The Winding Road to Discovering the Link between Genetic Material and DNA

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Abstract

This is an account of the three-centuries long journey to the discovery of the link between DNA and the transformation principle of heredity beginning with the discovery of the cell in 1665 and leading up to the 1953 discovery of the genetic code and the structure of DNA. This account also illustrates the way science works and how scientists do science as well as the fact that scientists are also subject to the same human foibles and short-comings as people in any field of endeavor. Their use of the scientific method helps them find the path back from false starts and erroneous conclusions but does not assure a smooth progression toward the truth. What emerges from this example is the scientists' search for explanations based on empirical evidence, with the goal of trying to disapprove, rather than prove, a given theory and explanation. As scientific knowledge increases, answers to scientific questions may become outdated, or they may generate a new set of questions that require new ways of thinking and conducting experiments. Science educators have already recognized the value of historical materials and events in fostering an accurate understanding of science and in achieving desirable, positive and realistic attitudes toward science and in developing scientifically aware citizens. This is simple because the history of science can provide a vital background for students, detailing how science and scientists work and how scientific knowledge is created, validated, and influenced. However, desirable attitudes and behaviors toward science are not likely to be achieved unless history of science is learned and appreciated by all young citizens. Thus, there is a need for educators to involve, investigate, and explore the application of historical science and to show how this can contribute to accurately and explicitly show what science is, how it works, how scientists operate as a social group and how human societies direct and react to scientific endeavors both locally and globally (McComas, 2015, Cherif, 1988, Klopfer, 1969). And it is here where the history of science, the nature of science and how scientists do science is of enduring interest to us as well as to many educators in the scientific community. For those who might use this essay as classroom reading material, we provide a set of questions as an appendix that teachers and faculty may use to reinforce understanding of the essay**.**

Key Words: DNA, Genetic Code, Scientific inquiry, scientific discovery, Scientific method, Empirical evidence, Theory and explanation, How science works, Humanity and civic engagement

1.   Introduction:

From the 17th century to the 20th century, the discovery of DNA and its link to genetic material began before the words *science* and *scientist* had even been coined (NPR 2010). To understand how far genetics has come, we will travel the path from 1635, when the cell was discovered, to the modern era where genetic engineering has spread beyond the laboratories of colleges, universities, and hospitals, to residential garages, closets, and backyards (Wolinsky, 2009; Bloom, 2009; Charisius, Friebe, and Karberg, 2013 a,b &,c; Wohlsen, 2015). Using scientific kits, amateur biologists are experimenting with DNA in their homes and backyards, well outside conventional laboratories (Bloom, 2009; Starr, 2009; Holloway, 2013; Wohlsen, 2015). This phenomenon

points to how far the fields of genetics, molecular biology, and biotechnology have come (Zimmer, 2012; Holloway, 2013).

For many years scientists had a difficult time accepting the fact that genes exist and could not agree on the nature of the transformation principle of heredity. Now people all over the world are able to purchase used equipment and cheap kits to experiment with DNA on their own. And parents can identify the genetic make-up of their unborn babies and make decisions that suit their understanding, beliefs, and circumstances.   But this account is about the winding road to the discovery of a link between the genetic materials and DNA. The reasons for this long and winding journey lie in several factors – the nature of the scientific method, and human nature itself (Cherif 1998).

In practice, science is a construction of the mind based on actual observations; it seeks to find better explanations for natural phenomena (Chopra, and Mlodinow, 2011; Willson, 1998; Futuyma, 1983). Science, by choice, "is limited to … questions that can be answered by the discovery of objective knowledge and the elucidation of natural laws of causation" (Futuyma 1983, p. 170).   The cornerstones of science are the concepts of testability and repeatability by agreed-upon empirical standards; other researchers must be able to obtain the same results by using the same procedures and materials. But another unfortunate component of science is human fallibility, called falsifiability. Sometimes scientists will believe so firmly in a hypothesis that they form the tests in a way that is certain to prove their theory, or misinterpret the data.

As Arthur Koestler has famously observed, "The progress of science is strewn, like an ancient desert trail, with the bleached skeletons of discarded theories which once seemed to possess eternal life" (Science Guardian 1989). Progress toward identifying the link between genetic material and DNA was not so much strewn with discarded theories as delayed in reaching its goals by the very human tendencies of otherwise open-minded scientists clinging to assumptions that were leading them down the wrong paths. Because of that we believe that it is important to give students some kind of historical material for its content and ideas so that they can learn and appreciate "how things have come to be as they are and that they might have been otherwise. It must be used to enlarge horizons, to shake complacency, and to stir the imagination." (Barrow, 1980; cited in Cherif, 1988, p. 33).

2.   Discovery of the Cell

A good place to start this journey is with the English physicist Robert Hooke (1635-1701), who reported to the Royal Society of London what he had seen under a microscope. With only thirty-times magnification, he saw a pattern of tiny rectangular holes in a thin slice of cork from the bark of an oak tree, and then saw a similar pattern in bones and plants. What he saw reminded him of the chambers in the Catholic Church, and thus, in 1665, he described and called them cells in his book *Micrographia: Or Some Physiological Descriptions of Miniature Bodies by Magnifying Glass.* Hooke's work contained drawings of the most outstanding microscopic observations ever made. In this book he "revealed to an enchanted public a universe of the very small that was far more diverse, crowded, and finely structured than anyone had ever come close to imagining" (Bryson 2003, p. 374). However, because Hooke's observations were limited by the magnifying power of his microscope, it was difficult for him to learn much about the internal structure and organization of cells. He couldn't draw the connection between cells and the basic components of life, "believing the structures to be cross sections of channels through the plant" (Daniels et al., 2007). He did observe that other plant tissues were filled with a juice-like substance, but didn't realize, for example, that he was seeing living cytoplasm.

Eleven years later, the London scientific community was shocked by an announcement from a Dutchman with an unquenchable curiosity, Anton van Leeuwenhoek (1632-1723), who not only claimed to have used microscopes that reached up to 275-times magnification, but also described for the first time microscopic organisms that he called animalcules. (We know them as bacteria today.) Many members of the Royal Society, including Hooke himself, wondered if this could be possible. Though Leeuwenhoek was not trained as a scientist, he made an improved microscope for every experiment he performed. One year later, in 1677, he used one of his single-lens microscopes to observe and describe spermatozoa. Leeuwenhoek didn't interpret his findings, just reported them, including these substances: bread mold, a bee's stinger, blood cells, teeth, hair, his own saliva, excrement, and semen. Most of these had never been seen microscopically before. All his findings were accompanied by exquisite drawings!

At first, the Royal Society was skeptical of Leeuwenhoek's discovery of microscopic one-celled organisms, partly because he was very secretive about his lens manufacturing techniques. Indeed, we still don't really know how he got such precise magnifications from his relatively primitive hand-held microscopes. It took the Royal Society a year using the latest devices of English technology to reproduce Leeuwenhoek's discoveries. Leeuwenhoek spent fifty years of his life reporting his discoveries of "little animals," or protozoa.

Through the late 1670s, Leeuwenhoek continued to send comprehensive data and detailed drawings of his sightings of bacteria and algae to the Royal Society, which gradually confirmed his results. In 1680 the Royal Society extended its prestigious membership to Leeuwenhoek, who continued to devote his time and energy to scientific research and made several vital discoveries even beyond the field of science.

