1

From Mendel to Molecules

Since the nineteenth century, scientists have been working to unravel the biological basis of inheritance. With Gregor Mendel's mid-nineteenth-century discovery of the basic mechanisms of heredity, genetics was born, and humanity took its first small steps toward deciphering the genetic code. No longer would heredity solely be the domain of philosophers and farmers. Indeed, Mendel's discoveries set the stage for major advances in genetics in the twentieth century and help put in motion the series of discoveries that led to the development of the sequencing of human and nonhuman genomes. This age of discovery, from Mendel to genome sequencing, is the subject of the first four chapters of this book. Chapter 1 covers some basic biology and tells the story of the evolution of genetics by examining some of the most significant discoveries in the field—discoveries that enabled the development of genomics. Chapter 2 looks specifically at the evolution of genetic and genomic sequencing technologies. Chapter 3 examines the human genome itself and the ways in which we are exploring and exploiting it now and in the future. And, finally, Chapter 4 looks at the sequencing and genome analysis tools of the post-genomic era also called next generation sequencing or (NGS).

Without any further ado, may we present to you the human genome!

This photo (Figure 1.1), also known as a karyotype, shows the 46 human chromosomes, the physical structures in the nuclei of your cells that carry almost the entire complement of your genetic material, also known as your genome. But don't let this two-dimensional representation of the genome fool you into believing in its simplicity. Almost 20 years ago biologist Richard Lewontin called DNA a "triple-helix" to explain how genes function, and how they interact with each other and the environment. This triple helix is largely inseparable, and genetics doesn't make sense unless taking these effects into account.

We could also have introduced you to your genome with a slew of the DNA sequence units—As, Ts, Gs, and Cs—in a string, or we could have shown you a picture of DNA in a test tube or even a picture of a nucleus of one of your cells where the DNA would be visible as dark stringy stuff. There are many ways to visualize the genome and this is part of its beauty.

Welcome to the Genome: A User's Guide to the Genetic Past, Present, and Future, Second Edition.
Rob DeSalle and Michael Yudell.

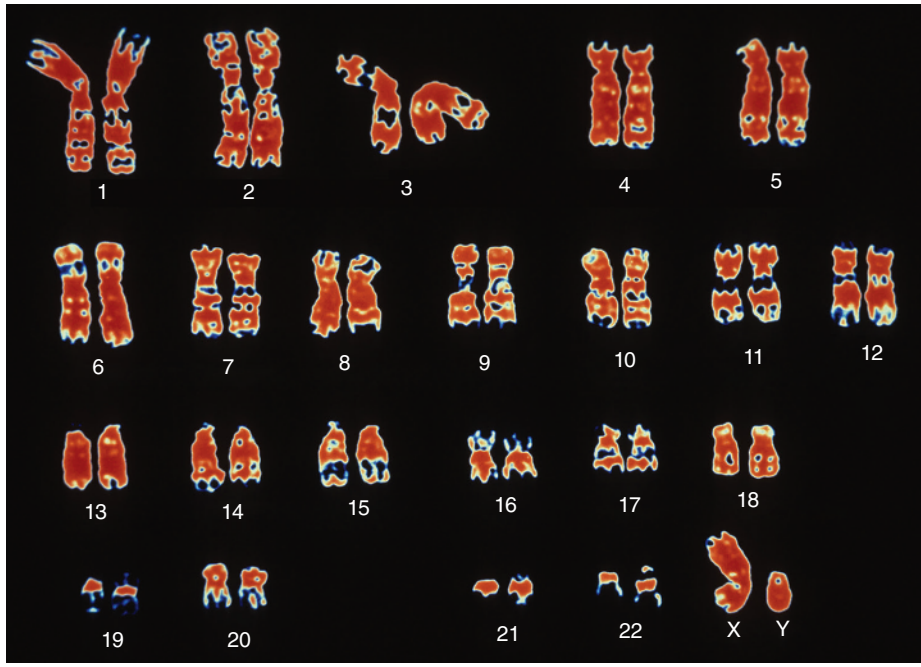

Figure 1.1 This picture, known as a karyotype, is a photograph of all 46 human chromosomes. With an X and a Y chromosome, this is a male's karyotype. A female's karyotype would show two X chromosomes. *Credit: Photo Researchers*

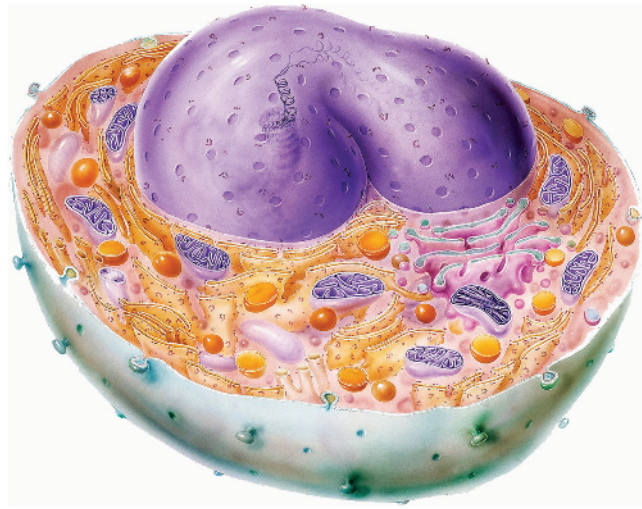

Figure 1.2 The nucleus of every human cell (the large purple mass inside the cell) contains DNA. Mitochondria, organelles in cells that produce energy (the smaller purple objects within the cell), also contain some DNA. *Credit: Wiley*

Still, to understand function, we do need to learn about basic form. And a karyotype, despite its limitations as a representation of the genome, illustrates that in almost all the cells in the human body there are 22 pairs of chromosomes and two sex-determining chromosomes. The double helices that make up your chromosomes are composed of deoxyribonucleic acid, also known as DNA, on which are found approximately 20,000 genes. These cells are called somatic cells, and they are found in almost all nonreproductive tissue.

Humans also have cells with 23 nonpaired chromosomes. In these cells, each chromosome is made up of a single double helix of DNA that contains approximately 20,000 genes. These cells are called germ cells and are the sperm and egg cells produced for reproduction. These germ cells carry a single genome's worth of DNA or more than 3 billion bases worth of nucleic acids.

Chromosomes are somewhat like genetic scaffolding—they hold in place the long, linearly arranged sequences of the nucleotides or base pairs that make up our genetic code. There are four different nucleotides that make up this code—adenine, thymine, guanine, and cytosine. These four nucleotides are commonly abbreviated as A, T, G, and C. Found along that scaffolding are our genes, which are made from DNA, the most basic building block of life. These genes code for proteins, which are the structural and machine-like molecules that make up our bodies, physiology, our mental state. Through the Human Genome Project scientists are not simply learning the order of this DNA sequence, but are also beginning to locate and study the genes that lie on our chromosomes. But not all DNA contains genes.

On average 3 billion base pairs exist in the collection of the chromosomes your mother transmitted to you. Add to that the chromosomes given to you by your father gave you and in your cells there are around 6 billion bases, a complete diploid human genome. There are long stretches of DNA between genes known as intergenic or noncoding regions. And even within genes some DNA may not code for proteins. These areas, when they are found within genes, are called introns. While these genomic regions were once believed to have no products and/or no function, scientists now understand that both introns and intergenic regions play a role in regulating DNA function. The Encyclopedia of DNA Elements or ENCODE Project estimates, for example, that while only 2.94% of the entire human genome is protein coding, 80.4% of genome sequences might govern the regulation of genes. (1) Unlike the human genome and all other eukaryotic genomes, however, bacterial genomes do not have introns and have very short intergenic regions. Curiously though, the archaea, a third major domain of life (in addition to eukaryotes and bacteria) do have introns, but not necessarily the same kind of introns as eukaryotes.

