Editorial

Mendel and his legacy

This is the last year of the first century of genetics, the science of heredity, since the belated rediscovery of Mendel's research in 1900. For many of today's biological scientists and physicians, Mendel remains an obscure figure; often his work is given only cursory treatment in school and undergraduate courses in the race to understand the exciting technology of DNA.

History has relegated Gregor Mendel to a position analogous to that held by Samuel Pepsy. Pepsy, usually portrayed as an amorous buffoon, had a rich life in science and society outside the brief confines of his diary; he was one of the principal architects of the British Navy. So is Mendel perceived as a humble bespectacled monk, obsessionally fertilizing drab pea plants and fudging his data in a monastery garden. Hitherto, biographical details have been scant but a comprehensive account of his life and work by a Czech geneticist close to it has revealed Mendel's eclectic genius. His scientific mastery and perfection were incomparable. This year is the quartercentenary of another revolutionary, Oliver Cromwell, of whom John Buchan said: 'a great man lays on posterity the duty of understanding him'. I cannot pretend completely to understand Mendel but it is salutary to review his legacy and pay homage to the man whose biological discoveries have so much influenced medical thinking this century.

Mendel's early experiments in plant hybridization were read in early 1865 at meetings of the Natural History Society in Brno and published the following year in the society's journal. There are two papers in genetics of the twelve or so Mendel published on diverse subjects and the first, of 45 pages, is long and detailed. Even in translation, the paper is magnificent in its exposition, clarity and analytical integrity: the symbols used today to teach students about two- and three-factor crosses are exactly those employed in the original manuscript. The experimental detail is fastidious and the practice was systematic and painstaking. Some will remember that Mendel took seven pairs of contrasting characters, affecting the seed (round/wrinkled; coat colour, colour of storage material within) and characters in the plant (distribution of flowers, shape and colour of the pods, length of stem). Later he studied flower colour. Mendel used the garden pea because the flowers of these and other leguminous plants were large enough for him to remove the anthers and pollinate artificially with a brush.

In his first paper, Mendel announced the principles of segregation and of independent assortment of characters having studied multi-trait crosses. He achieved this before chromosomes and their behaviour in meiosis had ever been observed: remarkably there are seven chromosome pairs in the garden pea. We now know that two of the characters studied by Mendel have genetic determinants on chromosome 1, three on chromosome 4, one on chromosome 5 and one on chromosome 7. Although four pairs of genes turn out to be syntenic, three of these are at loci so far apart on their respective chromosomes that the phenomenon of linkage would not have been discovered even in hundreds of experimental crosses. Two genes, alleles of which determine pod morphology and stem length respectively, may have shown significant linkage but these were not investigated.

It is thus either fortuitous or a mark of Mendel's genius that the principle of independent assortment was not violated.

A lesser-known publication of Mendel is his paper on hybrids of the various species of hawkweed (Hieracium). This was reported in 1870 in the same journal as the first publication. It demonstrates Mendel's continued involvement with breeding experiments using a favourite plant of his illustrious but disappointing correspondent, Carl Nägeli. Mendel had continued his experiments despite having been promoted (in 1868) to the responsible post of Prelate (Abbot) of the Augustinian monastery in Brno where he worked until his premature death at the age of 62 in 1884. He struggled with Hieracium because the fertilization experiments were technically difficult and the plants difficult to cultivate. The peculiar structure of their minute flowers presented a particular challenge: 'most complicated and tires the eye'. After struggling for four years, Mendel gave an account of his findings with some of the more fertile hybrids: he was unable to demon-
strate any segregation of the original parental traits. Unfortunately, the demands of his prelacy did not provide sufficient opportunity to continue this work with Hieracium or to examine the reputedly constant hybrids of the willow, Salix. Mendel was intrigued by the reduced fertility of his hybrids, and this tantalized him even after his practical work ceased in 1872. His notebooks show repeated calculations of combinations in the light of his earlier work with the garden pea—a matter he did not resolve but one which he had the intellectual courage to attack persistently.

It is only now that we know that the hawkweed is one type of plant that exhibits a most complex inheritable trick: a genetically-determined apogamy (parthenogenesis), thus resulting sometimes in constant and sometimes in variable progeny of self-fertilized hybrids. Mendel had confirmed his findings of variable hybrids in the bean, Phaseolus. Without wishing to enter the debate of whether he or others did or did not falsify the results, one can only conclude by saying that Mendel was right and reproducibly right, and did not falsify his intractable results with the enigmatic hawkweed.

Today the discoveries of Mendel are pre-eminent in biology. His genetic experiments formally started in 1856 or 1857; Charles Darwin published his Origin of Species in 1859, a copy of the 1862 German translation of which was bought by Mendel shortly after publication. Mendel was the son of a peasant farmer and had an early fascination for plant breeding which continued all his life but the strategic question behind the research reflected his hunger for an understanding of speciation. In the event, Mendel’s work provided the underpinning discovery that had eluded Darwin and his illustrious cousin, Galton: the quantitative understanding of heritable traits central to evolution. Clearly, the work of Mendel and Darwin surpassed anything thought possible before. It is astonishing that their independent discoveries, which provide mutual conceptual unification were arrived at almost simultaneously. Mendel’s annotations of several of Darwin’s texts, which he acquired for the monastery library, reveal his fascination but also irritation with the speculative aspects of Darwin’s exposition of heredity, and of the latter’s poor experimental techniques of cross-fertilization.

