

## From 'Particulate Factors' to 'Designer Genes': A Hundred Years of Genetics

It is the year 2000, most of the human genome has been sequenced, genetically engineered foods are on sale in supermarkets, and gene therapy is a reality rather than science fiction. We understand today how genes act to transform a fertilized egg into a fruitfly with a segmented body and paired legs and wings (or for that matter an unsegmented worm), and we even have great insight into exactly how heredity and environment interact to produce, through the wonderful process of evolution, the stunning array of diverse life-forms that inspire poets and scientists alike with their beauty. Indeed, biology today is almost nothing but genetics: practically every branch of biology, from development to physiology to ecology, is subsumed in the study of the transmission, expression and evolution of the hereditary material. The green revolution in agriculture was largely genetic in nature, and we are beginning to see the glimmerings of a similarly far reaching genetic revolution in medicine in the not too distant future.

Yet, just over a hundred years ago, the picture was vastly different. In 1900, just before the rediscovery of Mendel's Laws of Inheritance, heredity was still a mystery to biologists, and Darwin's theory of evolution by natural selection was still lacking the most important missing link: a mechanism for maintaining discrete hereditary variants in the face of interbreeding. Imagine the science of physics going from Galileo to Einstein in a hundred years, and you will get some feel for why many people would argue that the twentieth century was truly the century of genetics. This is a good time, then, to look back at the incredible and rapid strides we have made in our understanding of heredity in the twentieth century. It is also a good time to take a look at how Mendel's laws have stood the test of ten decades of genetic research.

Johann Mendel was born in 1822 in the village of Heinzendorf, then in the northernmost part of the Austrian empire and now in the Czech Republic. His father, Anton Mendel, was a moderately well-off peasant and Johann spent much of his childhood helping his family tend to fruit trees and bees. With some difficulty, due to financial limitations, he finished his schooling and went on to study philosophy for several years. In 1843 he joined the Augustinian Monastery of St. Thomas in Brünn (now Brno), partly, as he stated in his autobiography, to "be spared perpetual anxiety about a means of livelihood". Upon joining the monastery as a novice, Johann took on the monastic name of Gregor by which he is better known. In 1849, Mendel was assigned to teaching duties rather than pastoral work. He also had ample opportunity to indulge in his hobbies of gardening and bee-keeping in the extensive grounds of the monastery. Between 1851 and 1853, Mendel studied physics and botany at the University of Vienna and took up serious studies of hybridization after his return to the monastery.

Between 1856 and 1868, Mendel carried out a series of breeding experiments with peas and concluded from the results that certain 'particulate factors' were the units of inheritance, and that these factors were transmitted to and expressed in offspring in certain regular ways (Mendel's laws, with which we are all now familiar). Mendel summarized his work in two talks delivered to the Brünn Society of Natural Science, and the work was published in the proceedings of the society for 1866. The first talk described his experimental results, stressing the invariant ratios of different forms that were seen in hybrids arising from various crosses.

The second talk, a month later, laid out Mendel's explanation for these invariant ratios. The minutes of these meetings reveal that there were no questions or comments after Mendel's presentations. The audience, presumably, was completely taken aback by this 'new' sort of biology which dealt with quantitative results and probabilistic abstractions rather than concrete descriptions of structure or function. Yet, it seems that Mendel himself realized the significance of his work, telling a friend of his after one such meeting that his time would come.

Mendel's work, being truly ahead of its time, was not generally appreciated or understood. Mendel sent copies of his paper to Carl Nägeli at Munich, the leading German expert on plant hybridization at that time, and later exchanged a series of letters with him (an English translation of one of these letters is reproduced in this issue of *Resonance*). Nägeli, too, however, failed to see the significance of this work and appears to have regarded it as being largely an exercise in speculative reasoning (in his many writings on hybridization after his correspondence with Mendel, Nägeli does not mention Mendel's work even in passing). In 1868, Mendel became the abbot of the monastery and with increasing administrative duties his research essentially came to an end. Mendel died in 1884 after suffering from an ailment of the kidneys. Mendel was well liked and respected in Brunn, even by those who understood little of his science. He was known as a friendly, solicitous and compassionate person who genuinely cared for others. Upon his death the local newspaper paid him the following tribute: "His death deprives the poor of a benefactor, and mankind at large of a man of the noblest character, one who was a warm friend, a promoter of the natural sciences, and an exemplary priest".