Let's begin our tour of the human genome with a very basic lesson in genetic terminology. For example, what exactly is genetics, and how is it different from genomics? Genetics is the study of the mechanisms of heredity. The distinction between genetics and genomics is one of scale. Geneticists may study single or multiple human traits. In genomics, an organism's entire

collection of genes, or at least many of them, is examined to see how entire networks of genes influence various traits. A genome is the entire set of an organism's genetic material. The fundamental goal of the Human Genome Project was to sequence all of the DNA in the human genome. Sequencing a genome, whether human or nonhuman, simply means deciphering the linear arrangement of the DNA that makes up that genome. In eukaryotes (plants, animals, fungi, and single-celled organisms called protists), the vast majority of the genetic material is found in the cell's nucleus. The Human Genome Project has been primarily interested in the more than 3 billion base pairs of nuclear DNA. A tiny amount of DNA is also found in the mitochondria, a cellular structure responsible for the production of energy within a cell. Whereas the human nuclear genome contains more than 3 billion base pairs of DNA and approximately 20,000 genes (that's nearly 10,000 genes fewer than when the first edition of this book was published in 2005), the reference human mitochondrial genome contains only 16,568 bases and 37 genes. (2) Like bacteria, mitochondrial DNA, or mtDNA, has short intergenic regions and its genes do not contain introns. Another interesting characteristic of mtDNA is that it is always maternally inherited. This has made mtDNA very helpful to track female human evolutionary phenomena. These discoveries were made possible, in part, by sequencing mtDNA.

What about heredity? In the most basic sense we should think about heredity as the transmission of traits from one generation to the next. When we talk about heredity in this book we refer to the ways in which traits are passed between generations via genes. The term heredity is also sometimes used to describe the transmission of cultural traits. Such traits are shared through a variety of means including laws, parental guidance, and social institutions. Unlike genetics, however, there are no physical laws governing the nature of this type of transmission.

What are genes? Genes are regions of DNA and are the basic units of inheritance in all living organisms. These words, genes and DNA, are too often used interchangeably. Both genes and DNA are components of heredity, but we identify genes by examining regions of DNA. In other words, DNA is the basic molecular ingredient of life, whereas genes are discrete components of that molecular brew.

If you look at any family you'll see both shared and unique traits. Family members typically look alike, sharing many features such as eye color and nose shape, but they may also have very different body types and be susceptible to different diseases. This diversity is possible for two reasons. The first reason is that genes come in multiple forms. These alternative forms are known as alleles, and in sexual reproduction they are the staple of organismal diversity. According to the laws of genetics, siblings can inherit different traits from the same biological parents because there is an assortment of alleles that can be randomly passed along. The second reason is that the environment can exert a significant influence on the expression of genes. For example, an individual

may inherit a gene that makes him or her susceptible to lung cancer. Such susceptibility is typically revealed, however, only after years of genetic damage caused by cigarette smoking or other lung-related environmental impacts. (3) Recent advances in the field of epigenetics have brought new complexity to our understanding of how our genes interact with our environments, and how such interactions can be passed between generations (through the germline). Over the past decade epigenetic research has accelerated our understanding of how environmental factors can alter the peripheral structure of DNA—not the DNA sequence itself but the molecular structures that interact with and support the sequence—to elicit changes in the expression of a gene (the gene's phenotype).

So how *did* science progress from thinking about the mechanisms of heredity to understanding that genes are the basic units of heredity, to deciphering and finally manipulating the DNA code that underlies all life on Earth? The results of the Human Genome Project were the fruits of over a century of struggle by scientists around the globe. Most historians of science would measure this progress beginning with Gregor Mendel's work on pea plants during the middle of the nineteenth century. Although premodern thinkers did have a basic grasp of the idea of heredity—that is, that identifiable traits could be passed down from generation to generation—it was not until Mendel that science began to understand the mechanisms underlying the transmission of these traits. (4)

The journey from abstract notions of inheritance to the sequencing of the human genome abounds with stories of discoveries both great and small that led to where we are today. Science seldom progresses in a straight line. The genome was always there for us to find but took centuries to discover because knowledge and the technological application of that knowledge advance fitfully, revealing gradually more over time, and the social and cultural context that prioritizes different types of knowledge ebbs and flows with that time. Scientists have not always made the right choices. Even today, in what has been called the post-genomic age, we are likely making assumptions about our genes that future generations look back on and ask, "How could they have thought that?" The trials and errors of science are part of what makes this process so interesting.

Several major building blocks of life had to be discovered to make possible our entry into the genomic world. First, scientists needed to determine what constitutes the hereditary material that passes from one generation to the next. Second, they needed to find out what constitutes the biochemical basis for the expression of this intergenerational legacy. This endeavor required the ability to take cells apart and analyze the chemical components from different parts of cells. Scientists then needed to determine the ways in which these chemicals, the building blocks of life, interacted, how they were structured, and how that structure influenced the hereditary process. Finally, technologies needed to be developed to use this information to improve human health, agriculture, and our understanding of our place in the history of life on Earth.

It took almost 150 years from the discovery of the hereditary principles to the sequencing of the human genome. The stories behind these discoveries explain how scientists came to understand the biological basis of heredity. What follows does not represent the comprehensive history of all the important genetic work of the past century or so. Yet without the discoveries we highlight, the discovery of the genome would never have occurred or would have happened very differently.

The meanings and mechanisms of heredity were pondered and debated millennia before the development of modern genetics. In the fifth century BCE, the Greek dramatist Euripides wrestled with the complexities of the relationship between parent and child in his play *Electra:*

> I oft have seen,
>
> One of no worth a noble father shame,
>
> And from vile parents worthy children spring, Meanness oft groveling in the rich man's mind, And oft exalted spirits in the poor. (5)

Without knowledge of genes or genomes, premodern thinkers had many ideas concerning the nature of heredity, some of which were surprisingly sophisticated and accurate. To Euripides heredity must have been a mystifying and seemingly random process. How else could he and his contemporaries explain the inconsistencies among inherited traits within families? Other ancients carefully considered similar questions. Lucretius, a Roman philosopher, wrote that traits could skip generations, as children sometimes resembled their grandparents. (6) Around the globe, premodern farmers had already developed sophisticated breeding techniques that depended, in part, on a basic understanding of heredity. We know, for example, that the ancient Assyrians and Babylonians artificially pollinated date palm trees and that many animals, including sheep, camels, and horses were domesticated during ancient times. (7) The domestication and breeding of plants and animals shows that many early thinkers recognized that traits were passed between generations.

Perhaps the most advanced premodern thinker on heredity was Aristotle (384–322 BCE). (8) Aristotle dedicated much of his work to questions concerning the specific mechanisms of heredity. He theorized that inherited traits were passed between generations by what he called the *eidos*, or the blueprint, that gave form to a developing organism. Aristotle's *eidos* was entirely theoretical—he could not see this invisible configuration—a fact that makes his theory all the more remarkable. Aristotle understood the mechanisms of heredity only in the broadest sense and remained handicapped by the limited technology of his time, a primitive understanding of biology, and the cultural limitations of his worldview. Yet a keen perception, buttressed by his emphasis on observation and description, made him a brilliant interpreter of the natural world.

The concept of the *eidos* remained the most complete theory of heredity until the modern era of genetics. More than two millennia later scientists use a genetic language strikingly similar to Aristotle's. The *eidos* is in many ways analogous to the modern concept of a genome, and like Aristotle today's scientists often refer to a genome as a blueprint for life. (9)

IN THE ABBEY GARDEN

For close to two millennia few scientists approached Aristotle's understanding of heredity, though other theories were put forth during the centuries. Some, like the idea of the homunculus—the belief that every being was miniaturized and preformed in a reproductive cell—or the belief in panspermia—the idea that secretions from the entire body contribute to offspring—held sway for varying lengths of time. (10)

But before the late eighteenth century, ideas about what we today understand as heredity were quite different than our modern concept. Although similarities were recognized between parents and offspring and among families, such similarities, in a pre-hereditarian worldview, were not generated by a hereditary mechanism, but by the act of conception itself, the pregnancy that followed, the development of the embryo, the birth, and, finally, lactation. There could be no laws of heredity in a system that viewed each creation of plant and animal life as isolated events. (11)

However, beginning in the eighteenth century, disparate fields of thought concerning hereditary phenomena would begin to converge on the road to developing hereditary theories. (12) Medical science, for example, began to systematically characterize disease. The taxonomic language of natural history moved toward uniformity. Professional animal and plant breeders more actively sought to breed specific features. Scientists investigated preformationist theories. And anthropology, in seeking to understand physical differences between peoples and populations, investigated the origins of human diversity. (13) From these various scientific investigations would slowly emerge both a popular and scientific discourse that would, over time, shape emerging concepts of heredity.

