History of Genetics

Priyanshu Mahato, pm21ms002

Prehistoric Genetics

We have good empirical evidence that humans had an implicit knowledge of genetics from at least 15,000 BCE. Surprisingly as it may sound, the proof resides in the remnants of the first attempts at genetic engineering. This engineering took the form of what today is called artificial selection—the deliberate breeding of plants and animals for desired characteristics. The best empirical evidence comes from analyzing pollen in hermetically sealed ancient tombs and the dog.

Current phylogenetic analyses suggest that dogs evolved from wolves and were domesticated at least by 15,000 BCE in East Asia (Ostrander, Giger & Lindblad G Toh, 2008; Savolainen et al., 2002). The "at least" part of this temporal estimate derives from archaeological and DNA evidence of North American dogs suggesting that they were brought into the continent from Asia by the new world's original discoverers. Artificial selection of the dog for behavioural traits like herding, guarding, hunting, and retrieving is some of the best evidence for genetic influences on mammalian behaviour (Scott & Fuller, 1965)

Like many attempts to manipulate nature, early genetic engineering had unforeseen consequences. Merrill (1975) reports that the original progenitors for today's onions, lentils, ginger, and many other crops are extinct because our human ancestors selected them for fecundity. So-called "wild onions" and "wild ginger" are domestic varieties that "got loose" and outcompeted their wild-type ancestors.

Ancient Theories of Genetics

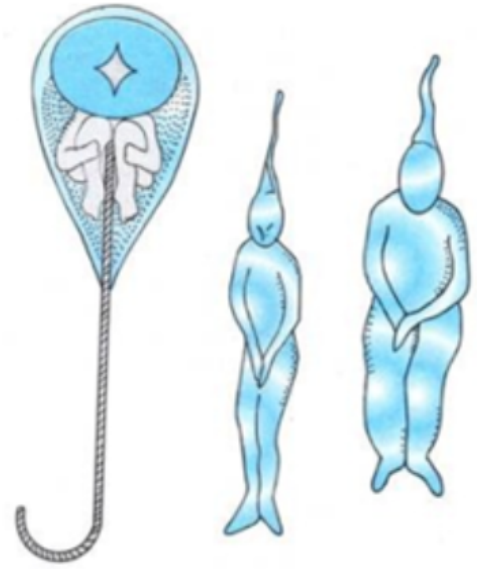
Hippocrates (460 - 377 BC), the founder of medical science, proposed a theory according to which minute particles from every part of the body entered the seminal substance of the parents, and by their fusion gave rise to a new individual exhibiting the traits of both of them.

From Aristotle (384 – 322 BC) to the 18th century it was assumed that the mother provides inert matter and father imparts the motion or life to this inert matter. He proposed that every part of the new organism was contained within the semen, which was formed by sanguineous (blood-like) nutrients. The menstrual blood of a woman passively contained each and every part of her body, which was shaped into a new organism by the action of the principle of motion of the sperm. During conception, the sperm (providing motion) produced qualitative changes in the matter of the female organism (inert). Aristotle was the first to attribute to the mother an essential role in the process of generation.

Leonardo da Vinci (1452 – 1519) and Regnier de Graff (1641 – 1673) proposed that the male

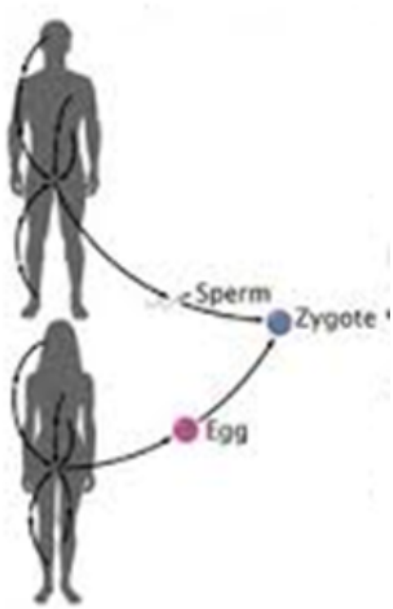
and female parents contribute equally to the heredity of offspring.

- **Theory of Preformation** : This theory was proposed by two Dutch biologists, Swammerdam and Bonnet (1679). This theory states that a miniature human called homunculus was already present in the egg and sperm (germ cells). In other words, a miniature human was performed in the gametes. It also proposes that an individual develops by simple enlargement of a tiny fully formed organism (a homunculus) that exists in the germ cell.
  On studying the development of avian embryos Malpighi (1628-94), said that he located a preformed embryo in the egg, which he said began development on coming into contact with sperm. This theory was soon discarded because this could not be proved scientifically.



- **Theory of Epigenesis:** A German biologist K. W. Wolf (1738 – 1794) proposed that neither the sperm nor the ovum contains a structure called the homunculus, but they contain gametes which contain an undifferentiated living substance capable of forming a well-organised body with tissues and organs after fertilization. This concept is known as epigenesis which is universally accepted.
  The theory suggested that many new organs and tissues, which were originally absent, develop *de novo (totally new beginning)* due to mysterious vital forces.
- **Theory of Pangenesis:** English Naturalist Charles Darwin (1809 – 1882) proposed Pangenesis, a developmental theory of heredity.

He suggested that all cells in an organism are capable of shedding minute particles (very small, exact but invisible copies of each body organ and component) called gemmules or pangenes, which are able to circulate throughout the body through the bloodstream and finally congregate in the gonads (sex organs). These gemmules are assembled in the gametes.
After fertilization, these gemmules move out to different parts of the body resulting in the development of the respective organ. A defective gemmule will lead to the development of a defective organ in an individual. This theory was given up because it did not have a scientific basis.



- **Contribution from Other Biologists:**

German botanist Joseph Gottlieb Koldreuter (1733 – 1806) with experiments with hybrids obtained from tobacco species concluded that inherited traits are particulate in nature. Koldreuter viewed his explanation as agreeing with the Aristotelian theory of generation through the semen of both parents. Koldreuter supported the theory of epigenesis, according to which the newly-formed germ is homogeneous, and differentiates only as it develops.

Knight (1799) and Goss (1824) performed the experiment on garden pea (*Pisum sativum*) and observed that the hybrids were uniform in character and segregation of characters occurred in the second generation. These experiments were the basis of Mendel's work. But Knight and Goss failed to formulate the laws of Inheritance.

German biologist August Weismann (1889) proposed that body tissues are of two types, viz., germplasm (reproductive cells) and somatoplasm (all other cells than reproductive cells). The transmission of characters from one generation to another takes place only through germplasm. Any change in the germplasm will lead to change in the next generation. This theory is accepted in a broad sense.