However, Leeuwenhoek's discoveries of bacteria and spermatozoa were more or less ignored for many years. Fortunately, in the 1860s, German physicist Ernst Abbe discovered a formula that could be used to enhance microscopes and produce sharper images, a formula that is still being used today to improve microscope design. In 1873, Ernst Abbe worked out a complete theory explaining how lens-generated images were produced in the microscope. He collaborated with the lens maker Carl Zeiss in the development of an improved microscope that provided sharper images, ending a frustrating period of trial-and-error in microscope building. The outcome of this collaboration led to the production of new Zeiss lenses that could observe objects measuring only 0.2 micrometers.

Finally, Leeuwenhoek's neglected discovery of bacteria was "rediscovered" by Louis Pasteur and Robert Kock in 1876. Despite the fact that Leeuwenhoek's work had opened up a totally new microscopic world, neither Hooke, van Leeuwenhoek, nor any of their contemporaries truly understood that cells themselves were living entities. It was not until lenses and microscopes had significantly improved that scientists began to understand the true structure and function of cells.

For almost 200 years after Hooke's discovery of the cell, scientists found cells in every organism they examined with a microscope. This in turn helped to change a few existing perceptions and led to new discoveries. For example, up to 1759, people generally believed that all organisms began as tiny minatures of the adult form inside the seed or sperm. But Kaspar Friedrich Wolff (1733-1794) was able to introduce the idea that plant and animal embryos started as unspecified cells that later differentiated into separate tissues, organs, and organ systems.

3. Discovery of the Cell Nucleus

In 1824, Henri Dutrochet (1767-1847) stated that animals and plants had similar cell structures, and in 1831, British botanist Robert Brown (1773-1858), discovered a little kernel or body within every cell that composed plant tissues. He named the kernel the nucleus. While others may have noticed the same thing, Brown was the only one to recognize it as a regular feature of plant cells. Around the same time Matthias Schleiden (1804-81) used the word *nucleolus* to describe a structure seen inside the nucleus, the part which now is known to be involved in the production of ribosomes.

The excitement of the discovery of the nucleus and nucleolus had raised storms of new questions that required further study. What else could be inside this nucleus? What role, if any, does the nucleus play in the survival of the cell, other cells, and in cell reproduction? What role, if any, does the nucleolus play within the nucleus and the cell itself? Could there be more than one nucleus for a given cell? Could there be a type of cell without a nucleus?

Questions such as these triggered a quest for discoveries. Studies conducted just a few years after Brown's discovery of the nucleus included those by the botanist Matthias Schleiden (1804-81) and the physiologist Theodor Schwann (1810-82). In 1838 Schleiden came to the conclusion that all plants were made of cells and that every plant came from a single cell. One year later Schwann reached the same deduction about animal cells. Thus both investigators concluded that all living things are made up of cells. Schwann published his observations in a book that stated two basic tenets of cell theory: (1) all organisms are made of one or more cells and (2) the cell is the basic unit of structure for all organisms.

Almost nineteen years after Schwann published his findings, the German pathologist Rudolf Virchow followed up on Brown's work by publishing *Cellular Pathology* (1858)*, in which he added a third important observation, supporting the work of Robert Remak, and proposed that all cells come from pre-existing living cells. The accumulation of these three scientific deductions led to the development of cell theory, which was first suggested

by Schleiden and Schwann in 1839, but later revised and expanded to include Virchow's notion that all cells arise from previously existing cells.

Scientists were very excited about the refinement of microscopy and advances in laboratory techniques. In 1873, Ernst Abbe discovered how to make lenses that provided sharper images for an improved microscope, though one with continuing problems. Since the interior of a cell is transparent, it was hard to differentiate the structures that were gray on gray. Then it was discovered that synthetic dyes (started by Perkin in 1856) could combine with some intracellular structures but not with others. The process allowed Robert Remak (1836-1921) to see and describe cell division. This revolutionized the study of cells and enabled scientists for the first time to clearly see, distinguish, and study various inner parts of the cell, including the nucleus and its contents. But the question remained: do all cells have a nucleus? Today scientists know that bacterial cells don't have a defined nucleus, but rather a region that is known as a nucleoid. In humans, red blood cells are the only cells that do not have a nucleus and must be produced in the bone marrow because they cannot divide.

4. Discovery of Chromosomes

It didn't escape observant scientists that weird things were taking place within the cells and the nucleus. The German botanist Eduard Adolf Strasburger (1844-1912) was the first to observe the nucleus of a dividing plant cell as well as some of the changes that took place during cell division among plants. In 1875, he described the material within the nucleus (which would later be called chromosomes by Wilhelm von Waldeyen-Hartz). In 1876-77, Strasburger successfully observed a sperm nucleus of a plant (and no detectable cytoplasm) entering the egg during plant fertilization. During the same period, Oscar Hertwing and Hermann Fol were able to observe that the nucleus of the sperm enters the egg during animal cell fertilization. By 1882, Strasburger concluded that new cell nuclei can only arise from the division of other nuclei and recommended dividing the protoplasm into two regions—one inside the nucleus, which he called nucleoplasm, and the other, which he called cytoplasm.

By now, the use of synthetic dyes had become common in biological laboratories and enabled scientists to conduct more essential studies. For example, the German anatomist Walter Flemming (1843-1905) used a dye that combined with a material in the form of filaments inside the nucleus that he had found to be the main constituent of chromatin (from the Greek word for color). Flemming, who was the first scientist to follow the chromatin filaments through the entire process of cell division, observed that during cell division the chromatin collected into short threadlike objects. He named this process mitosis, from the Greek word for thread.

In 1882, Flemming summarized and published his observations in *Cell Substance, Nucleus, and Cell Division*, in which he described mitosis in careful detail including the behavior of the stained filaments (chromatins) during cell division. Flemming's discoveries excited many scientists, spurring them to delve deeper into what was going on within cells.

One year later, Carl Nageli and August Weismann proposed the existence of a genetic material, which Nageli called idioplasm but Weisman subsequently termed germ plasm. The same year, Wilhelm Roux proposed that "the most important event of mitosis is the equal partitioning of 'nuclear qualities' to the daughter cells" (Brooker 2011, p. 60). In 1883, the Belgian cytologist Edouard van Beneden next made two significant discoveries. First, he found that the number of stained filaments of the chromatins (later called chromosomes) in the cells of a particular species was always the same, and that the number varied from species to species. Second, he discovered the role of these stained filaments in the formation of the sex cells. He noticed that instead of doubling with each cell division, the number of chromosomes reduced to half the usual number in the egg and sperm at the end of each cell division. This halving of genetic material in cell division was called *meiosis* (from the Greek word, to make smaller) to be distinguished from mitosis. This made sense since everyone was aware that humans gave birth to humans and cats to cats, and so on.

In short, Beneden was able to show that gametes contain only half the number of chromosomes and that fertilization restores the normal diploid number of the chromosomes. Together Flemming, Beneden, and Strasburger elucidated chromosome distribution during cell division. Furthermore, the collective set of scientific observations led Hertwing, Strasburger, and Weismann to confidently propose in 1884-85 that these stained filaments of chromatins were in fact the carriers of genetic material.