The work of Austrian monk Gregor Mendel, who bred peas in his abbey garden, built upon these growing discussions of heredity, and is credited with making the jump to studying heredity experimentally. But Mendel was not just a monk tending peas. The child of peasant farmers, he was a classically trained scientist raised in the greatest traditions of the Enlightenment. Intellectually nurtured by his family and schooled in the best academies and universities of Central Europe, the German-speaking Mendel spent his life dividing his affection between God and science. (14) In 1843, at the age of 21, Mendel entered the St. Thomas Monastery in Brünn in what is now the Czech Republic. (15)

In the Church Mendel found a community of scientists—botanists, zoologists, and geologists among them—working diligently in their fields and making important contributions to the scientific literature. Perhaps the most

important event in Mendel's early career occurred 10 years into his stay at St. Thomas. In 1851, at the behest of his abbot, Mendel was sent to Vienna University to study at the institute of Professor Christian Doppler, one of the pioneers of modern physics. For 2 years at Doppler's institute Mendel honed his scientific skills, taking courses in physics, chemistry, and mathematics, as well as entomology, botany, and plant physiology. The influence of physics was important to Mendel's later work on heredity. Physics taught Mendel that laws governed the natural world and that these laws could be uncovered through experimentation. (16) But it was ultimately Mendel's exposure to ongoing debates in heredity that transformed him into the scientist we remember today.

Mendel and his predecessors understood that traits could be passed between generations. A child with his mother's eyes and his father's nose was easy evidence of that. Breeding experiments with domesticated animals also suggested that traits were passed to offspring.

The prevailing theory during the nineteenth century, one to which even Charles Darwin mistakenly ascribed, was "blended inheritance." (17) This theory held that the characteristics of parents blended in their offspring. Experimentation in this area failed because, as Mendel was able to eventually determine, heredity was not a lump sum but rather a series of individual traits.

In 1856 Mendel began to study the mechanisms of inheritance, working with varieties of garden peas from the genus *Pisum*. (18) In the course of his experiments his garden flowered, as did his understanding of heredity. Mendel discovered several generalities from his experiments that remain the

Figure 1.3 Although it took decades for Gregor Mendel's work on pea plants to revolutionize hereditary theory, his impact is today still felt in the biological sciences. *Credit: American Museum of Natural History*

foundation of twentieth-century genetics. Any student of biology knows Mendel's work. Known as Mendel's laws, these basic tenets describe heredity in two simple mechanisms: the law of independent assortment and the law of segregation.

Mendel began an experiment with purebred peas. One breed had yellow seeds, the other green seeds. When purebred yellow-seeded peas were bred with each other, their offspring through the generations would have yellow seeds. Under the same circumstances, the green-seeded peas would always have green-seeded progeny. However, when he bred the purebred pea with yellow seeds to a purebred pea with green seeds, the offspring, or the first generation of this breeding cross, always had yellow seeds. The green seed trait seemed to be gone. Mendel called traits like the yellow-seed trait dominating (now called dominant) because in first-generation crosses they would always appear. (19) Traits like the green-seed trait were called recessive—although they disappeared completely in the first generation, they reappeared in the second. Thus, when Mendel took the yellow seeds from the first generation and either self-pollinated them or pollinated them with pollen from other yellow peas from the same first-generation breed, he discovered that some of these offspring, the second generation, again had the green seed trait. The plants, Mendel concluded, retained the ability to produce green seeds—of the second-generation seeds, 6022 were yellow and 2001 were green. Likewise, when he used six other traits, he found the same pattern in the second generation—traits that had disappeared in the first generation reappeared in the second. (20) The chart below shows the relationship between dominant and recessive traits in second-generation pea plants in the seven traits Mendel experimented with.

Dominant trait		Recessive trait	
Round seeds	5474	Wrinkled seeds	1850
Yellow seeds	6022	Green seeds	2001
Gray seed coats	705	White seed coats	224
Green pods	428	Yellow pods	152
Inflated pods	882	Constricted pods	299
Long stems	787	Short stems	277
Axial flowers	651	Terminal flowers	207

(21)

From these experimental data, Mendel made several conclusions that are at the heart of his revolutionary contribution to hereditary theory. From the 3:1—dominant to recessive—ratio in the second generation, Mendel concluded that the traits he studied came in two different forms and that these forms existed in pairs in the plant. Mendel called these forms factors. Today we call them genes. During the process of making reproductive cells, Mendel deduced, these genes segregate from each other—that is, the two copies of a gene that you get from each parent segregate, and in the subsequent reproductive cells, only one half of the pair is passed on to offspring. At

fertilization, a gene from each parent reconstitutes the pair. How else could Mendel explain how two yellow-seeded pea plants could produce offspring with green seeds? In this case, the green-seed trait was as much a part of the pea plant as the yellow-seed trait despite sometimes being hidden. Mendel also concluded that the factors that were dominant (in the left-hand column above) somehow overcame the factors that were recessive (in the right-hand column) when they were combined in offspring from crosses. When all first-generation plants were crossed, they had both kinds of factors. Mendel's calculations allowed him to predict a 3:1 ratio if the two factors were segregated. This is Mendel's first law, the law of segregation, which states that the factors specifying different alleles are separate or segregated, that only one may be carried by a gamete (an egg or sperm), and that gametes combine randomly. Therefore, a child has the same chance of inheriting allele A as it does allele B. (22)

Without the assistance of a calculator or computer, Mendel counted thousands and thousands of plants. Even more remarkable, he constructed lineages that had all possible combinations of two of the seven traits together. For example, he crossed a line of pea plants with round yellow seeds with a line whose seeds were wrinkled and green. This cross gave rise to first-generation plants with seeds that were all yellow and smooth. But when he crossed these first-generation plants to each other (a self-cross), an amazingly regular ratio in the offspring arose—the seeds of nine were yellow and round, three yellow and wrinkled, three green and round, and one green and wrinkled. Mendel reasoned that mating these first-generation plants was like taking the two possible types of each trait (e.g., seed texture and seed color) and throwing them into a hat. Nature then randomly chose from the hat how to combine the

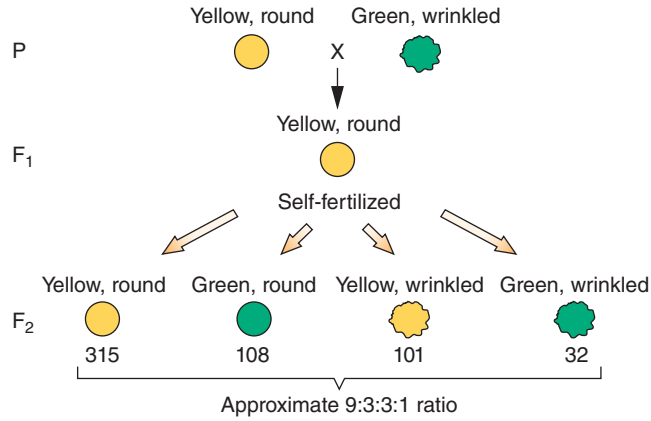

Figure 1.4 Mendel's first law of segregation says that alleles will segregate *randomly* between generations. Mendel's second law, the law of independent assortment, represented in the figure above, says that pairs of alleles will segregate *independently* between generations. (P = parents, F_1 = first generation, F_2 = second generation). *Credit: Wiley*

genes. Although the choice is random, the outcome is a remarkably regular ratio of 9:3:3:1. (23).

These observations are now known as Mendel's second law, the law of independent assortment—if two traits (genes) are being controlled with different controllers (alleles), offspring will be produced by random combinations of the controllers (alleles). (24) In other words, a trait is independently and randomly distributed among offspring.