- **Theory of Blending Inheritance:** By this theory, inherited traits were determined, randomly, from a range bounded by the homologous traits found in the parents. According to this theory maternal and paternal genetic material are mixed together after fertilization, just like two different coloured liquids in a cup. Thus, the height of a person, with one short parent and one tall parent, was thought to always be of some interim value between its two parents' heights.
  Blending theories failed to explain the behaviour of discontinuous traits, or discrete traits, that consisted of only two contrasting phenotypes, with no intermediate phenotypes between them. These discrete traits were not altered in offspring and could skip generations. The theory failed to explain that the offspring of black and white horses were black and not grey.

- **Moist Vapour Theory:** This theory was proposed by Pythagoras in which he believed that every part of the organism emits some kind of moist vapour. The vapors from all parts get aggregated to form different organs of the offspring.

- **Fluid Theory:** Empedocles proposed that each body part produces a fluid. The fluid of different body parts of the two parents mixes up and is used in the formation of an embryo. Any defect in the descent and mixing up of the results of the fluid in the missing characters of one parent or both parents.

- **Reproductive Blood Theory:** Aristotle thought that an embryo is produced due to the mixing of reproductive blood of the two parents. It is pure in the case of males and impure in the case of females. As a result, the male contributes more characteristics.

- **Particulate Theory**: Maupertuis proposed that each animal produced minute particles for reproduction, and a new individual is formed by the union of the particles of the two parents.

Intellectual Background for Modern Genetics: The Four L's

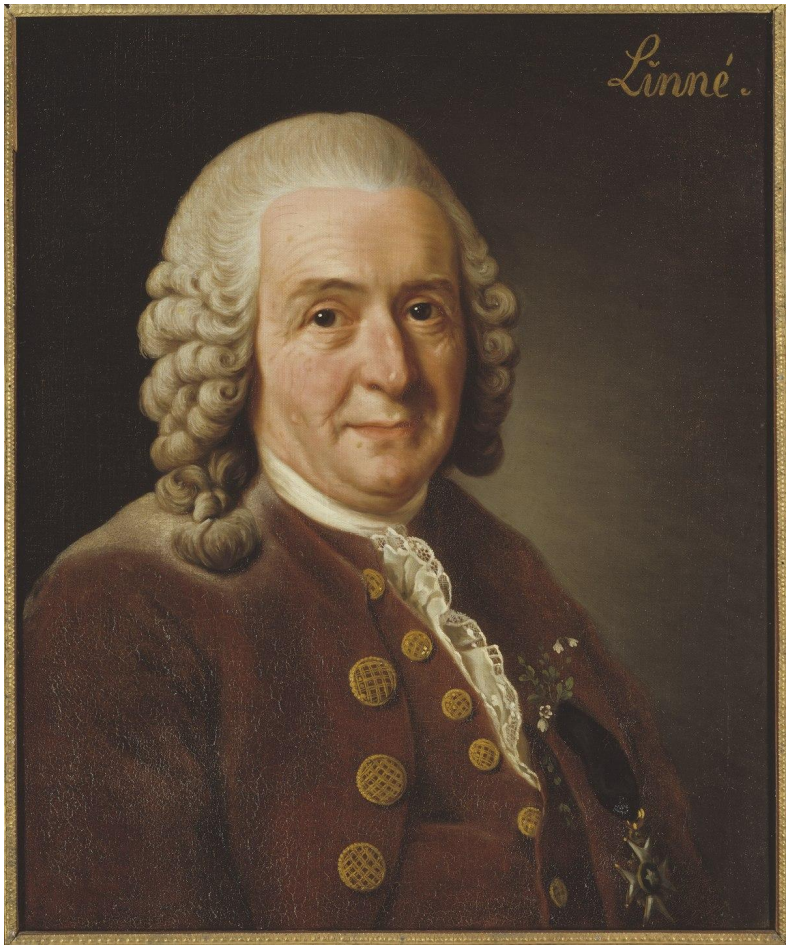
Genetics did not developed suddenly. Sure, there were very important contribution that radically changed the field. Think of Darwin or Mendel. But even Darwin's paradigm shift did not occur de novo. Instead, it evolved from the intellectual background of his time. Indeed, his grandfather, Erasmus Darwin, had written — albeit vaguely — about evolution. Here, we focus on "the four Ls" or four people whose surnames begin with the letter L that contributed to the intellectual climate that presaged genetics.

van Leeuwenhoek (1632 – 1723)

The first L is Anton van Leeuwenhoek. Many texts mistakenly credit van Leeuwenhoek with the invention of the microscope. Actually, that instrument was first developed around 1590, some 40 years before van Leeuwenhoek's birth, by two of his Dutch compatriots, the father and son team of spectacle makers, Zaccharis and Hans Janssen. Galileo further developed Janssens' invention into the telescope. The major contributions of van Leeuwenhoek were his significant improvements to the microscope that enabled him to observe what he termed animalcules, today called microbes or microorganisms. Many consider van Leeuwenhoek the father of

microbiology. Even if one were to dispute this, there is no doubt that he was the first to report on single cell organisms. Scientists of the day greeted his finding with suspicion and resistance. It was not until a team of impartial observers replicated van Leeuwenhoek's observations that microbes were accepted as a real phenomenon. Hence, his major contribution was to initiate a whole field of science that eventually led to the development of cell theory and the identification of chromosomes.

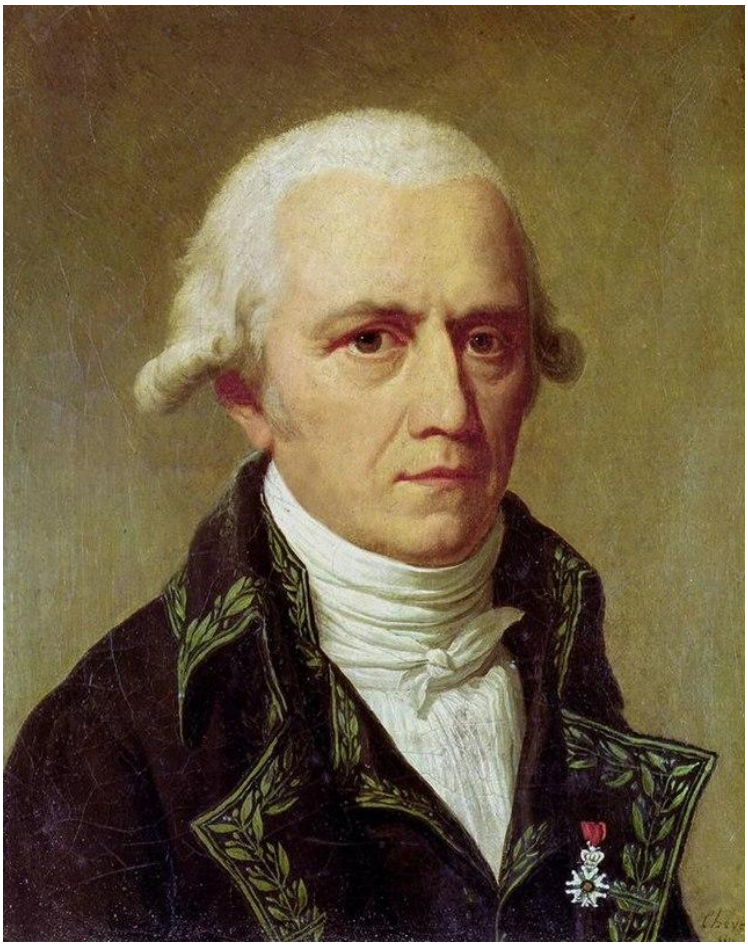
Linnaeus (1707 – 1778)