The following year, and based on his own studies and Walter Flemming's description of the behavior of stained filaments of chromatins during mitosis, Strasburger clarified the role that the stained filaments play in heredity— the fact that the content of the nucleus didn't disappear during cell division as previously thought—and also

coined the terms *chloroplast*, *cytoplasm*, *haploid*, *diploid*, and many more. Also in 1884, Strasburger, Hertwing, von Kolliker, and Weismann independently determined that the cell nucleus serves as the basis of inheritance. Six years later, these stained filaments or threadlike structures of chromatins were renamed chromosomes (from the Greek word meaning colored bodies) by the anatomist Heinrich von Waldeyer-Hartz.

The question then became, what constitutes the chemical structure of a given chromosome? The initial seeds for the development of the chromosomal theory of inheritance had inadvertently begun.

5. The Cell's Nucleus and the Discovery of Nucleic Acid

Fourteen years prior to the publication of Flemming's book, the young Swiss biochemist Johann Friedrich Miescher (1844-95) became fascinated with the concept of life and its building blocks. He moved to Tübingen to work with biochemist Hoppe-Seyler to explore the secrets of the life. Like most scientists who were interested in this area of study, he first focused on proteins and investigated the proteins in leucocyte cells. While working on his experiments in 1869, he took some remnants of white blood cells in pus from stained bandages that were isolated from the nucleus and extracted from them a substance with unexpected properties. To his surprise, the substance did not match those of proteins nor any known organic matter. It contained both nitrogen and phosphorus, and thus didn't belong to any of the three known food classes: fats, proteins, and carbohydrates. He knew that lipids are chains of hydrocarbons that repel water and are useful in forming protective biological membranes; that proteins are chains of amino acids responsible for many metabolic, structural, and chemical processes in the living body; and that carbohydrates are chains of sugar molecules with their distinctive ring-shaped structures and are the main source of energy for the body. So what role did this organic compound play in life? By this time, he was comfortable in proposing that a cell's nucleus probably had a specific chemistry.

Miescher then approached Hoppe-Seyler seeking confirmation of his discovery. Hoppe-Seyler further investigated the newly discovered substance. When he discovered a similar substance in yeast, it was named *nuclein* because it originated in the cell nucleus, and the discovery was announced as the first crude purification of nuclein. Later, when scientists discovered it had acidic properties, it was renamed *nucleic acid*. Miescher continued to examine the properties and composition of nucleic acid and by 1874 was able to isolate a refined amount of nucleic acid, an acidic, phosphorus-rich substance.

Miescher's discovery of nucleic acid was significant, although the molecular structure remained unknown for thirteen years more. This changed when the biochemist Albrecht Kossel (1853-1927) was able to separate the proteins and the nucleic acids from each other and then spent more than fifteen years working on the nucleic acid itself.

During these fifteen years, Kossel systematically set about studying and experimenting on nucleic acid and discovered that it consisted of phosphoric acid, a nitrogenous base, and sugars, structured in basic units called nucleosides. Specifically, he was able in 1885 to obtain from the nucleic acids substances that included double ring purine and single ring pyrimidine molecules. He showed how purine was composed of a six-membraned ring attached to a five-membraned imidazole ring, while the pyrimidine molecule was made up of a single six-membered heterocyclic ring of atoms, four carbons, and two nitrogens. Kossel also isolated two different purine bases, adenine and guanine, and three different pyrimidine bases, uracil, cytosine, and thymine. A nucleoside, which is a complex nitrogen-containing molecule, is always formed from a nitrate base, purine or pyrimidine, and a sugar, either ribose or deoxyribose. But he was not sure which type of sugar was present at that time. Kossel's work helped in opening a fundamental chapter in the field of genetics, and he was awarded a Nobel Prize in physiology and medicine in 1910.

Kossel continued his studies, motivated by his findings of the biological functions of the chemicals he studied and isolated. In 1912 he strongly restated his conviction about the importance of nucleic acids and cellular proteins as the chemical basis for genetics. Despite the fact that Miescher and Kossel's work was well known only among specialized scientists in the field, their work contributed to a greater understanding of heredity and triggered a new field of science known as molecular biology. But the question remained: which one constitutes the genetic material—the protein, the nucleic acid, both, or neither?

This is where the chemist Phoebus Levene (1869-1940) comes in, and we will meet him again later in our journey of discovery. Levene was a gifted research chemist, but even the gifted sometimes miss the point. In 1909 he discovered that ribose was the sugar in ribonucleic acid (RNA) and identified several of the components

in deoxyribonucleic acid (DNA), but he, along with many of his colleagues, thought that the genetic material was stored in the chromosomes, not in the DNA.

6.   Discovery of the Principles of Inheritance

People have been aware for a long time that we are conceived from mothers and fathers and develop into whole beings with multiple organs and organ systems. We have also understood that our offspring are born with some range of characteristics or traits resembling those of their parents. What we did not know until very recently was how genetic material was passed down to offspring. Long before understanding the nature and mechanisms of heredity and natural selection, farmers practiced selective breeding to achieve or preserve desirable traits among plants and animals. Unknown to the farmers, however, was the fact that through their selective breeding they were actually changing the gene pool of these living populations.

Despite the fact that farmers were inadvertently experimenting with genetic material and creating improved or new traits, scientific advancements in the field of genetics were slow and the scientific community remained unaware of how traits were passed on. It was not until three quarters of a century after Kossel's discovery of nucleic acid that the true and overwhelming importance of nucleic acid was realized. By now many aspects of the cell were known, including the fact that living organisms are made of cells, that cells contain cytoplasm and a nucleus, and that the nucleus contains chromatins which can be condensed to threadlike objects called chromosomes. In addition, it was known that mitotic division was a type of cell division that results in the formation of two daughter cells, each of which contains exactly the same number of chromosomes as the parent cell. Furthermore, DNA and its chemical structure were also known. While all of this information was of the highest significance, scientists were unable to draw the proper deductions because they did not know much about the principles of inheritance, and Mendel's genetic work was not yet rediscovered.

When Darwin wrote *On the Origin of Species*, one thing he couldn't explain was how species actually originated. He explained how a species could become stronger, faster, fitter, or better adapted, but not how a particular species came into being. A Scottish engineer, Fleming Jenkin, noticed a flaw in Darwin's theory. How could desirable traits continue to be passed on to progeny? Like whiskey being diluted with water, each subsequent generation would become more diluted until the trait would completely disappear. How could traits continue generation after generation?

7.   Inherited Characteristics

Among the scientists who made significant contributions to the understanding of the concept of heredity was Gregor Johann Mendel (1822-84), a botanist and Augustinian monk who was a contemporary of Darwin and indeed read his *On the Origin of Species*.

In addition to his program of self-education and a love for horticulture, which had begun in childhood on his father's farm, Mendel studied physics, chemistry, zoology, and botany at the University of Vienna. Upon his return to the Augustinian monastery in 1854, he was asked to teach natural sciences at the monastery's technical institute in Brno. In 1856 Mendel started his botanical investigations in the monastery gardens. Mendel had access to the monastery library, which was well endowed with works on horticulture, botany, and agriculture, as well as other areas of natural sciences. Furthermore, while there is evidence that Mendel had read Darwin's book, it is not known whether he had come across Darwin's idea, stated in 1868, that "each cell can produce a seed capable of producing an identical cell." We can conclude that he was not only intellectually ready and capable but also in an environment suitable for engaging in the research of discovery.