Mendel was either very lucky or very perceptive: it turns out that seven is the number of chromosomes of *Pisum*. For all seven of the traits he examined to show true independent assortment with respect to one another, none of them can be linked—that is, none of them can be on the same chromosome (or in the case of one of the traits he examined, they have to be very far apart on the same chromosome). (25) Mendel must have watched his peas very closely. Perhaps he recognized the pattern of segregation as he was weeding his garden and thus performed his experiment with an expectation based on his knowledge as a pea biologist. Or, perhaps, he selectively looked at his data and forgot to record crosses that deviated from the ratios 3:1 and 9:3:3:1. Either way, his conclusions have not been overturned.

Mendel died on January 6, 1884, nearly 20 years after his momentous study with *Pisum* had been published. (26) Even though its significance remained unheralded, Mendel's work as a scientist and as a servant of God was recognized by his peers. If Mendel had been luckier in choosing the journal in which to publish his findings, he might have been famous in his own time, but he published in an obscure scientific journal and died in genetic obscurity (his monastic calling guaranteed that). (27) Although his contemporaries did cite his work with *Pisum*, they probably did not comprehend its deeper meanings for what would become a cornerstone of hereditary theory. A tribute to Mendel by a fellow scientist in Brünn lauded him as one of the great scientists of his day who worked "almost exclusively on detailed natural scientific studies, in which he displayed a totally independent, unique way of thinking." (28) Unfortunately, it would take the world another 16 years after his death to uncover the greatness of Mendel's investigations.

The lack of attention to Mendel's work may also be explained by the near obsession with evolution in the mid-nineteenth century after the publication of Darwin's *The Origin of Species*. Darwin's work was published just 6 years before Mendel's and captured public attention well into the twentieth century, leaving Mendel's theory to languish quietly. (29)

The "rediscovery" of Mendel in 1900 was driven in part by what biologist Ernst Mayr calls "an accelerating interest in the problem of inheritance." (30) Incredibly, in the spring of that year three botanists—Hugo de Vries, Carl Correns, and Erich Tschermak—all claimed to have discovered laws of inheritance. They soon learned, unfortunately, that Mendel's work was nearly identical and had preceded them by 35 years. (31) In the coming decades, Mendel's laws of segregation and independent assortment would be tested on a wide variety of species.

IN THE FLY ROOM

With only four pairs of chromosomes, the ability to produce offspring at a pace that would make even the most reproductively prolific blush, and the fact that it can live in the austere environment of a laboratory storage bottle, the six-legged *Drosophila melanogaster*, or fruit fly, has been the workhorse of genetics for more than 100 years.

Beginning early in the twentieth century, Thomas Hunt Morgan and his students at Columbia University capitalized on *Drosophila*'s valuable qualities and began breeding fruit flies by the hundreds of thousands, hoping to find variations or mutations in fruit fly traits that would help explain Mendel's laws in real-life situations. Morgan's laboratory, dominated by work with *Drosophila*, became known as the fly room, a moniker that can only partly suggest the overwhelming number of flies present in a space that measured just 16 × 23 feet. (32) Today the fly room is frequented by one of the present authors—part of it still exists at Columbia University (if you are looking for it, it is now the men's bathroom on the sixth floor of Schermerhorn Hall).

During the 1910s, thanks in large part to the work conducted in the fly room, genetics shifted from simply testing Mendel's laws of inheritance to studying the physical arrangement of genes on chromosomes. Interestingly enough, the terminology of what we now call genetics was not even in place. Morgan and his genetically minded colleagues were pioneers in a field that was quickly becoming known as genetics, a word coined by botanist William Bateson in 1906. The word gene was itself first defined by the German biologist Wilhelm Johannsen in 1909. (33) The new terminology and the field of work and entity it describes are still used today.

Morgan, formerly a critic of Mendelian theory, came to embrace the new genetics because of some surprising results in his own research. In 1910 he discovered something startling among one of his breeds of *Drosophila*—a lone white-eyed male fly. When it was bred with a normal (red-eyed) female, all of the offspring had red eyes. When flies from the first generation were crossed, the white-eyed character reappeared, but surprisingly only in half of the males. Finally, when white-eyed males were bred with first-generation females, 50% of both males and females had white eyes. Morgan called this change a mutation and spent much of his career studying such mutations in order to decipher the nature of genes and the structure of chromosomes. (34)

Ultimately Morgan saw that Mendelian laws of segregation and independent assortment easily explained these patterns. Morgan's biographer Garland Allen suggests that these results were the main factor in Morgan's acceptance of Mendelism. (35)

The white-eyed *Drosophila* was a mutant variation of the normal red-eyed type. These types of mutations in physical characteristics became the means by which Morgan and his students at Columbia began to describe the physical entities of genes and chromosomes. People tend to think of genetic mutations as frightening, a change caused by exposure to something dangerous or a freakish

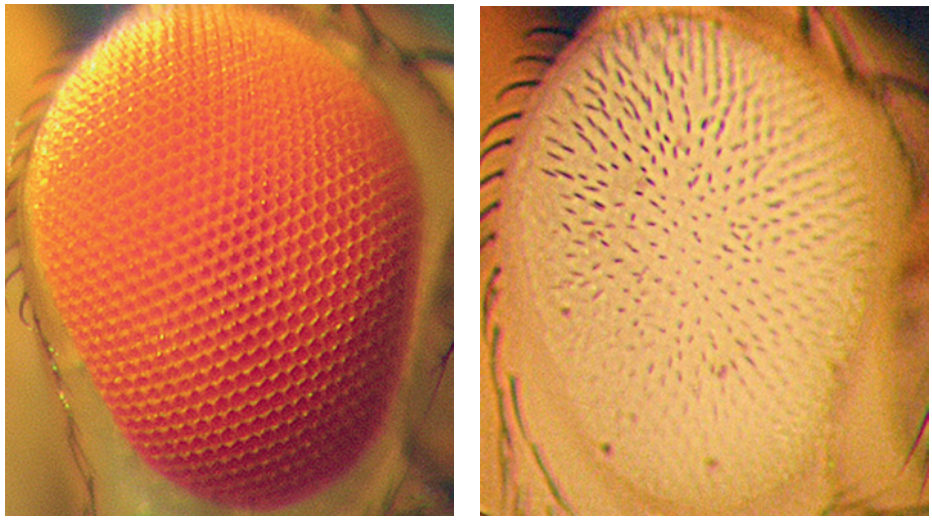

Figure 1.5 Most *Drosophilia* look like the red-eyed fly on the left. Morgan's discovery of and breeding experiments with the mutant white-eyed variety, as seen on the right, confirmed Mendel's basic laws and expanded them to include the linearity of genes on chromosomes. *Credit: Daniel Marenda, PhD and the Marenda Laboratory*

event or accident. A few things drive this fear. Most obvious is a misunderstanding of what a genetic mutation is and what it means for an organism. The other is that people have often described mutations as the result of exposure to atomic radiation either in real life (Nagasaki, Hiroshima, Chernobyl, or Fukushima) or in science fiction (Godzilla). It is true that the ill-effects on people exposed to high levels of radiation at atomic bomb sites are real and that cancer rates among survivors of Hiroshima and Nagasaki were substantially higher than normal because of mutations caused by the atomic bomb's radiation. (36) But mutations are generally not of this type, nor do they create the Godzilla-like creatures that have appeared in science fiction for the past half-century. Mutation comes from the Latin word meaning change, so a mutation is simply a change in an organism's DNA sequence—a change that may have no measurable effect on the organism or may confer either a beneficial or adverse effect. Random errors that occur during cell division are the most common cause of mutation. Most mutations are unpredictable, as are their effects.

