings* fertilizing an egg bearing the same factor produces a fly pure for long wings; a spermatozoon bearing *the factor for long wings* fertilizing an egg bearing *the factor for vestigial*[4] *wings* produces a hybrid fly that has long wings. (emphases added)

This way of referring to "factors for characters" is used throughout that book, and we read about "the factor of ebony" (p. 13), "the factor for red" (p. 18), and so on. But early in the book the authors explained that whereas it was "customary to speak of a particular character as the product of a single factor," everyone familiar with the phenomena of Mendelian inheritance was aware that the "so-called unit character is only the most obvious or most significant product of the postulated factor" (Morgan et al., 1915, p. 32). Therefore, a certain form of a gene that brought about the character described as vestigial wings could be described as the gene *for* vestigial wings. However, it was clear to those researchers that the notion of "genes for" was used only to indicate a correlation; a mutation in gene X brings about a different version of character Y. This was briefly described as "X is the gene for Y," but it was clear to researchers what this shorthand meant. However, even today in the public sphere this shorthand makes people draw unwarranted conclusions, which are discussed in Chapter 5. It is thus very important to note that the idea of genetic determinism may have not stemmed directly from researchers themselves, even though they might have themselves used genetic determinist expressions. To understand

[4] Refers to flies that only have small vestiges of the wings, and not fully formed ones.

the prevalence of genetic determinist ideas, it is also important to consider their social and economic origins. Eugenics developed worldwide between 1900 and 1940, and it was especially prominent in the United States, Britain, and Germany. Whereas genetics arguments were used, there were also political motivations. One of the major arguments in all countries was that it was not efficient to let genetic defects spread in the populations and deal with the consequences of taking care of these people. This argument is clearly socioeconomical and not genetic (Allen, 1997).

Another important idea in the book by Morgan and his colleagues was that genes are located sequentially on chromosomes like beads on a string (Morgan et al., 1915, pp. 131–132) referring to a figure on p. 60 of the same book (Figure 2.3a). This figure is indicative of how genes were conceived as discrete parts of chromosomes. Morgan and his collaborators had realized that several genes were not inherited independently; in contrast there was some kind of genetic linkage between them that in turn pointed to a physical linkage. Thus, genes could be conceived as beads on the same string. This conceptualization was essential for the process of crossing over[5] depicted in that figure, and the techniques used subsequently by Morgan and his colleagues for mapping genes. The first genetic map, i.e. the first map showing the linear arrangement of genes on chromosomes had been published two years earlier by Alfred Sturtevant (1891–1970) (Figure 2.3b), a student of Morgan (Sturtevant, 1913). In that paper, Sturtevant also set out the logic for genetic mapping. The number of crossovers per 100 cases was used as an index of the distance between any two genes (still described as factors in that paper). If one could thus determine the distances between genes A and B and between genes B and C, it would also be able to predict the distance between genes A and C. Therefore, the relative positions of genes could be empirically mapped on chromosomes, and this gave them a more material character than before. This understanding became possible at that time in part because of luck. Morgan and his collaborators worked with *Drosophila* that has four chromosomes only, and this made the identification of genes that were linked more

[5] Crossing over is the phenomenon of exchange of chromosome parts between two homologous chromosomes during meiosis, the cell division leading to the production of reproductive cells (gametes). This phenomenon results in new combinations of genes in offspring that did not exist in their parents.