Using his knowledge in botany, mathematics, and natural sciences, as well as his own experience with and love for horticulture, Mendel conducted research for eight years on pea plants, carefully documenting characteristics such as size, color, smoothness or wrinkling of seeds, position of flowers on the stem, and so forth. Mendel first of all noted that:

> When he crossed a dwarfed plant with a tall one he did not produce a medium-sized plant but a plant bearing the characteristics of one of its parent plants, which he was the first to call the dominant characteristics. However, when he reproduced this plant by self-fertilization, the characteristics of the grandparents always reappeared in the same proportion: three-quarters dominant to one-quarter recessive. Furthermore, these second generation hybrids always comprised one-quarter of individual plants resembling the original pure variety of one of the grandparents, another quarter resembling the pure variety of the other grandparent, and the remaining half resembling the hybrids of the first

generation. He therefore concluded that "It is now clear that hybrids produce seeds which possess one or the other of two different characteristics." He then deduced that there existed units of heredity, which would later be discovered as genes, which go in pairs and divide in the descendants. He called them AA and aa for the original constant (pure) varieties and Aa for the hybrids, a method of notation still used today.

(Messadie 1991, p. 90)

By observing and analyzing the inheritance patterns in pea plants, Mendel was able to deduce the fundamental principles of genetics by showing how inheritance could come in discrete packets of information called factors, which go in pairs and divide in the descendants. He showed how these factors, unseen by the eye, statistically control the inherited traits that peas possess following specific and regular mathematical ratios, which he successfully used to formulate the first scientifically sound laws of heredity. Specifically, he showed that when two factors combine, they produce an inherited pattern that can be counted and statistically measured.

The results of Mendel's empirical work were first presented in two lectures that he gave in 1865 to the newly founded Society of Natural Sciences in Brünn. The text of the lectures was published the following year in the Society's bulletin as two separate papers, one of them titled "Experiments on Plant Hybrids." In these papers, he concluded that hereditary factors involved in such attributes as short and tall, green and yellow, and wrinkled or smooth appearance of peas were controlled by mathematical rules following specific and regular ratios (Collins 2006). The bulletin of the Society of Natural Sciences was sent to various scholarly societies throughout the world but failed to arouse any interest. Mendel died in 1884, in complete obscurity.

It was thought that Mendel himself might not have understood the significance of his work. Whether this is true or not, Mendel's work was met with disinterest for 36 years. One reason could be because of the lack of understanding of chromosomes and their role of transmission in the process of inheritance. A second reason might be the lack of real empirical evidence and explanation for the differences and similarities among siblings and between parents and their children. A third reason could be that those who did read Mendel's work developed a suspicion of the accuracy of the results or of some sort of falsification in the outcomes of his investigation. The consensus of this type of criticism was that his outcomes seemed a bit too convenient:

The calculations which he published are a little too good to be totally true; they do not include the least margin for error, as if they had been given a push in the right direction by sheer genius. If this is indeed the case, it only serves to underline the power of his intuition! (Messadie 1991, p 91)

Whatever its causes, the skeptical reception of Mendel's work remains a prominent example of scientific obtuseness.

Before his death in 1884, Mendel reflected on the lack of interest in his findings within the scientific community: "My scientific work has brought me a great deal of satisfaction and I am convinced that it will be appreciated before long by the whole world." As we will see, Mendel was not only right, but also came to be highly regarded within the scientific community.

Unaware of Mendel's work, many other scientists kept searching for answers that Mendel's work had already provided. For example, in his 1893 book *Germ-Plasm: a Theory of Heredity* August Weismann concluded that there must be some sort of hereditary substance, though he was not sure what it was.

Furthermore, before the rediscovery of Mendel's work, Francis Galton (1822-1911), who invented the term *eugenics* in 1883 and was known for openly rejecting Jean Lamarck's idea of the inheritance of acquired characteristics, was an early advocate of hard heredity through selection alone. Through his own studies he recognized two sharply distinct classes of inherited characteristics: those which are alternative and those which blend—which he found in human eye color and human stature, respectively. When the parents differ in eye color, the children are like one parent or the other, the inheritance being characterized as alternative; but when the parents differ in height, the children are of intermediate stature, a blending effect (Castle 1933). Galton indeed came very close to rediscovering Mendel's theory of inheritance, but failed to make the eventual breakthrough because he was focused on continuous (polygenic), rather than discrete, traits.

Another important discovery made before the rediscovery of Mendel's work came from experiments conducted by biologist Hermann Henking. In 1891, while studying sperm formation of the Diptera insect, Henking noticed that not all the sperm cells had the same number of chromosomes. Some of them had 11 while others had 12 chromosomes. When he looked at the stages of meiosis leading up to the formation of the sperm cells, he

noticed not only the presence of a particular chromosome which was only found in half of the germ cells of the spermatozoa or spermatids, but also that the 12 chromosomes looked and behaved differently than the 11 chromosomes. Henking called this type of chromosome the "X" element because of its unknown nature. What was interesting was that when Henking used a light microscope to examine egg formation in female grasshoppers, he was unable to spot the X element. Later other scientists observed the same type of X chromosome in several other insects. Based on his observations, Henking hypothesized that this extra chromosome, the X element, must play some role in determining the sex of insects. He did not, however, find any direct evidence to support his hypothesis.

8.   Rediscovery of Mendel's Laws

Mendel was right in his prediction that when his work was rediscovered, it would be appreciated by the whole world. In 1900, sixteen years after Mendel's death, the significance of his work was realized and his principles and laws were finally recognized independently by Hugo de Vries (Netherlands), Karl Correns (Germany), and Erich Von Tschermak (Austria). As real scientists do, they attributed the rediscovery of the basic principles of genetics—the law of segregation, the law of independent assortment, and the concept of dominant and recessive characteristics—to Gregor Mendel. Then the English biologist William Bateson (1861-1926) and French scientist Lucien Cuenot (1886-1901) applied Mendel's laws to animal biology and discovered that heredity was governed by the same mechanisms defined in Mendel's work.

The rediscovery of Mendel's principle of heredity in 1900 spread among the scientific communities around the world and revitalized the search for a mechanism of heredity and its transformation principle. Many scientists aggressively continued, while many others began their investigations into the nature of hereditary material, the behavior of chromosomes during cell division, and the chemical composition of DNA.

Just one year after the rediscovery of Mendel's work, Thomas Montgomery was able to determine that maternal and paternal chromosomes pair with each other during meiosis, and C. E. McClung was able to show how the sex determination in insects was really due to the differences in chromosome composition. In 1902, Theodor Boveri "showed that when sea urchin eggs were fertilized by two sperm, the abnormal development of the embryo was related to an abnormal number of chromosomes" (Brooker 2012, p. 60). Working with grasshoppers, the American geneticist Walter Sutton (1877-1916) inferred that the behavior in meiosis followed the genetic phenomenon of which Mendel spoke. Based on this, Sutton showed how the chromosomes which seemed to disappear during interphase do not actually disintegrate but retain their continuity and individuality from one cell division to the next, an incredible achievement in science! But in 1906, William Bateson coined the term *genetic,* which really brought Mendel's work to the attention of the scientific community. This was only three years after the ultramicroscope was developed by Richard Zsigmondy and Heinrich Siedentopf, allowing users to see objects too small to be identified with an ordinary microscope.