There are two types of mutations. One is somatic (remember these are an organism's nonreproductive cells)—that is, its effects die with the organism. The other type of mutation occurs in the germline (in reproductive cells) and can be passed between generations. But cells are resilient. During cell division errors do occur, most of which are repaired by cellular mechanisms that are constantly at work to thwart the proliferation of cells with mutated nucleotides. During cell division, repair mechanisms check to make sure that the correct nucleotide has been selected at every stage of DNA synthesis. This is a tremendous task—in the human genome more than 3 billion bases are read and checked

each time a cell divides. These repair systems are redundant several times over. During mammalian cell division, for example, a gene called p53 plays an important role as a cellular safety device—it can stop cells with damaged DNA from reproducing themselves. This has earned this gene the nickname "guardian angel of the genome." (37) Mutations in the p53 gene seem to play a significant role in the development of human cancers. Typically, a mutated p53 is not as effective at controlling the proliferation of cells with damaged DNA, and dangerous mutations can grow over time to become cancers.

The cause of a mutation can be the result of exposure to radiation, but as was the case in the Morgan lab, the causes of mutations for a white-eyed variation were probably far more ordinary. The white-eyed trait most likely arose from a random error in the DNA replication process. Less likely, the mutation may have been caused by a mutagen, an agent that can cause mutation. Temperature changes during gestation, environmental exposures, certain viruses, radiation, ultraviolet light, and chemicals can all act as mutagens. By using the mutations found in *Drosophila*, Morgan was able to begin to map the *Drosophila* genome. (38) This was not like the modern genome sequence maps that we hear a lot about today. Indeed, although DNA had already been isolated from cellular material, it was not yet even suspected to be the "stuff" of heredity. Thus, there could be no map of the sequence of this genome, as neither science nor technology was even close to accomplishing this feat. Instead, Morgan began to map the location, or linear arrangement, of particular genes along *Drosophila* chromosomes. Working with a series of mutations, including variations in body color and wing shape, Morgan and his collaborators were able to create chromosome maps showing the location of certain genes on each of *Drosophila*'s four chromosomes. (39) Morgan's group, for example, determined that the white-eyed mutation lies on the X, or *Drosophila* sex chromosome. (40)

The beauty of Morgan's work, much like Mendel before him, stemmed from his powers of deduction. Morgan could never actually see the positions of genes on the *Drosophila* chromosomes, but he could create virtual maps based on his experiments and deductions. Faced with unknown and unpredictable challenges neither he nor his colleagues on the genetic frontier could have anticipated, Morgan's team was able to organize information in a fashion that is as elegant and relevant today as it was when his discoveries were made. Morgan's biographer Garland Allen notes that "there have been few research groups in modern biology that have functioned as effectively together as did Morgan's group in their fly room between 1910 and 1915." (41) To develop chromosome maps, the Morgan lab used a technique that came to be known as the three-point cross. Morgan reasoned that two genes very close to each other on a chromosome would appear to stay with each other even when other parts of the chromosome recombined. By looking at thousands and thousands of flies for visible mutations and breedings these mutations in the lab, Morgan was not only able to arrange these into linkage groups on chromosomes based on whether or not they segregated together, but also to say how the traits were organized on the chromosomes. (42)

But all was not well on the genetic frontier. These new and very powerful ideas concerning heredity, just beginning to make sense to some and still unknown to most, became a way to understand the world not only scientifically, but also socially.

EUGENICS—"PREVAILING SPEEDILY OVER THE LESS SUITABLE"

Morgan was not alone in his search for the mechanisms of heredity. The meanings of heredity captured the attention of natural and social scientists and, of course, the general public. While the work of Morgan and his colleagues dominated the scientific understanding of heredity during the first three decades of the twentieth century, a group of men and women known as eugenicists dominated the public understanding of heredity. These eugenicists, working under the assumption that all traits were heritable and genetic, burst onto the scene beginning in the 1890s, inspired by the work of Francis Galton in England. (43) Galton, a first cousin of Charles Darwin, defined the practice of eugenics as the science of giving "the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable." (44)

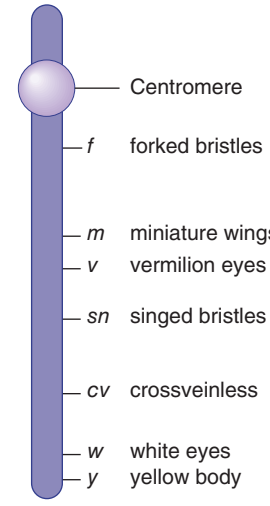

Figure 1.6 Morgan's experiments with *Drosophila* led to the development of the first map of an organism's genes. This modified map shows the location of some genes on the *Drosophila* X chromosome. *Credit: DNA Learning Center, Cold Spring Harbor Laboratory*

The early twentieth century was a turbulent time in world history, particularly in the United States, when an influx of immigrants from Europe and the migration of African Americans out of the Deep South were challenging America's cultural and racial hierarchy. (45) Discoveries in genetics were seized on to aid in the development of social theories concerning human difference. This ultimately gave rise to eugenics, the science of improving the qualities of humanity through selective breeding. Henry Fairfield Osborn, a prominent eugenicist and president of the American Museum of Natural History from 1908 to 1933, noted that "to know the worst as well as the best in heredity; to preserve and to select the best—these are the most essential forces in the future evolution of human society." (46) "The social application of eugenic theories," one historian writes, "led to specific, detrimental effects on the lives of scores of immigrant families in the United States and to the genocide against Jews in Germany." (47)

Immigration restrictions in the United States were buoyed by eugenicist sentiment. Harry Laughlin, the superintendent of the Eugenics Record Office at the Cold Spring Harbor Laboratory, appeared before Congress several times in the early 1920s promoting his belief that immigration was foremost a "biological problem." The Cold Spring Harbor Laboratory, headed by Charles

Davenport, was for all intents and purposes the headquarters of eugenics in the United States during first 40 years of the twentieth century. As Davenport's number two at the laboratory, Laughlin fervently promoted eugenics, maintaining, for example, that recent immigrants from eastern and southern Europe were afflicted "by a high degree of insanity, mental deficiency, and criminality." In his testimony before the House Committee on Immigration and Naturalization, Laughlin pleaded with Congress to restrict immigration so the United States would be allowed to "recruit and to develop our racial qualities." (48)

Sterilization laws across the United States were also inspired by eugenic sentiment. In the twentieth century at least 60,000 so-called "feeble-minded" and genetically unfit Americans were sterilized "in the name of eugenics." (49)

Criminals and those accused or convicted of sexual offenses were a primary concern of these eugenic laws. In 1907, the state of Indiana established the first sterilization law. By the early 1930s more than 29 other states had passed similar laws. (50) Advocates of criminal sterilization wrote that "criminals should be studied for evidence of dysgenic traits that are germinal in nature. Where found in serious degree parole should not be granted without sterilization." (51) "Criminality," "feeble-mindedness," and "idiocy" were all traits that eugenicists believed (mistakenly, of course) could be bred out of the species—traits eugenicists believed followed Mendelian patterns of inheritance and could therefore easily be excised. While California and North Carolina had the highest rates during the sterilization period, the last forced sterilization occurred in 1981 in Oregon. (52)

On matters of race, eugenicists were also quite vocal. This period "saw the dominance of the belief that human races differed hereditarily by important mental as well as physical traits, and that crosses between widely different races were biologically harmful." (53) Well-respected geneticists wrote openly that "miscegenation can only lead to unhappiness under present social conditions and must, we believe, under any social conditions be biologically wrong." (54) In this same spirit eugenic racial science became a deviously powerful force in the Third Reich.