Carl von Linné, better known by his Latinized surname, Linnaeus, was a Swedish physician and biologist, concerned with the classification of biological entities, a scientific enterprise of great popularity at the time. In 1735, he published the first edition of Systema Naturae that, in its brief 11 pages, provided the seeds for modern biological classification. His major contribution was not the organisms that Linnaeus classified. Rather, he established a set of rules for classification that gradually became universally accepted. There are several salient aspects of the Linnaean system. First, it is binomial (two names). In this system, an organism is referred to by two names—its genus and species—using Latin (but sometimes Greek) roots. Hence, we humans are

Homo(sapiens (wise man) and your pet cat is a member of Felis catus (cunning cat). Second, the system was based largely on external morphology. Third, the system was hierarchical. That is, species X is more closely related to species Y than to species Z if it looks more like Y than Z. An ant and a termite will be classified closer in the hierarchy than either would be with an elephant. Along with the biologists of his time, Linnaeus believed in the biblical account of creation. Hence, he viewed species as being created and then remaining fixed and immutable. The idea of evolution was developed by our third L.

Lamarck (1744 – 1829)



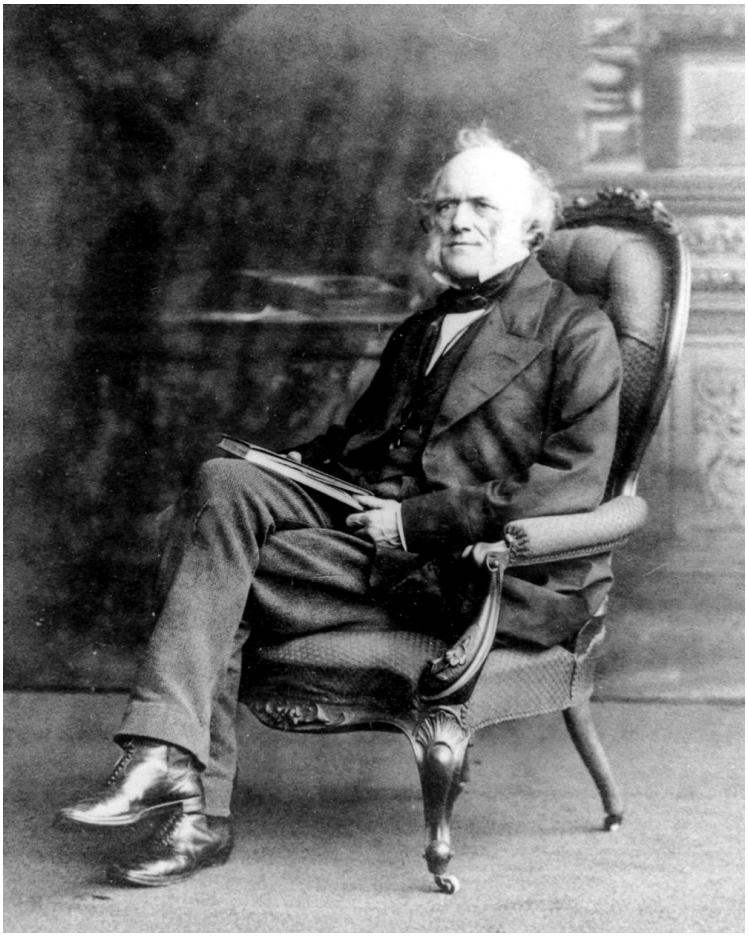
Lamarck, formally named Jean G Baptiste Pierre Antoine de Monet, Chevalier de Lamarck, is usually associated with the inheritance of acquired characteristics, a phenomenon that modern biology terms (in a somewhat derogatory sense) as Lamarckism. Sadly, this heritage overshadows his major contribution to the intellectual background of genetics—Lamarck was the first to propose a comprehensive theory of evolution.Lamarck's theory was not the first to challenge the literal biblical account of creation and its implication that species are fixed and

immutable. In the 1700s, the Scottish scholar James Burnett (Lord Monboddo), known today as one of the founders of linguistics, speculated that modern chimps and humans originated from a common ancestor. Just before the dawn of the nineteenth century, Erasmus Darwin's *Zoömania* also contained hints about evolution. Why have Monboddo and E. Darwin not been credited with "discovering evolution?" The answer is instructive to every student of science—the laurels often go not to the person who originates an important idea, but to the person who develops that idea into a comprehensive theory and/or the person that popularizes that idea. Let's spend a moment exploring a specific case about evolution. Consider the following quote from Erasmus Darwin:

"Would it be too bold to imagine that, in the great length of time since the earth began to exist, perhaps millions of ages before the commencement of the history of mankind would it be too bold to imagine that all warm blooded animals have arisen from one living filament, which the great First Cause endued with animality, with the power of acquiring new parts, attended with new propensities, directed by irritations, sensations, volitions and associations, and thus possessing the faculty of continuing to improve by its own inherent activity, and of delivering down these improvements by generation to its posterity, world without end!"

The implication for biology is clear. The term "First Cause" derives from one of the arguments made by the medieval scholar Thomas Aquinas for the existence of God. God's initial creation may not have resulted in a large number of immutable species. Instead, there was one "living filament" bequeathed with the traits that allow it to change in different directions over time. Changes to this single living filament (and its offspring) resulted in the myriad of species we observe today. This is clearly a statement about evolution. Lamarck, however, is credited as the "first modern evolutionist" because he developed a comprehensive theory about the process of evolution. Erasmus Darwin speculated that a camel and a giraffe may be contemporary manifestations of "one living filament." Lamarck took this a step further. Camels and giraffes have a common ancestor, but they differentiated in terms of their adaptations to different environments. In lush environments, the primordial ancestor of the camel and giraffe first ate the lower leaves of a tree and then stretched its neck to reach the higher leaves. This "stretched neck" was then transmitted to its offspring, and after a large numbers of generations, viola—we have a large number of animals with very long necks, members of a species that we now call the giraffe. Linnaeus' hierarchical classification implies that certain species are closely related while others are distantly associated. It is natural for biologists to ask the question "why are ants and termites more closely related than either is to an elephant?" Lamarck's theory provides an answer—ants and termites diverged more recently than either did from the ancestor of the elephant. In short, what Lamarck got right was the concept of change as a function of heritable transmission and adaptation to the environment. What he got wrong, and for which he has been disparaged ever since, was the mechanism of such change, his concept of the inheritance of acquired characteristics.