Many studies provided additional support for Sutton's deduction, but the concept of heredity was still filled with confusion and fragmented information. A number of scientists still had doubts and decided to embark on studies to clear the confusion within the field. Among these scientists was the American Thomas Hunt Morgan (1866-1945), who throughout his life was engaged in a number of unrelated experiments simultaneously and who advanced the science of genetics through his groundbreaking work on fruit flies.

Just four years after the rediscovery of Mendel's experiments with pea plants, Morgan decided to test his theories. He had serious reservations about Mendelian inheritance and how "factors" were passed from one generation to another. The possibility that these factors might be carried by chromosomes existed, but Morgan was not convinced and began a series of experiments expecting to prove that the simple laws discovered by Mendel were not universally true. The results, however, made Morgan a late convert to Mendelism. He moved from challenging Mendel's paradigm-shifting laws of inheritance to supporting them; this eventually made gene mapping possible. The work led to his receiving the Nobel prize in 1933.

While Morgan was busy with his experiments, the Danish botanist Wilhelm Johannsen (1857-1927), who had already introduced the term *genotype* to mean genetic information and *phenotype* to mean the expression of that genetic information, suggested in 1909 that Mendel's 'factors' be called *genes*, a suggestion that was immediately adopted and which made it easier to communicate among scientists. But what caused Morgan to change his perspective on Mendel's work and findings?

9.   Entering the Race: Morgan's Path into Genetics

In 1907, Morgan started to work with the fruit fly *drosophila* as an experimental animal. He selected *drosophila* for many reasons, including that it has only four chromosome pairs in each cell, can easily be bred by the hundreds, reaches productive parenthood in 8-10 days, and has a relatively brief generation time of about two weeks. Thus multiple generations could be obtained and observed in only a few months.

Unlike Mendel's peas, however, the wild fruit flies available to Morgan did not come with genetic differences, so he had to wait. After two years, Morgan had seen no significant mutations, but in 1910 his group noticed for the first time a white-eyed male among a mass of ordinary red-eyed flies. They finally spotted mutant individuals having phenotypic modifications that were heritable. Working with one of his graduate students, Morgan tried to induce mutations in his fruit flies. They soon discovered that X-rays enhanced mutations and were able to produce 85 different phenotypes, each carrying a mutation in a different gene.

Eager to see what would happen if a white-eyed male was repeatedly crossed with a red-eyed female, Morgan discovered that all the offspring were red-eyed regardless of their sex. But when these red-eyed offspring crossed with each other, the offspring were both red-eyed and white-eyed, and to his surprise, all the white-eyed flies were males. Morgan and his team repeated the experiment numerous times and obtained the same results every time.

Morgan was thrilled to discover these sex-linked characteristics, proving that males and females had distinct chromosomes. While the female fruit fly has a matching pair of X chromosomes, the male has one normal chromosome and a stub (an X chromosome and a Y chromosome). He discovered that a white-eyed gene on the female X chromosome could be overpowered by the other X in the pair, but a white-eyed gene on the male X chromosome had nothing to balance it on the Y chromosome.

Morgan also discovered that some characteristics were linked and inherited together, but that the linkage was not necessarily permanent. Every once in a while, the two linked characteristics were suddenly inherited independently. Morgan also observed that chromosomes sometimes interchanged parts so that two characteristics ordinarily on the same chromosome could sometimes appear on different chromosomes. For such genes, the new combinations of alleles predicted by Mendel were infrequent or even nonexistent. Morgan quickly realized that the number of linkage groups was the same as the number of different haploid chromosomes in the fruit fly, namely four. This was a profound realization! The number of chromosomes of a species was the physical basis for a specific linkage group. In 1910, Morgan confirmed the discovery of sex linkage with a simple method of mapping genes on the same chromosome. The unit of distance was called the centimorgan, or cM, to mean one genetic map unit.

In 1909 Morgan postulated that linked chromosomes could move to another chromosome or divide so that one gene would find itself on one chromosome and the other gene on another chromosome. This theory is known as translocation, or crossing over. After being verified by numerous trials, this theory somewhat redeemed Mendel's discovery of characteristics that were not present in either of the two parents.

Morgan verified that heredity is passed on through chromosomes and partly through sex chromosomes. Probably Morgan's most important discovery was that sexual characteristics are present in all cells of an organism, as well as innumerable other characteristics belonging in part to the male parent and in part to the female.

10.   Discovering the Link between Hereditary Material and DNA

By 1920 the existence of chromosomes as an organized structure of DNA was confirmed. It was also known that when a phosphate group is attached to a nucleoside it becomes a nucleotide. When the sugar is ribose, then the ribonucleotide is ribonucleic acid or RNA, and when the sugar is deoxyribose then you are dealing with deoxyribose nucleic acid or DNA.

The idea that every species has a specific number of chromosomes that distinguishes it from all other species was and still is a fascinating evolutionary fact. But sometimes seeing can be deceiving as in the case of the chromosomes in human cells. For example, in 1921 Theophilus Painter, who studied human chromosomes from stained slides collected from three different men's testes, claimed that there were 24 unpaired chromosomes in the sex cells of human testes and therefore 48 total chromosomes in somatic cells. This number was not disputed and was even confirmed by other researchers for 34 years. It was only in 1955 that Joe Hin Tjio and Albert

Levann, who used better microscopic and staining techniques, clearly counted only 23 pairs of chromosomes in somatic tissues. Then they recounted the chromosomes in Painter's earlier photos, and to their surprise, found only 23 chromosomes in the gametic tissues rather than 24. Other scientists confirmed Tjio and Levann's observations. Science thrives on the desire to know through doubt, verification, testing, etc. Yet it took more than 30 years to correct this significant error in the number of human chromosomes.

The scientific community had now recognized and identified chromosomes and knew that DNA existed inside the nucleus and that it was the constituent of the genetic chromatin, but the specific roles of the nucleic acids were not yet known. It took a combined experimental approach performed within living organisms (*in vivo*) and with studies in cell extracts or synthetic mixtures of cell components (*in vitro*), to finally make the link between hereditary material and DNA (Allison 2007).

For example, using an elegant *in vivo* experiment, the medical bacteriologist Fred Griffith from the British Ministry of Health described in 1928 how it was possible to convert one type of streptococcus pneumonia bacterium into a new type. More specifically, Griffith conducted his experiment using two different strains of bacteria: type R, which contained a rough outer coat and was nonvirulent in mice, and type S, which contained a smooth outer coat and was virulent in mice. He conducted his *in vivo* experiment using both pathogenic (virulent) and nonpathogenic (nonvirulent) strains of streptococcus pneumonia to infect mice and demonstrated how nonvirulent bacterial cells transform into virulent bacteria that cause pneumonia.

Griffith observed that live pneumococci with a rough capsule (type R) did not make mice ill when he infected them, and no living bacteria could be isolated from the mice. But when he injected type S bacteria into a mouse, the creature died. Then he used heat to create heat-killed type S bacteria and injected them into a mouse. The mouse survived, and no living bacteria were isolated from the mouse. Finally, he mixed living type R bacteria with heat-killed type S bacteria and injected them into mice. He observed that a chemical released from the killed cells (type S) caused the live cells (type R) to begin producing capsules. He also noticed that while several of these mice died, type S bacteria were recovered from the mice (Allison 2007, Messadie, 1991). Explaining the results shown in Table 1, Griffith observed that in Experiment 4 the heat-killed type S somehow converted the nonvirulent living R type to the virulent S type, naming the process "transformation," or the transforming principle. Specifically, he concluded that there was a transfer of some component of the pathogenic (S) bacteria which caused the nonpathogenic (R) bacteria to make the polysaccharide coat and overpower the mouse's immune system. In other words, genetic material from heat-killed virulent bacteria entered the nonvirulent cells transforming them into virulent bacteria.