To truly appreciate the almost prophetic nature of Mendel's conclusions from his experiments, we should take a look at what was known about inheritance at that time. Mendel's work came towards the end of almost 150 years of hybridization studies. Other workers before him had noticed that if one crossed two different true-breeding lines, the progeny were often uniform in appearance but that both parental traits reappeared in subsequent generations. Nobody, however, had ever tried to quantify the proportions in which the different types appeared. In fact, given the dominant view that inheritance involved some kind of 'blending' of paternal and maternal influences, the segregation of parental types in hybrid populations was something of a mystery. Chromosomes had not yet been discovered and, therefore, meiosis was unknown. And here was an obscure priest claiming that discrete particulate factors of inheritance existed in pairs in individuals, retaining their identity even if they were not expressed, and that parents passed on one member of each pair to their offspring. It is not, perhaps, surprising, that Mendel's work was not understood for many years.

In 1875, Strasburger described chromosomes, and Hertwig showed that fertilization involved the fusion of egg and sperm nuclei. In the next 15 years, a series of studies by Van Beneden, Hertwig, Rabl, Strasburger, Kölliker, Boveri, Flemming and Weismann established the nucleus as the seat of inheritance as well as the basic facts of mitotic and meiotic cell division. These findings set the stage for the eventual realization (by Sutton and Boveri, independently, in 1902-1903) that the behaviour of chromosomes during meiosis mirrored the predicted behaviour of Mendel's particulate factors of inheritance. Mendel's work itself was independently rediscovered and verified in 1900 by Carl Correns in Germany, Erich von Tschermak in



Austria and Hugo de Vries in the Netherlands, thus inaugurating the era of modern genetics.

After the rediscovery of Mendel's work, findings followed fast and furious. By the mid-1930s many of the basics of inheritance were understood. A whole lexicon of terminology was in place, the sequences of gene arrangement on chromosomes were being mapped, and Mendel's particulate factors had been shown to explain even the inheritance of continuous traits. Mendelism and Darwinism had been wedded to yield a composite genetic theory of adaptive evolution by natural selection. The next two decades yielded insights into how genes functioned by coding for enzymes, and also to the identification of DNA as the genetic material, and the elucidation of its double helical structure by Watson and Crick in 1953. In another 20 years, the mechanisms of DNA replication and expression were worked out, and today, as we all know, we can alter genes, design genes to our liking, and express genes from one organism in another.

In the midst of all these revolutionary advances in our understanding of heredity, Mendel's laws have stood the test of time well. Essentially, Mendel had managed to correctly deduce from his observed ratios of different types of progeny the behaviour of chromosomes during meiosis and fertilization even before chromosomes had been discovered. And since Mendel's laws are nothing more than a description of chromosome dynamics, they still hold true. Nevertheless, there are several exceptions to Mendel's laws. Genes physically close together on chromosomes do not assort independently during meiosis, a phenomenon called linkage. Genes on X and Y chromosomes, or those on mitochondrial or chloroplast DNA, are inherited in non-Mendelian ways. These, however, are exceptions to the letter rather than the spirit of Mendel's laws. In some cases, even the spirit of Mendel's laws is violated, due to phenomena unknown for many decades after the rediscovery of Mendel's work. Often some forms of a gene (alleles) are more successfully transmitted to offspring than others, either due to gametic selection or a phenomenon called meiotic drive. Sometimes it is not the transmission of genes but their expression that is non-Mendelian. This is the phenomenon of genome imprinting, that is now being intensively studied because of its involvement in many human disorders (this phenomenon and some of its interesting evolutionary implications are described in some detail in two articles in this issue of *Resonance*).

By and large, Mendel's work has clearly held its own in the face of new research. Subsequent work by others has validated what Mendel predicted, and though new phenomena have been discovered that may appear to violate his laws of inheritance, that is not really so in any fundamental manner. The basic framework of Mendelian inheritance is sound and deeply rooted in biological reality even though it was first conceived of in a rather abstract manner. Much like atoms, Mendel's particulate factors have finally acquired a structure and can be manipulated, split, recombined and harnessed for practical purposes. The hundred years of genetics after the rediscovery of Mendel's laws have, if anything, strengthened his claim to be considered one of the two (the other being Darwin) most important biologists of all time.

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