After 1900, Mendel’s findings were quickly reproduced in experiments employing other plant genera and in animals. His methodological contributions were of a meticulous quantitative analysis and the application of combinatorial methods to verify the unitary and discrete nature of heritable traits—exact science. Although Mendel never solved the problem of inheritance in Hieracium, he postulated the existence of several forms of the same trait—polygenic inheritance in modern terms—and also recognized the effects of environmental factors on their expression. Today the study of polygenic traits occurring in discrete classes of individuals with or without disease is an attractive focal point for medical research.

The classical recognition of monogenic traits in the inborn errors of metabolism by Archibald Garrod has a direct link to Mendel. Garrod, whose early work might best be described as the study of chemical pathology, first reported his study of chemical abnormalities in the urine and noted that often, more than one member of a family was affected by the ‘freak of metabolism’. In 1901, a year after the rediscovery of Mendel’s work, Garrod noted that there was an increased likelihood of first-cousin marriages amongst the parents of patients with alkaptonuria. At that stage, Garrod himself was not sufficiently equipped to understand the full significance of his observation. This depended on William Bateson, a brilliant Cambridge biologist, who had been struck by the rediscovery and confirmation of Mendel’s work on the continent. Bateson was the champion of Mendelism in Britain and first coined the term ‘genetics’. He immediately realized that alkaptonuria was an example of a recessive hereditary trait that behaved as a Mendelian recessive and from 1901 entered into vigorous correspondence with Garrod. It appears that Garrod did not fully comprehend the science of heredity for several years but he understood it well enough to propose the existence of the inborn errors of metabolism. This prompted his life’s work, leading to the concept of chemical individuality and in his second major book, the recognition of an individual’s genetic susceptibility to disease: ‘The inborn factors in disease’ which appeared in 1931. It was thus Garrod, through his direct links with Mendelian thought, who provided the theoretical underpinning of much contemporary research to determine the role of genes in susceptibility to common diseases.

The importance of genetic linkage was realised by the great American geneticist Thomas Hunt Morgan, who was born in the same year that Mendel’s paper first appeared. Morgan in his early studies with Drosophila demonstrated and extended the concept of genetic linkage or gametic coupling, originally discovered by Bateson and colleagues in the sweet pea. Morgan observed linkage of genes for eye colour in the fly and showed that this was related to inheritance of sex. He observed the occurrence of spontaneous mutation in Drosophila populations; he later postulated the linear arrangements of genes on the chromosomes and the concept of recombination resulting from crossovers.

It is ironic that Morgan was awarded a Nobel prize in physiology or medicine, for although he recognized that man inherits his characters in the same way as other animals, he was critical of the potential
of humans to furnish informative material for genetic analysis. Morgan recognised that genetics would be increasingly helpful in identifying the risks of transmitting hereditary traits, especially in marriages between individuals with hereditary diseases in their ancestry. However, he also wrote: ‘I am aware of course of ancient attempts to identify certain gross physical human types—the bilious, the lymphatic, the nervous and the sanguine dispositions, and of more modern attempts to classify human beings into the cerebral, respiratory, digestive and muscular or more briefly into aesthenics and pycnics. Some of these are supposed to be susceptible to certain ailments or diseases than other types, which in turn have their own constitutional characteristics. These well-intended efforts are, however, so far in advance of our genetic information that the geneticist may be excused if he refuses to discuss them seriously. …’

Is it not surprising still to read in textbooks that pernicious anaemia frequently affects individuals of a Nordic constitution with blue eyes and a broad face and the like? In the event, Morgan provided the basis for quantitative studies of genetic linkage which have been critical for the identification of single genes responsible for human traits in latter-day strategies for positional cloning.

Mendel did not discover genetic linkage but at the end of his first paper reported experiments with beans that almost certainly show that he was aware of another phenomenon, later elaborated by Bateson as epistasis. In epistasis, several genes that affect the same trait interact to influence the final phenotype, as clearly demonstrated in Mendel’s case by the flower pigments. This is revealed in Mendel’s designation of the symbols A₁ and A₂, representing a crimson colour of bean flowers contrasted with a little ‘a’ denoting the white colour—this suggesting the idea of composite series in the progeny of Phaseolus hybrids. Later breeding experiments with other plant genera led to his supposition that a composite series of characters were influencing the colour traits leading to floral diversity. Perhaps the fascination of this for Mendel was the increased combinatorial complexity of characters that were not mutually exclusive. The studies provide experimental evidence of discrete traits in inheritance that can be reconciled with the continuous, rather than the discontinuous evolution of traits leading to speciation. Identification of epistasis with the realization that individual traits may be affected by several genes leading to interactions, eventually led to the genetic dissection of complex biosynthetic pathways. This was most vividly shown by George Beadle and Edward Tatum in their studies of Drosophila eye colour and auxotrophic factors in the mould Neurospora leading to the ‘one gene-one-enzyme hypothesis’.