Table 1 Samples of Griffith's Experimental Results

	Experiment 1 Live type S	**Experiment 2** Live type R	**Experiment 3** Dead type S	**Experiment 4** type R + type S
Types of bacteria that were injected into live mice	Living type S encapsulated bacteria	Living type R non-encapsulated bacteria	Heat-killed type S encapsulated bacteria	Living type R non-encapsulated and heat-killed type S encapsulated
Observation of reaction after several days	Mouse died	Mouse survived and remained healthy	Mouse survived and remained healthy	Mouse died
Results: What was recovered from mice	Type S encapsulated bacteria were isolated from dead mice	No living bacteria were isolated from the mice	No colonies of living bacteria were isolated from the mice	Colonies of type S encapsulated bacteria were isolated from dead mice
Conclusions	Type S bacteria were isolated from the dead mice	A few colonies of type R non-encapsulated bacteria were isolated from mice, but were destroyed by phagocytes.	No living bacteria were isolated from the mice	Live Type S bacteria were isolated from the dead mice

However, while Griffith's experiment clearly showed that there was a transfer of some chemicals between the two bacteria, it didn't shed light on the nature of the transforming principle during that time. No one knew the nature of Griffith's transforming principle, not even Griffith himself.

Other biologists repeated Griffith's experiments and reported the same chemical extracted from the encapsulated cells and found that it was capable of transformation. The transmission of genetic information from one organism to another outside the process of fertilization stirred excitement in the biological community. Many scientists were spurred to continue the search for the nature of the transformation principle as well as the nature of genetic material.

11. Understanding the Transformation Principle

Nearly twelve years passed with no further development of Griffith's transforming principle. Then in 1940 two German physicists, Erwin Schrödinger and Max Delbruck provided the scientific community with a decisive advance in the understanding of DNA. In *What Is Life?* Schrödinger tried to account for events within a living cell by using chemistry and physics alone. He clearly stated that there were yet-to-be-discovered biological mechanisms, called genes, which were still incomprehensible.

Craig Venter explains why Schrödinger's book (*What Is Life?*) was, and still is, very influential:

> It confronted the central problems of biology – heredity and how organisms harness energy to maintain order – from a bold new perspective. With clarity and concision he argued that life had to obey the laws of physics and, as a corollary, that one could use the laws of physics to make important deductions about the nature of life. Schrödinger observed that chromosomes must contain "some kind of code-script determining the entire pattern of the individual's future development." He deduced that the code-script had to contain "a well-ordered association of atoms, endowed with sufficient resistivity to keep its order permanently" and explained how the number of atoms in an "aperiodic crystal" could carry sufficient information for heredity. He used the term "crystal" to suggest stability, and characterized it as "aperiodic," which unlike a periodic, repeating pattern … could have high *information* content. Schrödinger argued that this crystal did not have to be extremely complex to hold a vast number of permutations and could be as basic as a binary code, such as Morse code. (Venter 2013, p 3)

Surprisingly, however, most researchers in the first half of the twentieth century continued to believe that inherited traits were carried by proteins, since they appeared to be the most diverse molecules in living things (Collins 2006, Venter 2013). But all this changed four years after the publication of Schrödinger's book, when the results from a creative *in vitro* experiment conducted by Oswald Avery and his colleagues were published, unveiling as an unexpected surprise that Griffith's transforming principle was actually DNA.

Avery's discovery was significant for three reasons. First, though the "existence of DNA had been known for almost a hundred years, it was previously considered to be little more than nuclear packing material, of no particular interest" (Collins 2006, 101). Second, scientists had not yet discovered that bacteria contained DNA or genes, though DNA was known to be a component of eukaryotic chromosomes (Allison 2007). Third, Phoebus Leven's tetranucleotide model for the structure of DNA was still widely accepted. Scientists thought that DNA was too simple a molecule to influence the development or heredity of plants and animals; they also believed that DNA is an inert and not a reactive molecule, hence unlikely to assume an important functional ability such as this.

Oswald Avery, whose mother had died from pneumonia, was very interested in infectious disease. As a medical doctor, he was aware that until the late 1930s pneumonia killed about a third of those who contracted it. The illness affects the lungs in which the alveoli and bronchioles in the lower respiratory system become filled with fluid. This happens when the lower respiratory organs, which are normally devoid of microorganisms, are filled with bacteria and these bacteria overwhelm the defenses of the respiratory system. There are still around three million cases of pneumonia a year in the United States alone, and pneumonia continues to be the number one killer of children worldwide.

Avery wondered why some of the patients in the pneumonia ward died, while others recovered, even though they were all infected with the same bacteria. To this end, he embarked on a journey of empirical research and collaboration with other colleagues to uncover the mysteries of pneumonia.

The first step in this journey was his collaboration with A. Raymond Dochez. Dochez found that blood in the urine of dying patients consisted of a soluble substance not found in blood in the urine of the recovered patients. However, Dochez and Avery misidentified the substance as a protein, a mistake easily made at the time because many of the scientists interested in this topic were looking at protein to uncover the secret of genetic material. The common assumption was that if you were not looking at or within the protein molecules, you were wasting your time. But the significance of the Dochez-Avery discovery became clear in 1922 after Griffith found that there were two types of pneumococci: rough, non-virulent ones and smooth, virulent ones covered in a slimy mucous shell. It turned out that this slimy substance was the same as the one found in the infected patients, the one that was misidentified as a non-active substance of protein.

Avery thought that whatever had caused the dead type S bacteria (the smooth virulent ones) to transform the live type R bacteria (the rough, non-virulent ones) into virulent bacteria in Griffith's experiment was a single transforming substance. But he wondered if the same results could be achieved without using mice or any other living organisms as hosts; in other words, could this be done *in vitro* instead of *in vivo* experimentally? He conducted *in vitro* experiments to test his hypothesis.

12. Avery's Sticking Point

For twelve years, Avery and his colleagues searched for the transforming substance with no luck until Avery's collaborator, Melvyn McCarty, discovered a way to break open the bacterial coat with bile juice and dissolve the bacterial contents in water. When he and Avery added some of this solution to a culture of rough bacteria, the organisms were transformed into smooth, virulent bacteria (Perutz 1995). Like many scientists, Avery and McCarty thought that a protein might be the transforming substance. But after testing this idea with enzymes known to split proteins, they saw no transforming activity. They then used an enzyme known to split ribonucleic acid, but it also left the transforming activity intact. These two experiments eliminated both protein and RNA as potential candidates for the transforming principle.

After realizing that the transforming substance was not a protein or ribonucleic acid, Avery and McCarty decided to add alcohol to their solution, which created a white, slimy gel. They dissolved the gel in water and added it to their culture of rough pneumococci. The next morning, they found that it had transformed the rough pneumococci into smooth ones. Naturally, they wondered what the gel was made of. After staining the gel with analytical dyes, they found that it was made of deoxyribonucleic acid, DNA. How can this be, they wondered, since, according to the prevailing view of the time, DNA is supposed to be a passive, uncomplicated molecule?