Eugenicists also supported racist thought in their claims about the genetic nature of black–white differences. Davenport's work wasn't simply a reflection of the racism of his times; his work provided scientific rationale and a language for that racism. For example, Charles Davenport offered his scientific expertise in the study of skin color difference, the application of eugenic doctrines to segregation and anti-miscegenation laws, and ultimately to the definition of race itself. (55)

It is important to note that Nazi eugenics drew both scientific and ideological inspiration from its American counterpart. Madison Grant's eugenic tract *The Passing of the Great Race: The Racial Basis of European History*, which preceded the rise of Nazism by more than a decade, nonetheless influenced German ideas about racial purity. The book, translated into German, explicitly stated, "The laws of nature require the obliteration of the unfit." (56) American eugenicists

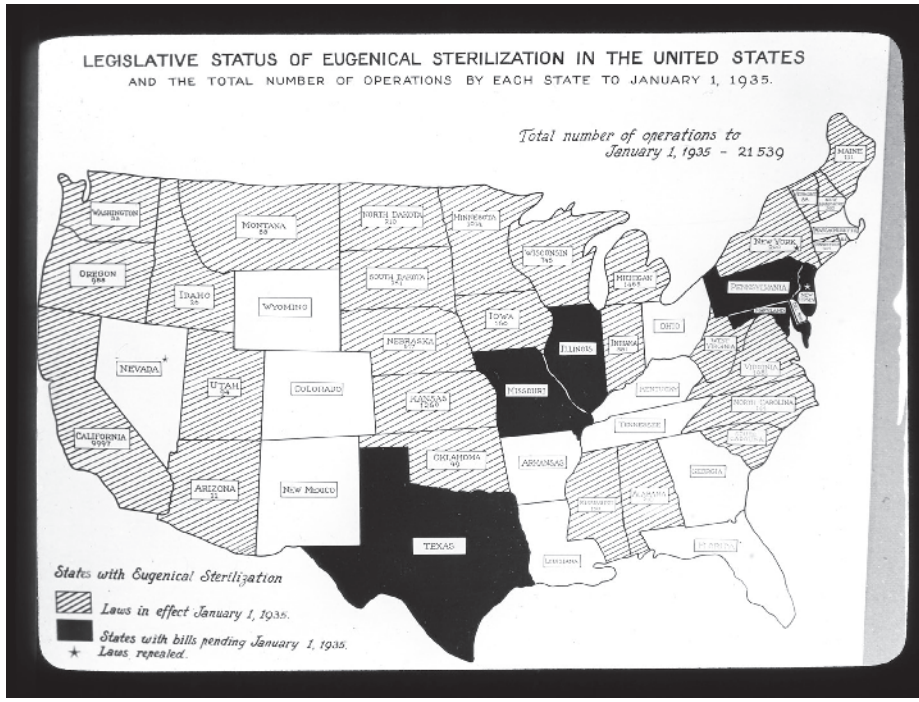

Figure 1.7 This eugenic map shows an estimate, state by state, of the number of individuals sterilized in the United States through January 1935. *Credit: DNA Learning Center, Cold Spring Harbor Laboratory*

themselves highlighted their ties to the Nazis, writing: "To one versed in the history of eugenic sterilization in America, the text of the German statute reads almost like the American model sterilization law." (57) The ties went even deeper. Philanthropists, including the Rockefeller Foundation, gave grants to German eugenicists even after the rise of Hitler. (58) And even in the wake of mass sterilizations, concentration camps, and gas chambers the support of American eugenicists continued. Support that included a 1935 visiting of Harry Laughlin to the University of Heidelberg where he was acknowledged as "one of the most important pioneers in the field of racial hygiene" (59) and the visit to Berlin in 1935 by Clarence Campbell, head of the Eugenic Research Association. Campbell proclaimed that the Nazi approach to eugenics "sets a pattern which other nations and other racial groups must follow if they do not wish to fall behind in their racial quality, in the racial accomplishments, and in the prospects for survival." (60) These types of relationships set the stage for the distribution, in the United States in 1937, by American eugenicists, of a Nazi eugenic propaganda film. (61)

After World War II outward support for eugenics became unacceptable to most biologists. The eugenic horrors of the Holocaust all but guaranteed that. And work by prominent geneticists "countered the eugenicists' simplistic

assertions that complex behavioral traits are governed by simple genes." (62) But even though eugenics as an organized movement ended, eugenic ideas and enactments did not. States and territories like North Carolina and Puerto Rico saw continued sterilizations in the post-World War II era, (63) and globally, in countries from Mexico to Japan to Iran. (64) Throughout the twentieth century ideas about heredity, social behavior, and human breeding have come in various guises, creating a fear among some that the Human Genome Project could open the door to eugenics once again.

"A VERITABLE 'AVALANCHE' OF NUCLEIC-ACID RESEARCH"

Despite the horrors of eugenics, by the 1930s the ideas of Charles Darwin were once again making headlines as the scientific search for the mechanisms of heredity continued. Darwin's theory of evolution lacked the mechanism to explain heredity. His theory articulated a "big picture" of evolution. He was right when he explained the ways in which evolution worked, but his theory was incomplete without genetics. Darwin's theory could not explain how evolutionary traits were passed through time. (65) Evolutionary biologists like R. A. Fisher, J. B. S. Haldane, and Sewell Wright successfully bridged the gap between evolution and genetics and spent their careers developing the mathematical framework for incorporating Mendelian genetics into evolutionary biology. This significant body of work led to what is known as the Modern Synthesis in biology, the merger of Darwinian and Mendelian science. This allowed scientists like Theodosius Dobzhansky, Ernst Mayr, and George Gaylord Simpson, who were based more in data collection than in theory, to develop an empirical approach to evolutionary biology and to open up evolutionary ideas for a broader interpretation in a genetic context. (66)

While the Modern Synthesis provided a framework for understanding questions about heredity in the context of evolution, other scientists were still trying to determine the chemical components of the hereditary material. Some remained wedded to the belief that proteins transmitted traits between generations, among them Hermann Muller, who had originally worked in Thomas Hunt Morgan's laboratory, whereas others argued that nucleic acids were the fundamental elements of life. (67) No one had been able to prove this either way until a series of ingenious experiments conducted in 1944 by Oswald Avery, Maclyn McCarty, and Colin MacLeod showed that nucleic acids constituted genes. (68)

Working with pneumococcal bacteria, the cause of pneumonia, Avery, McCarty, and MacLeod showed that a benign or harmless strain of pneumococci could be made virulent if mixed with dead bacteria from the same species of pneumococci that were of the virulent type. The benign strain somehow picked up the characteristics of the virulent strain and itself became a deadly form of the bacteria. Just how did this happen? How did the bacterium transform itself? Somehow, a substance in the dead virulent strain was picked up by the

active strain. This "transforming principle," as it became known, altered the bacteria. To show this, the scientists isolated proteins from the virulent strain and mixed them in a laboratory culture with the benign strain. No effect was measured—the bacteria were unchanged. However, when nucleotides from the virulent strain were isolated and mixed with the benign strain, the bacterial culture turned virulent. There it was. They had purified the bacterium's proteins from its nucleic acids. DNA was the transforming material and the chemical component of genes. One biologist called the findings "electrifying" and became "convinced that it was now conclusively demonstrated that DNA was the genetic material." (69)

Every living thing on Earth—every plant and animal, every bacterium, and even viruses—shares one of the most fundamental structures of life, molecules called nucleic acids. When DNA came to be known as the stuff of heredity, focus immediately shifted from simply understanding its function to understanding its physical structure and chemical characteristics as well. Although work in this area had begun over 70 years earlier in Germany when Friedrich Miescher discovered nucleic acids in 1869, it was Avery, McCarty, and MacLeod's discovery that unleashed what one observer called a "veritable 'avalanche' of nucleic-acid research." (70) Many scientists in related fields excitedly began studying DNA, including biochemist Erwin Chargaff, who remodeled himself as a molecular biologist and shifted his work to studying nucleic acids. This was a particularly common move among biochemists, who were well suited for DNA research because of their training in chemistry and biology.

With DNA's structure as yet unknown, Chargaff turned his attention to the chemical characteristics of nucleic acids. In DNA there were four known bases—adenine, guanine, cytosine, and thymine–which are commonly referred to by their first letters, A, G, C, and T. Each of these bases has different structures and characteristics. Analyzing the number of these bases with a chromatographic technique, Chargaff came to a startling conclusion—in all the organisms he studied the amount of A in any given cell was always equal to the amount of T in the same cell. The same went for G and C. The ratio of A to T and G to C was always 1. This 1:1 ratio became known as Chargaff's rule and is still one of the cornerstones of molecular biology. (71)

Chargaff's rule

$$\%A = \%T, \%G = \%C$$

and

$$A + G = C + T$$

Many wondered how Nature could be so exact across all species on Earth. The significance of Chargaff's rule would not be entirely clear until the three-dimensional structure of nucleic acids was determined. To do this, scientists had to take an actual look at the physical structure of DNA, which they began to do in the 1940s. Once they "saw DNA," the pieces of the puzzle fell into place very quickly.