Lyell (1797 – 1875)



The last L is Charles Lyell, a Scottish lawyer turned geologist. Lyell's contributions to pre genetic thought are much less attributable to him as an individual than they are to his overall field. He is given credit here because his surname begins with the letter L (making it easier to remember) and because he authored one of the classic books of the day—one that greatly influenced the young Charles Darwin—the *Principles of Geology*, published in several volumes from 1830 to 1833.

Lyell's major importance resides in the fact that he compiled and systematized the thought that became the origins of modern geology (to which he, himself, made important contributions). The prevailing opinion about the origins of earth and biological species was taken from the two accounts of creation in Genesis, the first book of the bible. Around 1600, Bishop James Ussher used temporal estimates of the genealogies in Genesis and other biblical texts to conclude that creation occurred on October 23, 4004 BCE. The modern geology summarized in Lyell's text seriously challenged that view. It proposed that contemporary geological formations (e.g., the Rocky Mountains, the Sahara desert, the white cliffs of Dover) were the result of natural,

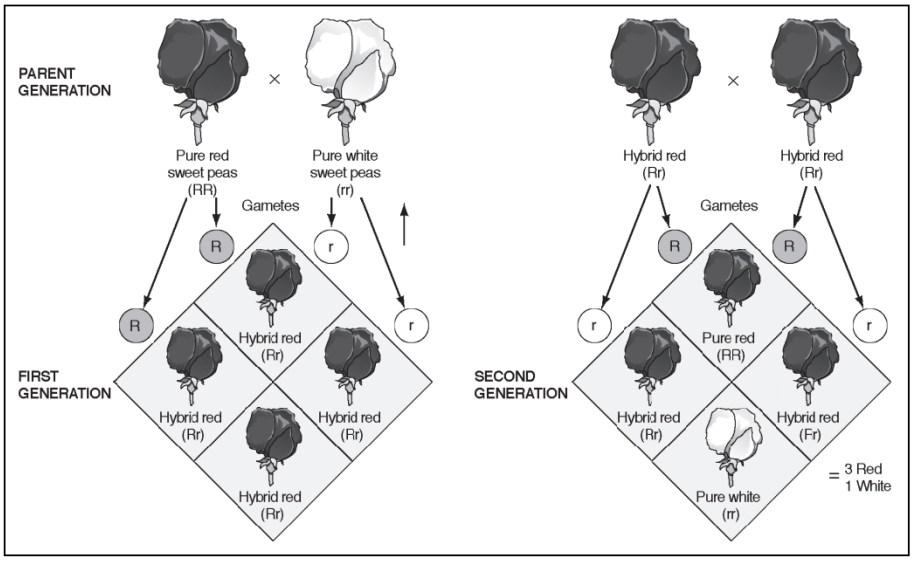
physical process occurring over millions of years. At this point many of you might infer that Lyell's greatest contribution was his (as well as other geologists of the time) contention over the timing of the earth. Interesting enough, Lyell attributes this challenge to Lamarck: "That the earth is quite as old as he [Lamarck] supposes, has long been my creed" (Lyell, 1881, Vol. 1, p. 168).

The concept in modern geology of an old versus young earth is undoubtedly a major contribution to science, but it should not overshadow another (and arguably more important) contribution—namely, that changes over time are the result of natural processes and not divine intervention. Why does the Thames twist and turn in serpentine fashion? According to modern geology, this is the result of differential erosion, the undercutting of riverbanks in soft versus hard strata, and other physical and identifiable processes. The task of science is to identify and explicate these physical processes.

In his voyage on the Beagle, Charles Darwin had a copy of Lyell's *Principles of Geology*. Hence, he was familiar with the concepts of the age of the planet being much longer than that implied by the bible and that things change gradually over time according to physical principles.

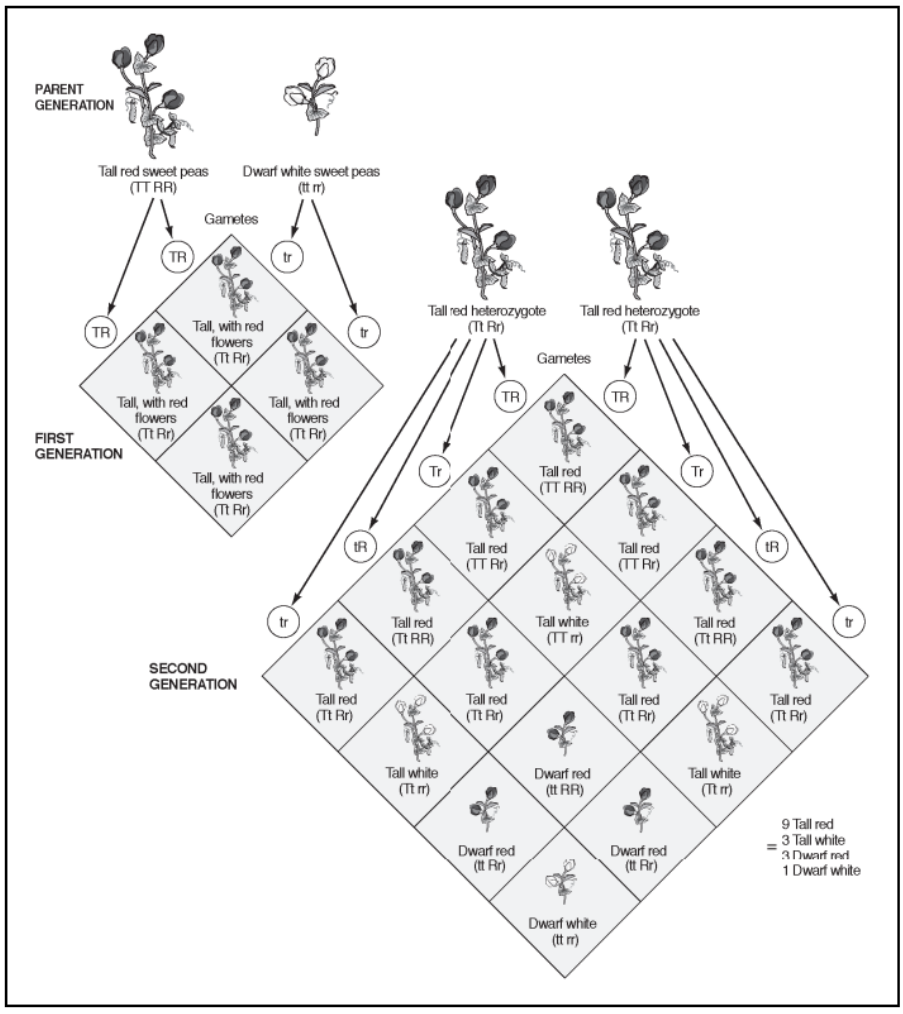
Mendelian Genetics

The legacy of Mendel's pioneering studies of hybridization in the pea continues to influence the way we understand modern genetics. But what sort of picture did Mendel himself have of his work and its ultimate uses, and how does that picture compare with the collection of ideas and methodologies that was put forward in his name and later became known as 'Mendelism'? With genetics standing at the center of our present biomedical and biotechnological research, an examination of the history of our concepts in the field can help us better understand what we should and should not expect from current genetic claims. For that enterprise there is no better starting place than Mendel himself.