To check their findings, Avery and McCarty treated their solution with an enzyme that splits DNA. The enzyme destroyed the transforming activity of their extract, which was proof that the transforming activity rested in the DNA. Because the transformation was heritable, it was realized that the DNA had to contain a gene. If so, then DNA was an active molecule and almost certainly was the active agent in heredity. This was, as Bryson (2003) puts it, an exceedingly tricky experiment that led to an incredible result in 1943, when DNA was thought to be no more than an inert skeleton supporting the proteins.

Avery, along with McMarty and Colin M. MacLeod, published their results in the *Journal of Experimental Medicine* in 1944, through which they showed how an innocuous strain of bacteria was made permanently infectious by crossing it with alien DNA. Because Avery himself was shocked with their results, the paper was written without even mentioning the word *gene*. It is still considered one of the most important papers ever published in the field of biology.

Oswald Avery and his associates discovered that DNA was the genetic material in bacteria and realized that the transforming substance was DNA. They had discovered the missing link between genetic material and DNA. Avery's contribution to science, particularly the field of genetics, is so great that many scientists today, such as the biochemist Erwin Chargaff, believe he deserved two Nobel Prizes. Unfortunately, most biochemists at Avery's time, including those on the Nobel Committee, were reluctant to believe that DNA had such an important function.

The problem was that scientists were reluctant to let go of the idea that proteins were the key component of genetic material. Because proteins are large molecules that control the chemistry of the body, they were thought to be the keys to living tissue. Nevertheless, Oswald Avery —a man who never even dreamed of being a scientist and came to the medical field later in life, after completing degrees in literature and philosophy — was able to make one of the most significant discoveries in science by proving conclusively that DNA, not

protein, was the transforming principle and the basic genetic material in chromosomes of the cell. Indeed, his great discovery is one of the most important of the past century, although his contribution was not appreciated for many years.

While Avery, MacLeod, and McCarty's experiments showed without a doubt that DNA is the genetic material in bacteria, they didn't know if DNA was the universal genetic material for all organisms. Numerous experiments would overwhelmingly support Avery's conclusions.

In 1949, Roger and Colette Vendrely together with Andre Boivin were able to show that all tissues in an animal contain a constant amount of DNA. They also found that only half as much DNA was in the nuclei of sperm cells as in body cells, which enabled them to confirm Avery's discovery once and for all.

By now, part of the structure of DNA was known to contain four different nitrogen bases: adenine (A) and guanine (G), and cytosine (C) and thymine (T). The question still being asked was, "How did DNA do it?" How did DNA carry the vast amounts of information that enabled a single human egg to develop into an entire human being, and carry the traits of the parents? How did a grasshopper egg develop into a grasshopper, or an egg into a chicken? What was in their structure that enabled the embryonic cells to differentiate into their own cells, tissues, organs, organ systems, and whole beings?

The biochemist Erwin Chargaff started solving this question in 1950 by showing that DNA contains equal amounts of the bases A and T, and G and C. This means that the number of purine groups is equal to the number of pyrimidine groups. In 1952, additional evidence to vindicate Avery's thesis that DNA is the molecule that contains genetic information was provided by Alfred Hershey and Martha Chase, who worked with bacteriophage (viruses) that were infected with *Escherichia coli*. Hershey and Chase confirmed that DNA was the hereditary material.

The overwhelming evidence that DNA was the transforming principle triggered a race to discover the structure of DNA. But first, what did Hershey and Chase do that enabled them to confirm Avery's discovery once and for all?

In the post-World War II years, the availability and utility of radioactive material (radioisotopes) in scientific research had made them the emerging tool of research. It was also well known by this time that the Bacteriophage T2 virus (or the virus bacterium eater) contained DNA within a protein coat. It was also known that while DNA contains phosphorus but no sulfur, protein is composed of some sulfur (in the amino acids methionine and cysteine) but no phosphorus. Based on this, all of the phosphorus in a bacteriophage must be located in the DNA, and sulphur must be found only in the amino acids methionine and cysteine located in the protein coat of the virus. Hershey and Chase designed experiments to test this hypothesis and to determine whether protein or DNA carried the genetic information to make a new bacteriophage.

Using specific radioisotopes, Hershey and Chase conducted laboratory experiments by tagging the DNA of one bacteriophage T2 with radioactive isotope 32-phosphorous (32P) and the protein coat of another T2 particle with radioactive isotope 35-sulfar (35S). They used these labeled T2 particles to separately infect two different suspensions of *Escherichia coli*.

> Following infection, Hershey and Chase exposed the cell-phage complexes to a high shear force by placing them in a blender. This force stripped the attached phage "ghosts" (phage without the nucleic acid) from the host cells. They then used centrifugation to separate the E. coli cells from the phage ghosts and assayed for radioactivity in the two fractions. The cells and injected phage material were assayed for progeny phage by the plague technique. (Allison 2007, p 454)

The analysis of Hershey and Chase's experiments yielded a very significant result that showed that it was the bacteriophage nucleic acid and not the protein coat that really entered the host cell during infection. It was additional proof that the nucleic acid—not the protein coat—carried the genetic information required for replication.

13. Completing the Journey I: The Race to Find the Structure of DNA

Bill Bryson (2003) points out that in the early 1950s, Linus Pauling was thought of as the primary candidate for discovering the structure of DNA because he was "a pioneer in the field of x-ray crystallography, a technique that would prove crucial to peering into the heart of DNA" (p. 403). However, Pauling became convinced that the structure of DNA was a triple helix. Then in April 1953, American biochemist James Watson and British

physicist Francis Crick surprised the world by publishing a short but extremely important paper in the journal *Nature,* titled "Molecular Structure of Nucleic Acids: Structure for Deoxyribose Nucleic Acid." In the paper, they proposed a double-stranded, helical structure for DNA.

Empowered with solid prior and current knowledge in the field and their own creative ingenuity, Watson and Crick used cardboard and metal wires to construct various possibilities for the structure of DNA molecules. They succeeded in demonstrating that DNA consisted of two chains of nucleotides arranged as a double helix, with the purine and pyrimidine bases facing each other and the phosphate links on the outside. And before the world could really discuss the meaning of this, they followed up by publishing another important paper in 1954 in which they posited a method by which a DNA molecule could duplicate itself precisely. In their model, DNA replicates itself exactly so that a cell during cell division could pass on identical genetic information to each daughter cell.

Of course, in their discovery of the structure of DNA, Watson and Crick relied on the work of others, especially those who were also looking for answers outside the realm of proteins. For example, they made use of the α-helical secondary structure of proteins proposed by Linus Pauling in 1951; they took into consideration the disproving of Phoebus Levene's tetranucleotide hypothesis by Edwin Chargaff; and they relied on a key X-ray diffraction photograph called "Photograph 51" of the "B" form of DNA that was taken by biophysicist Rosalind Franklin in 1952 and from which she deduced that the DNA molecule ought to be helical in structure "with the phosphate groups that bound the units together located on the outside of the helix" (Asimov, p. 656). Watson and Crick must have secured this photograph from Franklin's supervisor, the physicist Maurice Wilkins, who most likely made it available to them without Franklin's consent. But regardless of how Watson and Crick got the photo and the role "Photograph 51" of the "B" form of DNA played in the discovery of the structure of DNA, their proposed molecular structure of the DNA molecule made so much sense that it was accepted at once. The importance of DNA within living cells was no longer a point of dispute. Watson and Crick had discovered that DNA was the genetic material that stored and transferred information; it was the unknown process behind the transforming principle.