A STRUCTURAL MILESTONE

Genetics in the twentieth century saw many milestones, including the work we have already described by scientists like Morgan, Avery, and Chargaff. This work and the work of their collaborators and colleagues propelled the revolution in genetics forward. Their discoveries alone are striking for the ways in which they advanced thinking in heredity. The discovery of the structure of DNA in 1953, however, has garnered all of the headlines. On both sides of the Atlantic scientists were working on cracking the structure of DNA. Solving this puzzle was important because it would expose the fundamental structure of heredity and show how the molecule at the center of life replicates itself and functions. Although chemists had already identified the molecular components of DNA—"that nucleic acids were very large molecules built up from smaller building blocks, the nucleotides"—James Watson remembers that in the years preceding the discovery of DNA's structure "there was almost nothing chemical that the geneticist could grasp at." (72) Three prominent groups worked on solving this problem: James Watson and Francis Crick at Cambridge University, Maurice Wilkins and Rosalind Franklin at King's College, London, and Linus Pauling and Robert Corey at the California Institute of Technology.

Work on unraveling the structure of DNA was most intense during 1952 and early 1953. In January 1953 Pauling's group claimed that it had solved the puzzle, proposing that DNA was a triple-stranded helix. Pauling, who had already uncovered the structure of proteins, was perhaps overzealous in his

Figure 1.8 James Watson and Francis Crick are seen here at Cambridge University around the time of their discovery of the structure of DNA. *Credit: DNA Learning Center, Cold Spring Harbor Laboratory*

pursuit of deciphering the structure of DNA, and as a result, one of the greatest chemists in the world made an error in his calculations. (73) Scientists in England quickly picked up on Pauling's mistake. Watson and Crick recognized the error immediately as one they had almost made more than a year earlier. In the wake of this miscalculation they quickened the pace of their own research. (74)

In the early 1950s the Cavendish Laboratory at Cambridge University housed an amazing faculty of physicists, biologists, and chemists who helped create an atmosphere in which Watson and Crick could conceive of and construct models of the structure of DNA. One of the important experimental tools that Watson and Crick utilized was "pictures" of molecules. This required special physical and chemical techniques because molecules are so small. Snapshots could be taken of these extremely small molecules by first making crystals of proteins and other small molecules like nucleic acids. To take a "snapshot" of DNA, small waves of X-rays were passed through the crystals. The diffraction of these X-rays by the atoms in the DNA crystal were in essence "pictures" of these extremely small molecules. This technique, known as X-ray crystallography, allowed the scientists at Cavendish and other laboratories to interpret the three-dimensional structure for any molecule that could be crystallized.

Rosalind Franklin, a physical chemist at King's College, London, was also working on solving the structure of DNA and happened to be one of the world's leading X-ray crystallographers.

Figure 1.9 Once called the "dark lady" by her colleague Maurice Wilkins, Rosalind Franklin's valuable scientific work and her important role in the discovery of the structure of DNA have often been overlooked. *Credit: DNA Learning Center, Cold Spring Harbor Laboratory*

Her DNA photos were once described as "among the most beautiful X-ray photographs of any substance ever taken." (75) Just a few weeks into 1953, one of these snapshots was shown to James Watson without her knowledge or permission. Watson wrote in *The Double Helix*, his memoir of the discovery of the structure of DNA, that "the instant I saw the picture my mouth fell open and my pulse began to race." (76) Franklin's superior X-ray crystallography enabled Watson and Crick to take the intellectual leap they had needed to complete their model of DNA.

Using X-ray data, including the measurements of the shape of DNA shown in Franklin's photo, Watson and Crick, piece by piece, figured out that DNA was shaped like a spiral staircase or a double helix. (77) The hereditary molecule was two chains of nucleic acids connected to one another like two snakes coiled together. The sugar backbones of the nucleotides are like supports under each step in a staircase. The nucleotide bases bond to form structures that are like steps, each one rotated slightly in relation to its neighbors in the stack. The steps that span from rail to rail of each side of the staircase are of equal length because of the specific way that two nucleotides pair. To develop their model of DNA, Watson and Crick followed Chargaff's rules closely and discovered that the double helix was complementary. That is, to form the staircase an A on one strand is always directly across from and connected to a T on the other; likewise, a G on one strand is always directly across from and connected to a C on the other. The complementary nature of the double helix revealed how DNA replicated itself and passed genetic information between generations. This process occurs during cell division when the double helix splits apart and makes identical copies of itself.

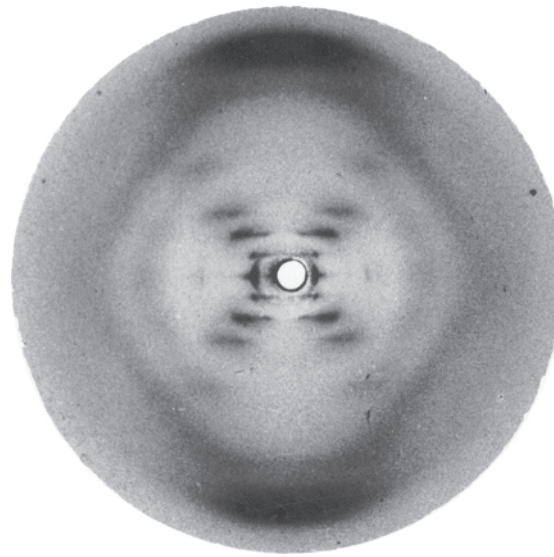

Figure 1.10 Franklin's X-ray crystallography of DNA, shown to James Watson without her knowledge, helped Watson and Crick solve the puzzle of DNA. Franklin was renowned for her X-ray crystallography talents. *Credit: Normal Collection for the History of Molecular Biology*

Chargaff's rules made Watson and Crick's three-dimensional model a reality. The great strength of Watson and Crick lay in their ability to reconcile their model with existing science. None of the other participants in this discovery put the pieces together quite as Watson and Crick had. And so they built their model.

There are three important chemical forces that hold together the DNA molecule. The first chemical bond, hydrogen bonds between a G and a C or an A and a T, connects the two strands of the helix. These bonds are relatively weak and can be broken apart by acids and/or heat. At approximately 90 °C the hydrogen bonds across a double helix can be broken, allowing the two strands of the double helix to separate.

The second kind of bond, the phosphodiester bond, keeps the Gs, As, Ts, and Cs together along a helix's strand. These bonds can be made on both ends of a base and to any other base, resulting in long strands of Gs, As, Ts, and Cs. Phosphodiester bonds are the strongmen of the helix, withstanding high

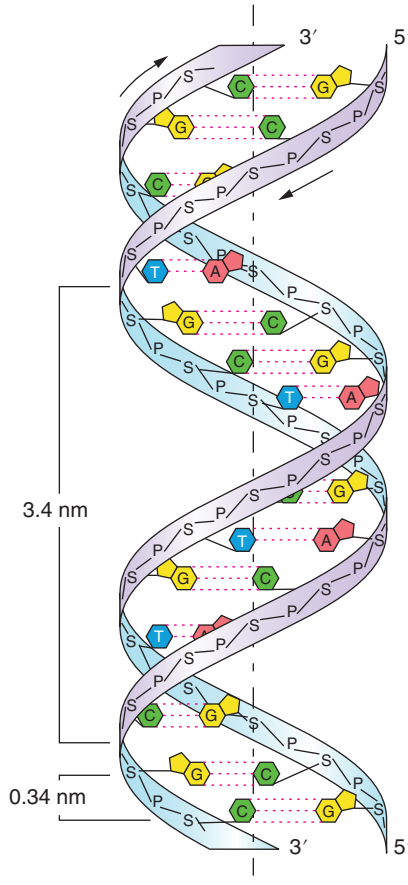

Figure 1.11 This diagram shows the double helix structure of DNA. In the model you can see where hydrogen bonds bond the nucleic acids to one another and also the sugar-phosphate backbone that holds the helix in place. *Credit: Wiley Publishers*

temperatures and even highly acidic conditions. It is the position of these bonds on the nucleotide carbon rings that gives DNA its helical twist, its third dimension. Molecular biology takes advantage of the characteristics of both hydrogen and phosphodiester bonds all the time. Because of the difference in relative strengths between these bonds, scientists would later figure out how to separate the two DNA strands. Why is this so important? Because to make copies of a double helix, you need to have both strands—let's call them the Watson and Crick strands—as a template. If they are bonded in a double helix, they cannot be used to replicate themselves. By melting the weak hydrogen bonds between the two strands, the freed strands can now be copied.