Mendel's law of segregation. *Hans & Cassidy, Cengage Gale.*

The first major publicist for Mendel's work was William Bateson (1865–1926) in England. Through the Royal Horticultural Society, Bateson had Mendel's paper translated into English for the first time, and wrote a general exposition that laid out the basic principles of what soon came to be known as 'Mendelism'. Bateson's work brought Mendel to the attention of numerous workers in England, Scandinavia and the United States, in particular to many of those involved in practical animal and plant breeding. Although there was reluctance in some quarters to embrace Mendel's work immediately – especially among academic biologists – by the end of the first decade of the 20th century, the theory had gained a considerable following. However, the explanation Mendel offered for his breeding data seemed reminiscent of so many of the speculative, particulate theories of heredity that had abounded in the post-Darwinian era, including Darwin's own 'provisional hypothesis of pangenesis', August Weismannn's elaborate theory of 'ids, idants and biophors', Ernst Haeckel's imaginary 'plastidules', and Hugo de Vries' postulated 'pangenes'. Consequently, to some, at least, Mendel's work seemed like just one more of the sort of abstract proposals they had encountered all too frequently. In point of fact the paper probably seemed extraordinarily dense, with no illustrations but numerous binomial expansions, which were likely to have been a putoff for many biologists who at the time were notoriously math-shy.



Mendel's law of independent assortment. *Hans & Cassidy, Cengage Gale.*

What ultimately served to establish Mendelism on more firm ground between 1900 and 1915 was: (1) its extension to an increasingly wide variety of organisms; and (2) its unification with the cytological work on chromosomes carried out principally through the work of Thomas Hunt Morgan (1866–1945) and his young, enthusiastic team of investigators at Columbia University between 1911 and 1925. The work of the Morgan school demonstrated that the abstract elements or 'factors' discussed by early 20thcentury Mendelians could be regarded as discrete, material units arranged linearly along the chromosomes, and that observed variations in the patterns of inheritance of traits could be traced to the mechanics of chromosome behavior during meiosis (gamete formation). Mendel's factors (after 1909 referred to as 'genes') thus seemed to be real, material units, not metaphysical postulates. In recognition of this work, Morgan was awarded the first ever Nobel Prize for research in genetics in 1933. Therefore, a common picture of Mendelian theory has emerged from this early work.

Birth of Genetics as a Unified Field

In 1900, Mendel's results were independently replicated by three people: the Dutch botanist Hugo de Vries, the Austrian Erich von Tschermak (whose grandfather, ironically, was Mendel's botany professor), and the German Carl Correns (ironically again, the student of Nägeli, one of the discoverers of chromosomes and Mendel's correspondent). It is often stated that they "rediscovered" Mendel, but that is misnomer. What they did is to expose modern science to Mendel. Mendel's work had been sporadically cited between its date of publication and 1900, but nobody seriously considered its implications. It is more correct to say that 1900 was the year in which Mendel was finally appreciated. Around the same time, the English biologist William Bateson read Mendel and became an enthusiastic advocate. He translated Mendel into English and dubbed the new field "genetics," a term already in use but in the vague sense as something pertaining to origins. He also introduced the terms allele, zygote, heterozygote, and homozygote. In 1904, he along with Reginald Punnett (who gave us the eponymous square) described genetic linkage, but got the mechanism wrong. He did not believe that chromosomes had anything to do with Mendelian inheritance.

The work in Thomas Hunt Morgan's lab from 1910 through 1914 firmly united the Mendelian and Early Cell Biology lines of inquiry. Using fruit flies (Drosophila), Morgan and his collaborators proposed that gene were linearly arranged on the chromosome, giving us the "beads on a string" model of the genome. They also demonstrated sex linkage and identified the sex chromosomes.

In Morgan's lab, Alfred Sturtevant produced the first genetic map. Because of Morgan's contributions, the unit of distance along chromosomes was called a Morgan and one hundredth of that unit a centiMorgan (cM). Things did not go so smoothly with the Darwinian trend. Two heirs of the Darwinian Galtonian trend, Karl Pearson and his colleague Raphael Weldon, held that Mendel's theory is fine for qualitative/discrete traits like yellow versus green pea seed color but could not account for continuous variation. Continuous variation involved traits like height—we all have height but we all possess different amounts of it. They suspected that there were other mechanisms involved in hereditary transmission besides Mendel's units. The Mendelists, especially the aforementioned William Bateson, vigorously disagreed, some going to far as to claim that obvious continuous traits like bristle number on a fly actually fell into two categories, few and many.

The situation was finally resolved in 1918 when Ronald Fisher published a classic paper, The correlation between relatives in the supposition of Mendelian inheritance. Here, Fisher demonstrated that a Mendelian inheritance could account for continuous variation when a number of genes contributed to a trait and the effect of each individual gene was small.

Hence, one can make an argument that genetics as a unified field was "born" in 1918, the year in which the first World War ended.

Chromosomal Theory of Inheritance

In *The Theory of the Gene* (1926), Morgan asserted that the ability to quantify or number genes enables researchers to accurately predict the distribution of specific traits and characteristics. He contended that the mathematical principles governing genetics qualify it as science.

In 1933 Morgan was awarded the Nobel Prize in Physiology or Medicine for his groundbreaking contributions to the understanding of inheritance. Muller also became a distinguished geneticist, and after pursuing research on flies to determine if he could induce genetic changes using radiation, he turned his attention to studies of twins to gain a better understanding of human genetics.

Bridges eventually discovered the first chromosomal deficiency as well as chromosomal duplication in fruit flies. He served in various academic capacities at Columbia University, the Carnegie Institution, and the California Institute of Technology and was a member of the National Academy of Sciences and a fellow of the American Association for the Advancement of Science.

Sturtevant was awarded the National Medal of Science in 1968. His most notable contribution to genetics was the detailed outline and instruction he provided about gene mapping—the process of determining the linear sequence of genes in genetic material. In 1913 he began construction of a chromosome map of the fruit fly that was completed in 1951. Because of his work in gene mapping, he is often referred to as the father of the Human Genome Project, the comprehensive map of humanity's 20,000 to 25,000 genes. His book *A History of Genetics* (1965) recounts the ideas, events, scientists, and philosophies that shaped the development of genetics.

Classical Genetics

Another American geneticist awarded a Nobel Prize was Barbara McClintock (1902–1992), who described key methods of exchange of genetic information. Performing chromosomal studies of maize in the botany department at Cornell University, she observed colored kernels on an ear of corn that should have been clear. McClintock hypothesized that the genetic information that normally would have been conveyed to repress color had somehow been lost. She explained this loss by seeking and ultimately producing cytological proof of jumping genes, which could be released from their original position and inserted, or transposed, into a new position. This genetic phenomenon of chromosomes exchanging pieces became known as crossing over, or recombination.