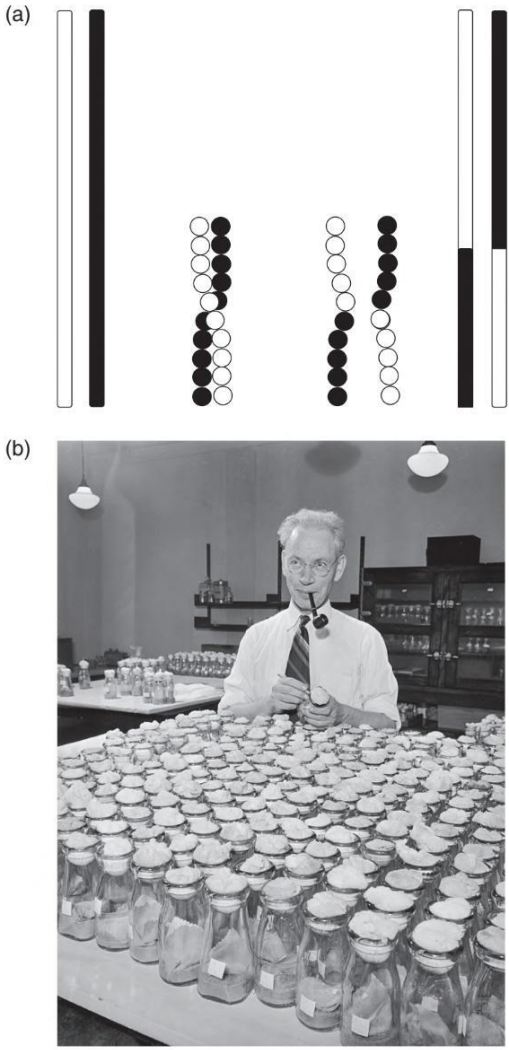

FIGURE 2.3 (a) A figure like this in the 1915 book by Morgan and his colleagues represented chromosomes like strings consisting of beads that were the genes, called unit factors at that time. It also depicted how crossing over took place and resulted in different combinations of genes, e.g. "black & white," instead of "black only" or "white only" (based on Morgan et al., 1915, p. 60). (b) Alfred Sturtevant produced the first map showing the linear arrangement of genes on chromosomes; here in front of numerous bottles with fruit-flies (© Bernard Hoffman).

probable than if the organism had forty-six chromosomes, as we do. Figure 2.4 presents how the alleles of different genes can be combined in the reproductive cells (gametes) after meiosis, depending on whether they are linked or not, for a simple case such as an individual with genotype RrYy of Figure 1.3.

Morgan and his colleagues dominated the field described as classical genetics. It was due to their adoption of the term "gene" that it became widely used. Morgan used the term for the first time in 1917: "The germ plasm must, therefore, be made up of independent elements of some kind. It is these elements that we call genetic factors or more briefly genes. This evidence teaches us nothing further about the nature of the postulated genes, or of their location in the germ plasm." (Morgan, 1917, pp. 514–515). Then Morgan made the interesting remark: "Why, it may be asked, is it not simpler to deal with the characters themselves, as in fact Mendel did, rather than introduce an imaginary entity, the gene" (p. 517). He nevertheless defended the need to use the concept of gene, even if there was no evidence about the nature and localization of genes. This was done for heuristic purposes that had to do with explaining the phenomena observed, as the gene concept had already been a very valuable heuristic tool for conducting research (for a discussion of the conceptual shift from unit factors to genes, see Darden, 1991, pp. 168–190).

Morgan and his colleagues studied several characters in *Drosophila*, such as eye color, which were related to sex chromosomes and so exhibited different ratios than those observed by Mendel and presented in Figures 1.2 and 1.3. Ratios like 3:1 and 9:3:3:1 were observed in the majority of cases for genes located on chromosomes found in both sexes, which are called autosomes.[6] However, when genes were located on sex chromosomes instead of autosomes, these ratios changed. The reason for this is that, whereas in organisms like *Drosophila* there always exist two alleles for a gene located on autosomes, there are some genes located on X chromosomes for which there is no corresponding allele in males because they only have one X chromosome. In this case, assuming that there exist two alleles, e.g. X^A and X^a, females can be homozygous (X^AX^A or X^aX^a) or heterozygous (X^AX^a), whereas males are

[6] Sex chromosomes were identified for the first time in 1905 by Nettie M. Stevens (1861–1912) and Edmund B. Wilson (Brush, 1978; Ogilvie & Choquette, 1981).