The race to uncover the structure of DNA became the stuff of scientific legend after the publication in 1968 of James Watson's *The Double Helix*. Watson's telling of the DNA story drew ire from within the small community of scientists in which he himself worked. Facing strong objections from Francis Crick, Linus Pauling, Maurice Wilkins, and the family of Rosalind Franklin over the way in which Watson characterized all of the major players in the discovery, Harvard University Press dropped the book. (78) Of particular concern was Watson's portrayal of Franklin, who was just 37 when she died in 1958 of ovarian cancer and whose role in the discovery was reduced in *The Double Helix* to that of an incompetent scientist and hot-tempered woman. (79) Watson's book, picked up by another publisher, went on to become a best-seller, and for almost 30 years the story of the discovery of DNA was told by *The Double Helix*. It is only recently, with the publication of a new biography and with acknowledgments by Watson that Franklin's work was "key" to their success, that Franklin's image as a brilliant scientist was rehabilitated. Years after his own co-discovery of the structure of the double helix, Francis Crick suggested that Franklin was just months away from solving the puzzle herself. (80)

As late as 1933, Thomas Hunt Morgan suggested that there is "no consensus opinion amongst geneticists as to what the genes are—whether they are real or purely fictitious." (81) Working deductively, working on instinct, Morgan could never be sure that his gene maps or the work on genes conducted by his many colleagues amounted to anything. But beginning with Avery, McCarty, and MacLeod's discovery in 1943 that DNA was the "stuff" of heredity, the gene became less an intellectual or theoretical entity and more a material reality. Watson and Crick's discovery of the actual physical structure of DNA finally created a consensus among geneticists that genes were real and led genetics and molecular biology into a new and exciting realm. With the basics of heredity worked out, molecular biology became a driving force in science as the working characteristics of the gene came under scrutiny and study.

To complicate matters, research on and expansion of ideas about how phenotypes might be generated in a heritable fashion apart from genetics first formulated by C. H. Waddington and called epigenetics have made the biology of genes and inheritance even more complex and interesting. Epigenetics is what its name from the Greek implies—"beside genetics". More precisely it concerns the expression of heritable phenotypes without changes in the DNA of

the genome. In other words, epigenetic effects are heritable phenotypic effects without changes in genotype. The most famous case used to demonstrate this phenomenon is the Dutch Hunger Winter. A follow-up study done on women who suffered through all or part of this 5-month-long famine that occurred near the end of World War II (the cause of the famine—which killed 20,000—was a Nazi blockade of food and fuel) revealed some important "heritable" problems. (82) It was reported that during the height of the famine, average caloric intake was less than 400 calories per day (the equivalent of say four pieces of toast). After the war a long-term study of people who survived the famine was undertaken to determine the impact of famine on the offspring of women whose children were exposed prenatally to famine. As Laura C. Schultz puts it "the Dutch Hunger Winter study, from which results were first published in 1976, provides an almost perfectly designed, although tragic, human experiment in the effects of intrauterine deprivation on subsequent adult health." (83)

The sad but remarkable results were that diabetes, obesity, microalbuminuria (a kidney malfunction), psychological and cognitive problems, and cardiovascular disease were seen in higher frequency in the offspring of women who lived through the famine than in the offspring of children of their siblings who were not exposed to famine. More remarkable was that women whose fetuses experienced the famine later in prenatal development were affected more severely than fetuses who experienced the famine earlier in their prenatal development (those fetuses that were conceived close to the end of the famine). Researchers could clearly show that this phenomenon was not due to DNA sequence changes. What then could cause this drastic change in the susceptibility to the offspring of women exposed to famine?

To understand this phenomenon completely we need first to describe the structure of DNA as it resides on our chromosomes. The DNA of our chromosomes is wrapped into what is called chromatin. First, the double helix is wrapped twice around a protein complex called a histone core. The histone cores have short parts of their proteins that "tail" off of the wrapped DNA. These "histone tails" are where the epigenetic action takes place, because these parts of the histone proteins can easily be modified by chemical reactions like the addition of methyl groups or acetyl groups. If a histone tail is methylated (or phosphorylated, acetylated, ubiquitylated, or sumoylated) this modification changes the shape of the histone core and disrupts the tightly wound chromatin altering the availability of the DNA in that region to transcription and hence gene expression of that region of the chromosome. Methylation can also occur on the DNA strand itself and this alters the availability of the region of DNA that is methylated to transcription.

Researchers were able to examine the methylation patterns of the DNA in an important gene called insulin-like growth factor II (IGF2) of women who suffered through the Dutch Hunger Winter. Six decades after the famine, women exposed to it had much less methylation of IGF2 than women who escaped the famine. The implication of the study is that early mammalian development is an incredibly important stage where DNA sequences are highly prone to

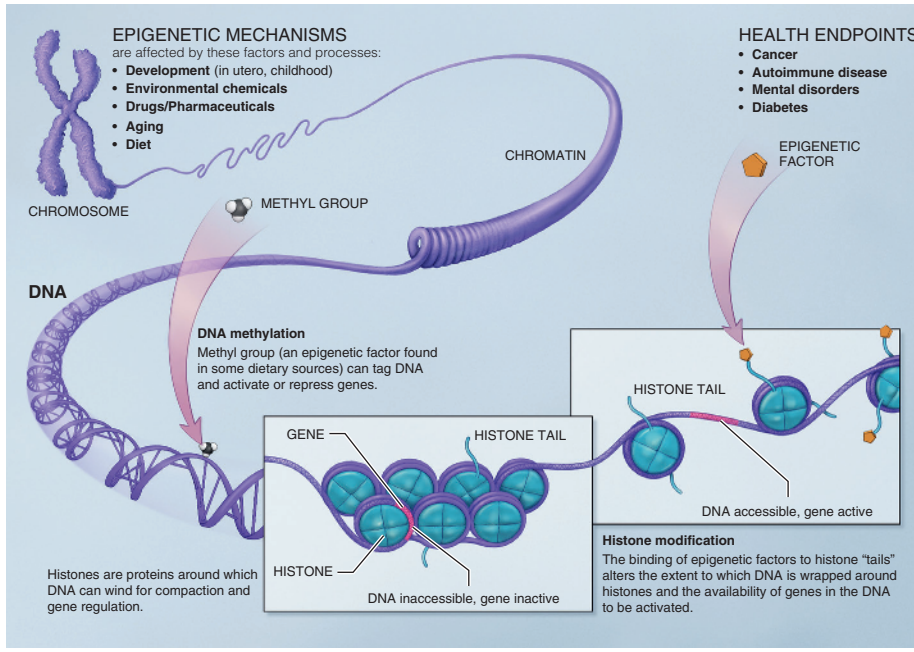

Figure 1.12 The mechanisms of epigenetics. *Credit: National Institutes of Health*

methylation tags as a result of some environmental shock like famine. Such methylation alters the gene expression of important genes involved in many phenotypes. More importantly, these methylation patterns can persist for long periods of time.

The Dutch Hunger Winter case is only one of many where epigenetic factors like DNA methylation and histone modification have an impact on human health. Epigenetic factors are also important in other organisms and have been implicated in many evolutionary phenomena. (83)

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