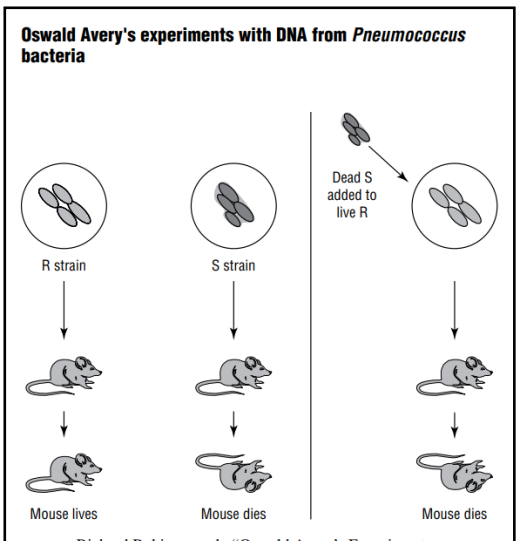
With another pioneering female researcher, Harriet Creighton (1909–2004), McClintock published a series of research studies, including a 1931 paper that offered tangible evidence that genetic information crossed over during the early stages of meiosis (cell division). Along with

the 1983 Nobel Prize in Physiology or Medicine, McClintock received the prestigious Albert Lasker Basic Medical Research Award in 1981, making her the most celebrated female geneticist in history.

During the same period, the British microbiologist Frederick Griffith (1879–1941) performed experiments with Streptococcus pneumoniae, demonstrating that the ability to cause deadly pneumoniain mice could betransferred from one strain of bacteria to another. Griffith observed that the hereditary ability of bacteria to cause pneumonia could be altered by a transforming principle. Even though Griffith mistakenly believed the transforming factor was a protein, his observation offered the first tangible evidence linking deoxyribonucleic acid (DNA, the molecule that carries the genetic code) to heredity in cells. His experiment provided a framework for researching the biochemical basis of heredity in bacteria. In 1944 the Canadian biologist Oswald Theodore Avery (1877– 1955), along with the American microbiologist Colin Munro Macleod (1909–1972) and the American bacteriologist Maclyn McCarty (1911–2005), performed studies demonstrating that Griffith's transforming factor was DNA rather than simply a protein. Among the experiments Avery, Macleod, and McCarty performed was one similar to Griffith's, which confirmed that DNA from one strain of bacteria could transform a harmless strain of bacteria into a deadly strain. Their findings gave credence to the premise that DNA was the molecular basis for genetic information.

Nearly half of the twentieth century was devoted to classical genetics research and the development of increasingly detailed and accurate descriptions of genes and their transmission. In 1929 the American organic chemist Phoebus A. Levene (1869–1940) isolated and discovered the structure of the individual units of DNA. Called nucleotides, the molecular building blocks of DNA are composed of deoxyribose (a sugar molecule), a phosphate molecule, and four types of nucleic acid bases.

Also in 1929 Theophilus Shickel Painter (1889–1969), an American cytologist, made the first estimate of the number of human chromosomes. His count of 48 was off by only 2—25 years later researchers were able to stain and view human chromosomes microscopically to determine that they number 46. Analysis of chromosome number and structure would become pivotal to medical diagnosis of diseases and disorders associated with altered chromosomal numbers or structure.



Oswald Avery's experiments with DNA from *Pneumococcus* bacteria

SOURCE: Richard Robinson, ed., "Oswald Avery's Experiments Showed That DNA from Dead S Strain of *Pneumococcus* Bacteria Could Transform a Harmless Strain into a Deadly Strain," in *Genetics*, vol. 1, *A–D*, Macmillan Reference USA, 2002

Another milestone in the first half of the twentieth century was the determination by the American chemist Linus Pauling (1901–1994) that sickle-cell anemia (the presence of oxygendeficient, abnormal red blood cells that cause affected individuals to suffer from obstruction of capillaries, resulting in pain and potential organ damage) was caused by the change in

a single amino acid (a building block of protein) of hemoglobin (the oxygen-bearing, iron-containing protein in red blood cells). Pauling's work paved the way for research showing that genetic information is used by cells to direct the synthesis of protein and that mutation (a change in genetic information) can directly cause a change in a protein. This explains hereditary genetic disorders such as sickle-cell anemia.

From 1950 to 1952 the American geneticists Martha Cowles Chase (1927–2003) and Alfred Day Hershey (1908– 1997) conducted experiments that provided definitive proof that DNA was genetic material. In research that would be widely recounted as the ‘‘Waring blender experiment,’’ the investigators dislodged virus particles that infect bacteria by spinning them in a blender and found that the viral DNA, and not the viral protein, that remains inside the bacteria directed the growth and multiplication of new viruses.

Emergence of Modern Genetics

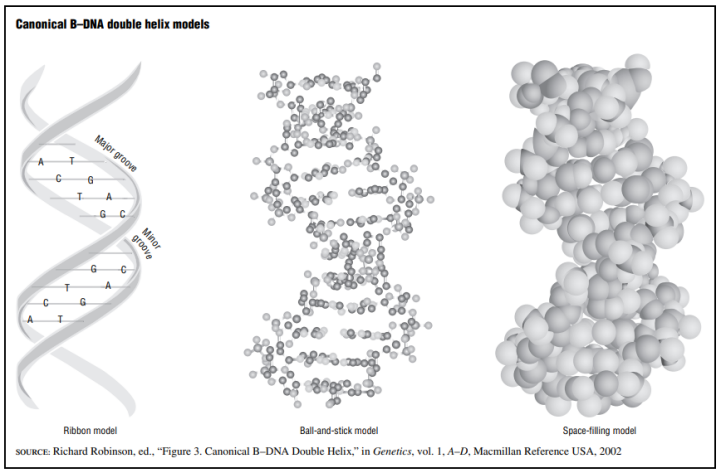
The period of classical genetics focused on refining and improving the structural understanding of DNA. In contrast, modern genetics seeks to understand the processes of heredity and how genes work.

Many historians consider 1953—the year that the American geneticist James D. Watson (1928–) and the British biophysicist Francis Crick (1916–2004) famously described the structure of DNA—as the birth of modern genetics. It is important, however, to remember that Watson and Crick's historic accomplishment was not the discovery of DNA— Miescher had identified nucleic acid in cells nearly a century earlier. Similarly, even though Watson and Crick earned recognition and public acclaim for their landmark research, it would not have been possible without the efforts of their predecessors and colleagues such as the British biophysicist Maurice Wilkins (1916–2004) and the British molecular biologist Rosalind Elsie Franklin (1920–1958). Wilkins and Franklin were the molecular biologists who in 1951 obtained sharp X-ray diffraction photographs of DNA crystals, revealing a regular, repeating pattern of molecular building blocks that correspond to the components of DNA. (Wilkins shared the Nobel Prize with Watson and Crick, but Franklin was ineligible to share the prize because she died in 1958, four years before it was awarded.)