Indeed, Watson and Crick's unveiled molecular structure of DNA triggered an intense period of discovery and innovation that continues to this day. This significant breakthrough in science forever changed our world. In 1962, Watson, Crick, and Wilkins received the Nobel Prize for physiology and medicine as a result of their work in modeling the DNA molecule. By that time, Rosalind Franklin was already dead, her contributions not similarly recognized, since the Nobel Prize is not awarded to dead people regardless of the significance of their work.

The discovery of the structure of DNA was voted the greatest UK scientific breakthrough of all time by more than 400 UK academics. Indeed, it is the most significant discovery ever made in genetic and molecular biology. Today, synthetic biologists have started to learn how to engineer genomes that could enable them to go from gathering information to reproducing organisms (Biello and Harmon 2010).

As Tom Siegfried (2010), the editor-in-chief of *Science News* wrote:

> Among the molecules of life, DNA is the MVP. It provides the mechanism for heredity, the blueprints for proteins and the recipe for reproduction.... It helps explain the secrets of many dark diseases. And it gives scientists one of the best tools and toys available for playing around in the nanoworld.... No doubt DNA's nanotechnological ability will also be applied to making tiny electronic parts for a computer that could fit inside an eyelash (p 2).

The discovery of DNA's structure and its ability to replicate has inspired scientists, science fiction writers, and artists for years! It has enthralled Hollywood and the general public, and changed the way we produce crops and raise animals. Criminals have been convicted with DNA evidence and the wrongly convicted have been freed. All aspects of our society have been affected and continue to evolve as our understanding of DNA continues to expand.

14. Completing the Journey II: Formation of the Central Dogma in Biology

The discovery of DNA structure, however, was not enough for understanding how genetic information flows with living cells and how this information transfers into physical traits that we can observe. This question was finally addressed in detail by Francis Crick in 1970. Crick was able to show precisely how the DNA code works, which led to the formation of the Central Dogma in biology, which defined the way genetic information flows through a biological system. Simply stated: DNA to RNA to Protein. As Venter puts it, "The DNA-Code-Script has come to dominate biological sciences, so much so that biology in the twenty-first century has become an information science" (p 5).

15. Summary and Conclusions

Through dedication, accurate observations, well designed experimentation, and informed inferences and interpretation, Gregor Mendel was able to show empirically in 1866 that the transmission of traits from parents to offspring follows a pattern of segregation and independent assortment. But these facts remained unknown for almost 50 years before their rediscovery. During this time, Strasburger, Hertwing, von Kolliker, and Weismann independently identified, in 1884, that the cell nucleus is the basis of inheritance. One year later, Hertwing, Strasburger, and Weismann proposed that chromosomes are carriers of genetic material. In 1900 DeVries, Correns, and von Tschermak independently rediscovered Mendel's laws of inheritance. Two years later, Walter Sutton and Theodre Boveri proposed a chromosomal basis for heredity based on their own observation of how chromosomes behaved during cell division, specifically, meiosis. DNA was discovered by the Swiss biochemist Friedrich Mirscher who in 1869 found the molecules in the nuclei of white blood cells and called them nuclein. Oswald Avery and his colleagues discovered that DNA is the genetic blueprint material of living things in early 1944. Using bacteriophage in their 1952 experiment, Alfred Hershey and Martha Chase conclusively confirmed that DNA was the hereditary material, and in 1953, Watson and Crick deciphered the double-helix structure of DNA. In 1970, Crick described in detail the flow of genetic information within a living cell.

All these discoveries contributed to our current understanding: DNA is the hereditary material found in our cells; there is a constant amount of DNA in all cells of the same living organism (with only half of the same amount in the sex cells); each chromosome is a single molecule of DNA; living organisms have a specific number of chromosomes and these chromosomes duplicate and divide equally during mitosis cell division between the two newly doubled cells, which are halved during the meiosis cell division between the four newly formed cells. As shown, the journey to discover the link between genetic material and DNA took a winding road that delayed the ultimate discovery. One of the side tracks—the belief that protein is genetic material—kept the journey from reaching its goal sooner and recognizing DNA as the information-carrier, "perhaps by as much as half a century" (Venter 2013, p 24).

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Appendix

Critical Thinking Questions

The following critical thinking questions were designed to engage readers and students to help them comprehend the materials in this paper and to achieve in-depth learning and analysis.

1. Why do you think Oswald Avery didn't receive the Nobel Prize when other scientists believed he should have received not only one but two Prizes for his work?
2. Why do you think that many scientists prior to and during Oswald Avery's discovery didn't consider DNA a serious candidate for genetic material?
3. Was Oswald Avery's failure to receive a Nobel Prize a result of bad luck, human behavior and jealousy, or just a serious scientific uncertainty at that time?
4. Identify the elements of the scientific method and provide an example of each.
5. As you learned about the scientific method, which element of the method was most apparent to you and which one was least?
6. Why is the significance of a given scientific discovery often not realized until its "rediscovery" years later?
7. Select one of the scientists you learned about in reading this paper. Conduct research on that scientist and write a two-page report on his/her scientific contributions, something he or she was involved in outside the realm of science, and why you selected this particular scientist.
8. Compare and contrast *vitro* and *vivo* experimental procedures.
9. Why do you think it took both *in vitro* and *in vivo* types of experiments to really crack the secret of the transformation principle (the genetic material)?
10. It has been said that unlike Oswald Avery's discovery, the discovery of the structure of DNA was ready to happen during that time, which makes Avery's work even more significant scientifically. Do you agree or disagree, and why?
11. Why is it important that Alfred Hershey and Martha Chase's work was done with bacteriophage (viruses) infected with *Escherichia coli*, and not with any known type of living organisms, to confirm beyond a doubt that DNA was the heredity material?
12. How many of the scientists mentioned in this paper have received the Nobel Prize for their significant scientific contributions to science and to our understanding of the world?
13. If you had to write a letter to one of the scientists mentioned in this paper, which one would you select? Why? What would you write?
14. Einstein is cited as saying that "no number of experiments can prove me right, but one experiment can prove me wrong." Explain what Einstein meant.
15. Fred Griffith discovered the transformation principle, but wasn't exactly sure what it was or how to explain it. In your own words, how would you describe the transformation principle?
16. Oswald Avery and many other scientists have struggled to get their work recognized and accepted by the scientific community. Do you think the scientific community should be very cautious and rigid concerning what they accept or should they be more open in their acceptance of scientific discoveries?
17. Why do you think no one challenged for so many years Theophilus Painter's finding that the human male testes cell has 24 chromosomes?
18. It has been said that science is less a body of established facts than a process and a way of knowing. Do you agree or disagree? Explain.
19. Why do you think red blood cells are the only cells in the human body that cannot divide and go through cell division?
20. Why was Mendel unable to observe gene linkages in his study of pea plants, but Morgan was able to do so in his study of fruit flies?

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