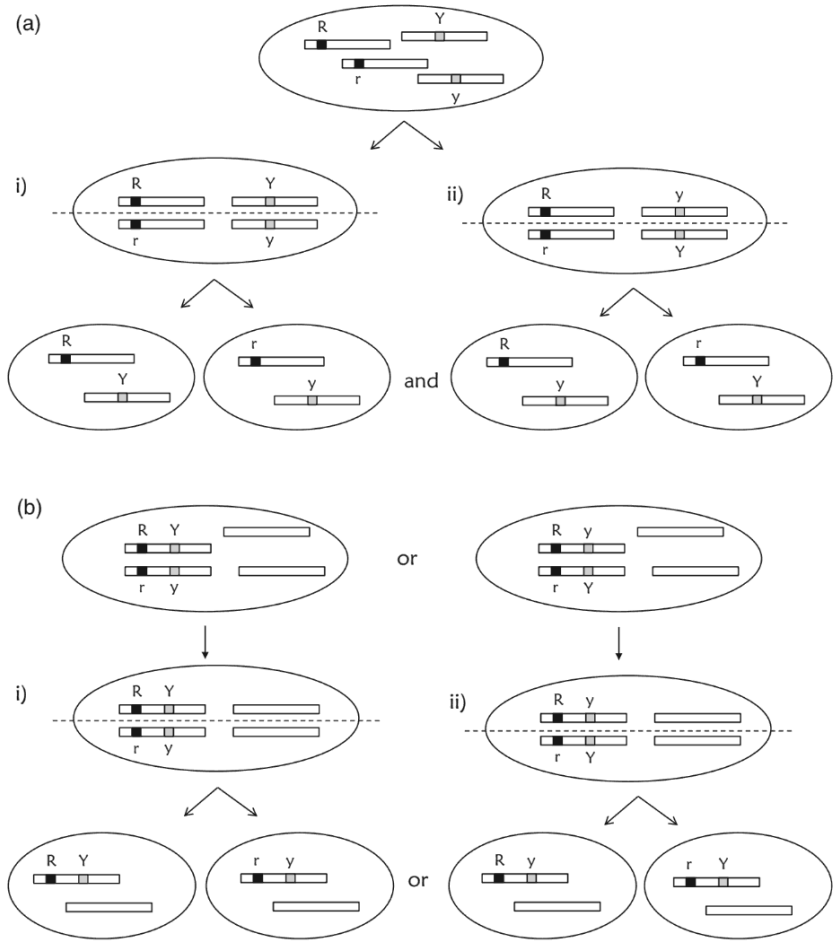

FIGURE 2.4 (a) How the alleles of the same gene are segregated and how the alleles of two genes located on two different chromosomes are independently assorted in the gametes during meiosis. In some cells procedure (i) will take place whereas in others procedure (ii) will take place, the two procedures being equally probable. Because the genes are independent, all possible gametes (RY, Ry, rY, ry) are produced by an individual. (b) When genes are located on the same chromosome, and are thus "linked," not all combinations are possible. What matters in this case is which alleles are linked (e.g. whether R is linked with y and r with Y, or R with Y and r with y). An individual will thus have either gametes RY and ry (i) or Ry and rY (ii) The replication of the genetic material is ignored in this figure, as it was not known at the time, although it was believed that genes could be replicated. Therefore, the figure should only be considered in qualitative, not quantitative, terms.

FIGURE 2.6 Two scientists who provided crucial evidence that genes are material entities: (a) Hermann Muller (© Bettmann) (b) Barbara McClintock (© Universal History Archive).

reported that treatment of sperm with relatively heavy doses of X-rays caused an increase in mutation rate in *Drosophila* of about 15,000 percent in the treatment group compared to the control group. What was more interesting was that the characteristics of the mutations produced by X-rays were generally similar to those previously observed in *Drosophila*. Actually, most of the already known mutant phenotypes were produced during the experiments. Muller noted that the interest of these experiments lied "in their bearing on the problems of the composition and behavior of chromosomes and genes" (p. 86). That his experiments produced most of the mutant phenotypes already observed in *Drosophila* suggested that genes had some material composition that was altered by X-rays (see Falk, 2009, pp. 131–140). This provided crucial evidence that genes should be material entities of some kind.

Additional, crucial evidence that genes were material entities came from studies of crossing over (Figure 2.3a). This phenomenon was taken for granted as early as 1915, but it was only in 1931 that Barbara McClintock (1902–1992) (Figure 2.6b) and her colleague Harriet Creighton (1909–2004) showed that there was a correspondence between chromosomes exchanging parts and the recombination of phenotypes,

and therefore that genetic information and genes were carried on chromosomes. As the authors put it, their aim was to show that cytological crossing over occurs and that it is accompanied by genetic crossing over. McClintock had found that in a certain strain of corn, chromosome 9 had "a conspicuous knob at the end of the short arm." Therefore, in order to show the correlation between cytological and genetic crossing over, it was necessary to have plants that differed in the presence of the knob and of particular linked genes. By crossing plants that differed appropriately in these characteristics, it was shown that cytological crossing over occurred and that was accompanied by the expected types of genetic crossing over. It was thus concluded that chromosomes of the same pair exchanged parts at the same time they exchanged genes assumed to be located on these regions (Creighton & McClintock, 1931).

Morgan received the 1933 Nobel Prize in Physiology and Medicine "for his discoveries concerning the role played by the chromosome in heredity." In his Nobel lecture he emphasized that it would be "somewhat hazardous to apply only the simpler rules of Mendelian inheritance; for, the development of many inherited characters depends both on the presence of modifying factors and on the external environment for their expression." In other words, Morgan suggested that the simple Mendelian genetics could not account for the development of phenotypes as "the gene generally produces more than one visible effect on the individual, and … there may be also many invisible effects of the same gene." The view that genes affect but do not determine characters continued to characterize his thinking. In the same lecture Morgan also clearly explained why at that point it did not make much difference for geneticists to be aware of what genes were made of: "There is no consensus of opinion amongst geneticists as to what the genes are – whether they are real or purely fictitious – because at the level at which the genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle."[8] Therefore, the gene was still a hypothetical entity, a conceptual tool with a heuristic value. By that time, it had been found that genes were located on chromosomes, and thus could be made by some material substance. But the definitive answer to the question "what

[8] "Thomas H. Morgan – Nobel Lecture: The Relation of Genetics to Physiology and Medicine." Nobelprize.org. Nobel Media AB 2014. Web. www.nobelprize.org/nobelprizes/medicine/laureates/1933/morgan-lecture.html