Another pioneer in biochemistry, the Austrian Erwin Chargaff (1905–2002), also provided information about DNA that paved the way for Watson and Crick. Chargaff suggested that DNA contained equal amounts of the four nucleotides: the nitrogenous (containing nitrogen, a nonmetallic element that constitutes almost four-fifths of the air by volume) bases adenine (A) and thymine (T), and guanine (G), and cytosine (C). In DNA there is always one A for each T, and one G for each C. This relationship became known as base pairing or Chargaff's rules, which also includes the observation that the ratio of AT to GC varies from species to species but remains consistent across different cell types within each species.

Watson and Crick Model of DNA

Using the X-ray images of DNA created by Franklin and Wilkins, who also worked in the Cavendish Laboratory, Watson and Crick worked out and then began to build models of DNA. Crick contributed his understanding of X-ray diffraction techniques and imaging and relied on Watson's expertise in genetics. In 1953 Watson and Crick published the paper ''Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid'' (Nature, vol. 171, no. 4356, April 25, 1953), which contained the famously understated first lines, ''We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.'' Watson and Crick then described the shape of a double helix, an elegant structure that resembles a latticework spiral staircase.



SOURCE: Richard Robinson, ed., "Figure 3. Canonical B–DNA Double Helix," in *Genetics*, vol. 1, *A–D*, Macmillan Reference USA, 2002

Their model enabled scientists to better understand functions such as carrying hereditary information to direct protein synthesis, replication, and mutation at the molecular level. The three-dimensional Watson and Crick model consists of two strings of nucleotides connected across like a ladder. Each rung of the ladder contains an A-T pair or a G-C pair, which is consistent with Chargaff's rule that there is an A for every T and a G for every C in DNA. Watson and Crick posited that changes in the sequence of nucleotide pairs in the double helix would produce mutations.

Milestones in Modern Genetics

Geneticists and other researchers made remarkable strides during the second half of the twentieth century. In 1956 the American biochemist Vernon M. Ingram (1924– 2006), who would soon be recognized as the father of molecular medicine, identified the single base difference between normal and sickle-cell hemoglobin. The implications of his finding that the mutation of a single letter in the DNA genetic code was sufficient to cause a hereditary medical disorder were far reaching. This greater insight into the mechanisms of sickle-cell disease suggested directions for

research into prevention and treatment. It prompted research that uncovered other diseases with similar causes, such as hemophilia (an inherited blood disease associated with insufficient clotting factors and excessive bleeding) and cystic fibrosis (an inherited disease of the mucous glands that produces problems associated with the lungs and pancreas). Just three years later, the first human chromosome abnormality was identified: people with Down syndrome were found to have an extra chromosome, demonstrating that it is a genetic disorder that may be diagnosed by direct examination of the chromosomes.

Ingram's work has been the foundation for current research to map genetic variations that affect human health. For example, in 1989, more than 30 years after Ingram's initial work, the gene for cystic fibrosis was identified and a genetic test for the gene mutation was developed.

Using radioactive labeling to track each strand of the DNA in bacteria, the American molecular biologist Matthew Stanley Meselson (1930–) and the American geneticist Franklin W. Stahl (1929–) demonstrated with an experiment in 1958 that the replication of DNA in bacteria is semiconservative. Semiconservative replication occurs as the double helix unwinds at several points and knits a new strand along each of the old strands. Meselson and Stahl's experiment revealed that one strand remained intact and combined with a newly synthesized strand when DNA replicated, precisely as Watson and Crick's model predicted. In other words, each of the two new molecules created contains one of the two parent strands and one new strand.

In the early 1960s Crick, the American biochemist Marshall Nirenberg (1927–), the Russian-born American physicist George Gamow (1904–1968), and other researchers performed experiments that detected a direct relationship between DNA nucleotide sequences and the sequence of the amino acid building blocks of proteins. They determined that the 4 nucleotide letters (A, T, C, and G) may be combined into 64 different triplets. The triplets are code for instructions that determine the amino acid structure of proteins. Ribosomes are cellular organelles (membrane-bound cell compartments) that interpret a sequence of genetic code three letters at a time and link together amino acid building blocks of proteins specified by the triplets to construct a specific protein. The 64 triplets of nucleotides that can be coded in the DNA—which are copied during cell division, infrequently mutate, and are read by the cell to direct protein synthesis—make up the universal genetic code for all cells and viruses.

Human Genome Project and More

The Human Genome Project (HGP) set as one of its goals the determination of the entire nucleotide sequence of the more than 3 billion bases of DNA contained in the nucleus of a human cell. Initial discussions about the feasibility and value of conducting the HGP began in 1986. The following year the first automated DNA sequencer was produced commercially. Automated sequencing, which enabled researchers to decode millions, as opposed to thousands, of letters of genetic code per day, was a pivotal technological advance for the HGP, which began in 1987 under the auspices of the U.S. Department of Energy (DOE).

The 2001 publication of the human genome estimated that humans have between 30,000 and 35,000 genes. The HGP was completed in 2003, the same year that Cold Spring Harbor Laboratory held educational events to commemorate and celebrate the fiftieth anniversary of the discovery of the double helical structure of DNA. In October 2004 human gene count estimates were revised downward to between 20,000 and 25,000. During 2005 and 2006 sequencing of more than 10 human chromosomes was completed, including the human X chromosome, which is one of the two sex chromosomes; the other is the Y chromosome.

In 2006 Roger D. Kornberg (1947–), an American structural biologist at Stanford University, was awarded the Nobel Prize in Chemistry for determining the intricate way in which information in the DNA of a gene is copied to provide the instructions for building and running a

living cell. In 2007 the Nobel Prize in Physiology or Medicine was awarded jointly to Mario R. Capecchi (1937–), Sir Martin J. Evans (1941–), and Oliver Smithies (1925–), acknowledging their landmark discoveries about the use of embryonic stem cells (undifferentiated cells from the embryo that have the potential to become a wide variety of specialized cell types) to introduce gene modifications in mice, and their development of a technique known as gene targeting that is used to inactivate single genes. The postgenomic era began with a firestorm of controversies about the direction of genetic research, human cloning, stem cell research, and genetically modified food and crops.