In his Nobel lecture, Beadle paid handsome tribute to the then little-recognized work of Garrod; but the credit surely must also go to Bateson and Mendel.

The genetic revolution in biology and medicine shows little sign of abating. In contrast, Mendel’s discoveries, having eluded recognition in his lifetime, have passed through periods of glorification as well as ideological exclusion and Stalinist tyranny (under the influence of the infamous Soviet neo-Marxist, Trofim Lysenko)—which all but obliterated the Augustinian monastery in Moravia where Mendel worked. Perhaps worst of all, is latter-day cynical indifference that stems from assumed familiarity with Mendel’s work. All this has been compounded by the unjustified taint that he cheated. Despite persecution under Nazism, and vicious anti-Mendelian ideology later promulgated by the Communists in Czechoslovakia, Vítězslav Orel, and his predecessor Kříženecký have provided compelling evidence of the originality and intellectual conviction of Mendel.

The archives of the Mendel museum, started by Kříženecký despite the breakdown of his health following imprisonment by the Communists, document the intellectual scene in which he and his fellow monks worked in the waning years of the Hapsburg Empire, of which Moravia was but a small part. The Augustinian monastery of St. Thomas in Brno provided a high standard of education as well as pastoral and medical care to the local population. Mendel’s contemporaries in the monastery, which he entered after leaving the local gymnasium rather than return to his beleaguered family on the farm in Heinzendorf, were distinguished by their national and international activities. It was a community of intellectuals with diverse liberal views united by their interests in natural philosophy and education.

Are there lessons for us to learn from Mendel’s example? Mendel’s early development was thoughtfully supported by the Abbot he was to succeed, Cyrill Napp, a philosopher and an expert vine grower and apple cultivator. Also in the monastic community was Klácel, who held revolutionary views about Czech nationalist identity and had been a student of Hegel; Klácel was a strong friend of Mendel until he left the monastery to settle in the United States in 1869, where he lectured on Darwinian evolution. Tomáš Bratráněk, Mendel’s competitor for the prelacy, was a renowned university teacher, Goethe scholar and author of publications in natural philosophy who ultimately became Rector of the University of Cracow. Finally there was Pavel Křížkovský, a talented musician and composer as well as choirmaster in the monastery. Křížkovský created a brilliant teaching environment including the organ school that greatly influenced the emerging genius of the musician Leop Janáček who entered the monastery as a chorister of 11 and remained there for many years. A prodigious organist like his mentor, he
maintained the affiliation throughout his life. Indeed, it was the 29-year-old Janáček, by then a choirmaster and emerging composer, who conducted the requiem at Mendel’s funeral held in the monastery church.

Mendel was in many ways a modern investigator who did not work in a vacuum. His need to prove himself and follow his ideals found the support of an inspiring and loyal mentor; while he did not have any social advantages or an influential pedigree of his own to draw upon, he was attracted to, and accepted by, a scientifically-minded group in a liberal atmosphere of debate. The support of the monastery had enabled him to study at Vienna University as a mature student. Here he was further influenced by established scientists—among them Franz Unger, who had written on the hybridization of plants and had used artificial pollination to create new varieties. In Vienna, Christian Doppler, the discoverer of the Doppler effect and author of textbooks on combinatorial theory and probability taught Mendel physics, and Redtenbacher, a pupil of Leibig, taught him chemistry.

To praise Mendel’s environment is not to detract from the man. For although he could not know of the processes taking place in the formation of gametes, he made the correct assumption that hereditary determinants segregate in the germ cells in such a way that each gamete contains only unitary elements. Moreover, Mendel justified the validity of this assumption by putting it to crucial experimental tests. As Morgan himself stated: ‘his analysis was a wonderful feat of reasoning. He verified his reasoning by the recommended experimental procedure of science’.

Other aspects of Mendel’s life are instructive for contemporary scientists. His last years in the monastery were burdened by administrative responsibilities and poisoned by disputes with the pervasive officialdom of the Austro-Hungarian Empire. Ultimately, his equanimity and health was undermined by courageous but rigid attempts to resist crippling taxation; this led to Mendel’s alienation by junior clerics. Quite soon after his death, however, taxation of the monastery was rescinded.

Several lasting images of Mendel as monk and Prelate survive. In his book, Bateson chose two: from 1880 we see the distinguished figure of Mendel as Prelate with a double chin, frustrated in his desire to continue the experiments in apiculture, meteorology and plant breeding that he was earlier so driven to do. I cherish the photograph of 1862, in which we see the 40-year-old Mendel, already five years into his critical plant breeding experiments: his sparkling expression somehow shows that he knew that the discoveries in which he invested his hope and quiet ambition, would be of lasting value. Denied the vision of immortality granted to ordinary individuals through their offspring, it may be said that Johann Mendel, who sacrificed himself as the novice Gregor to the monastery for education and research, achieved a unique genetic permanence of his own.

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References