Origins of Genetic Engineering

The late 1960s and early 1970s were marked by research that would lay the groundwork for modern genetic engineering technology. In 1966 DNA was found to be present not only in chromosomes but also in the mitochondria. The first single gene was isolated in 1969, and the following year the first artificial gene was created. In 1972 the American biochemist Paul Berg (1926 –) developed a technique to splice DNA fragments from different organisms and created the first recombinant DNA, or DNA molecules formed by combining segments of DNA, usually from different types of organisms. In 1980 Berg was awarded the Nobel Prize in Chemistry for

this achievement, which is now referred to as recombinant DNA technology. In 1976 an artificial gene inserted into a bacterium functioned normally. The following year DNA from a virus was fully decoded, and three researchers, working independently, developed methods to sequence DNA—in other words, to determine how the building blocks of DNA (the nucleotides A, C, G, and T) are ordered along the DNA strand. In 1978 bacteria were engineered to produce insulin, a pancreatic hormone that regulates carbohydrate metabolism by controlling blood glucose levels. Just four years later, the Eli Lilly pharmaceutical company marketed the first genetically engineered drug: a type of human insulin grown in genetically modified bacteria.

In 1980 the U.S. Supreme Court decision in *Diamond v. Chakrabarty* (447 U.S. 303) permitted patents for genetically modified organisms; the first one was awarded to the General Electric Company for bacteria to assist in clearing oil spills. The following year, a gene was transferred from one animal species to another. In 1983 the first artificial chromosome was created. In the same year, the marker—the usually dominant gene or trait that serves to identify genes or traits linked with it—for Huntington's disease (an inherited disease that affects the functioning of both the body and brain) was identified; in 1993 the disease gene was identified.

In 1984 the observation that some nonfunctioning DNA is different in each individual launched research to refine tools and techniques developed by the British geneticist Sir Alec John Jeffreys (1950–) at the University of Leicester in England that perform genetic fingerprinting. Initially, the technique was used to determine the paternity of children, but it rapidly gained acceptance among forensic medicine specialists, who are often called on to assist in the investigation of crimes and interpret medicolegal issues.

The 1985 invention of the polymerase chain reaction (PCR), which amplifies (or produces many copies of) DNA, enabled geneticists, medical researchers, and forensic specialists to analyze and manipulate DNA from the smallest samples. PCR allowed biochemical analysis of eventrace amounts of DNA. InA Short History of Genetics and Genetic Engineering (2003, http://www.dna50.com/dna50.swf), Ricki Lewis and Bernard Possidente describe the American biochemist Kary B. Mullis's (1944–) development of PCR as the ''genetic equivalent of a printing press,'' with the potential to revolutionize genetics in the same way that the printing press had revolutionized mass communications.

Five years later, in 1990, the first gene therapy was administered. Gene therapy introduces or alters genetic material to compensate for a genetic mistake that causes disease.

The patient was a four-year-old girl with the inherited immunodeficiency disorder adenine deaminase deficiency. If left untreated, the deficiency is fatal. Given along with conventional medical therapy, the gene therapy treatment was considered effective. The 1999 death of another gene therapy patient, as a result of an immune reaction to the treatment, tempered enthusiasm for gene therapy and prompted medical researchers to reconsider its safety and effectiveness.

Cloning (the production of genetically identical organisms) was performed first with carrots. A cell fromthe root of a carrot plant was used to generate a new plant. By the early 1950s scientists had cloned tadpoles, and during the 1970s attempts were under way to clone mice, cows, and

sheep. These clones were created using embryos, and many did not produce healthy offspring, offspring with normal life spans, or offspring with the ability to reproduce. In 1993 researchers at George Washington University in Washington, D.C., cloned nearly fifty human embryos, but their experiment was terminated after just six days.
In 1996 the British embryologist Ian Wilmut (1944 –) and his colleagues at the Roslin Institute in Scotland successfully cloned the first adult mammal that was able to reproduce. Dolly the cloned sheep, named for the country singer Dolly Parton, focused public attention on the practical and ethical considerations of cloning.

Conclusion

As we look forward, it is clear that one of the most important forefronts of modern genetic research lies in the area of what has been variously called ‘the genetics of development’, ‘developmental genetics’, and when combined with evolutionary theory, the ‘evolution of development’ or ‘Evo–Devo’ for short. These emerging fields, which synthesize the classical genetics of the first half of the 20th century with the molecular genetics and evolutionary biology of the second half, promise to yield a more complex, and hopefully more realistic picture of how the genome guides the individual organism from fertilization to adulthood. We are standing at a divide between an old and a new genetics, between a mosaic and mechanical and a holistic and integrated view of the organism that promises to yield exciting results in the years ahead. It behoves us to understand the pathway that has brought us to this historic juncture, not only so that we may take the fullest advantage of our newest research paths, but also that we avoid the disastrous social consequences that can arise from misplaced expectations of what genetics can do. Like all other scientific and technological findings, we must first understand the science itself and its history to recognize both its potential and its limitations.

Bibliography

Fisher, R.A. (1918). , The Correlation Between Relatives on the Supposition of Mendelian Inheritance. Transactions of the Royal Society of Edinburgh. 52:399G433.

Henig, R.M. (2000) The Monk in the Garden: The Lost and Found Genius of Gregor Mendel. New York: Houghton Mifflin Harcourt.

Lyell K. (Ed., 1881). The life, letters and journals of Sir Charles Lyell. 2 vols, London: J. Murray. Reprinted in 1983 by AMS Press, New York.

Merell, D. J. (1975). Introduction to Genetics. New York: Norton.

Ostrander, E.A., Giger, U. & Lindblad-Toh, K. (Eds., 2008) The Dog and its Genome. Cold Spring Harbor, NY: Cold Spring Harbor Press.

Santayana, G. (1905G1906). The Life or Reason, or, The phases of Human Progress. Vol1: Reason in Common Sense. New York: Scribner.

Savolainen, P. Zhang, Y., Luo, J., Lundeberg,J. & Leitner, T. (2002). Genetic evidence for an East Aasian origin of domestic dogs. Science, 298, 1610G1613.

Scott & Fuller (1965).
Stent, G.S. (1971). Molecular Genetics: An Introductory Narrative. San Francisco: W.H. Freeman

Sturtevant, A. H. (1965). A History of Genetics. New York: Harper and Row.

Vorzimmer, P.J., (1968) Darwin and Mendel: The Historical Connection, Isis, 59, 77G 82.

Allen, Garland. (2003). Mendel and modern genetics: The legacy for today. Endeavour. 27. 63-8. 10.1016/S0160-9327(03)00065-6.
https://www.researchgate.net/publication/10714832_Mendel_and_modern_genetics_The_legacy_for_today

Allen GE (1978) *Thomas Hunt Morgan: The Man and His Science.* Princeton, NJ: Princeton University Press.

Judson HF (1996) *The Eighth Day of Creation: Makers of the Revolution in Biology.* Plainview, NY: Cold Spring Harbor Laboratory Press.

Orel V (1996) *Gregor Mendel: The First Geneticist.* Oxford, UK: Oxford University Press.

The University of California, Irvine. The History Of Genetics
https://www.math.uci.edu/~brusso/The_History_of_Genetics.pdf

Lucia Hindorff, Ph.D., M.P.H. Mendelian Inheritance
https://www.genome.gov/genetics-glossary/Mendelian-Inheritance