# A Century of Mendelism in Human Genetics

EDITED BY
Milo Keynes
A. W. F. Edwards
Robert Peel

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The Galton Institute

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Proceedings of a symposium organised by the Galton Institute and held at the Royal Society of Medicine, London, 2001

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# Contents

**Appendix:**

# Notes on the Contributors

**Sir Patrick Bateson,** Sc.D., FRS, Professor of Ethology, University of Cambridge; Provost of King's College, Cambridge

**William Bateson,** FRS, Fellow, St John's College, Cambridge in 1900

**John Bell,** DM, FRCP, Regius Professor of Medicine, University of Oxford; John Radcliffe Hospital, Oxford

**Michael Bulmer,** D.Sc., FRS, Emeritus Professor, Biological Sciences, Rutgers University, New Jersey; The Old Vicarage, Chittlehampton, Umberleigh, Devon

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**M.A.Ferguson-Smith,** FRCPath, FRS, Emeritus Professor of Pathology, University of Cambridge; Department of Clinical Veterinary Medicine, Cambridge

**Milo Keynes,** M.D., FRCS, Galton Institute; Hon. Fellow, Darwin College, Cambridge

**Alfred G.Knudson, M.D.,** Fox Chase Cancer Center, Philadelphia, Pennsylvania

**Lucio Luzzatto,** M.D., Director, Istituto Nazionale per la Ricerca sul Cancro, Geneva

**Eileen Magnello,** D.Phil., Wellcome Trust Centre for the History of Medicine at University College London

**Newton E.Morton,** Hon. FRCP, Professor of Genetic Epidemiology, University of Southampton; Southampton General Hospital, Southampton

**Sir David Weatherall,** D.M., FRCP, FRS, Emeritus Regius Professor of Medicine, University of Oxford; Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford

# Preface

The symposium “A Century of Mendelism in Human Genetics”, arranged by the Galton Institute and held at the Royal Society of Medicine in London on 30 and 31 October 2001, has a relevance to the Human Genome Project. Besides being of general medical concern, its proceedings will be of particular interest to departments of genetics and medical genetics, as well as to historians of science and medicine.

In 1901 William Bateson, FRS, Fellow of St John’s CoUege, Cambridge, published a lecture (reprinted here as an appendix), which he had delivered the year before to the Royal Horticultural Society in London. In this he recognised the importance of the work completed by Gregor Mendel in 1865 and brought it to the notice of the scientific world. Archibald Garrod, working on patients with alkaptonuria, read Bateson’s paper and, realising the relevance of Mendel’s law to human disease applied it to this “inborn error in metabolism” in 1902. He thus introduced Mendelism into what was to become medical genetics, as the term “genetics” was only coined by Bateson in 1905.

The contributions in the first part of the proceedings are historical. Francis Galton (1822–1911) began his efforts to discover the laws of inheritance in man on reading *On the Origin of Species* on its publication in 1859, writing his first work on heredity in 1865, which culminated in his “Theory of Ancestral Inheritance” in 1897. This theory was championed by the biometricians in bitter controversy with the Mendelians before the full acceptance of Mendelism. The second part is concerned with human genetics from 1950 and ends with a chapter on “Genetics and the Future of Medicine”. The Galton Lecture for 2001 given by Allan Bradley, FRS, Director of the Sanger Institute, Hinxton, Cambridge, on “The Human Genome Project” has not been included.

There is no index to this book, as we found that making one was a work of supererogation, which we therefore abandoned. Half the entries, such as “Mendel” and “Galton”, were giving so many leads to so many papers as to be unhelpful, and half were leading to a single paper already obviously relevant from its title alone.

**A Note on the Galton Institute**

This learned scientific society was founded in 1907 as the Eugenics Education Society, changing its name to the Eugenics Society in 1926, and becoming the Galton Institute in 1989. Francis Galton defined eugenics as “the scientific study of the biological and social factors which improve or impair the inborn qualities of human beings and of future generations” in 1883. The Institute is committed to environmental and genetic studies, and its membership is drawn from a wide range of disciplines, including the biological and social sciences, economics, medicine and law.

# The First Fifty Years of Mendelism

# 1.
# The Introduction of Mendelism into Human Genetics

Milo Keynes

On 8 May 1900, William Bateson (1861–1926), Fellow of St John's College, Cambridge, gave a paper, "Problems of Heredity as a Subject for Horticultural Investigation", to the Royal Horticultural Society in London, published in the Society's journal[1] the next year (and here reprinted as an appendix). According to Robert Olby's reassessment of 1987[2], a few days before delivering the lecture Bateson was handed an offprint: "Sur la loi de disjonction des hybrides",[3] published in *Comptes Rendus de l'Académie des Sciences* sometime before 21 April. This had been sent to the hybridist Charles Hurst (1870–1947), a collaborator of Bateson since 1899, by its author, Hugo de Vries (1848–1935) of Amsterdam. Bateson's widow, Beatrice, mistakenly wrote in 1928[4] that Bateson "read Mendel's actual paper on peas for the first time" on the train to London and incorporated it in his lecture. In fact, he read de Vries's offprint, in which there was no reference to Mendel's paper. Bateson's lecture was then delivered without mention of Mendel's name or his work.

The *Comptes Rendus*[3] offprint was a summary of a paper[5] by de Vries on the segregation of hybrids published in the *Berichte der Deutschen Botanischen Gesellschaft* on 25 April, a copy of which de Vries sent to Hurst on 19 May and after Bateson's lecture. This did refer to the paper given in 1865 by Gregor Mendel (1822–1884) on "Versuche über Pflanzen-Hybriden"[6] ["Experiments in Plant Hybridisation"], which gave the results of Mendel's 20,000 experiments, made between 1857 and 1863, in crossing varieties of the garden pea, *Pisum sativum*. That paper was also the first to employ the theory of probability in biology. As shown by Olby,[2] Mendel had done the work to try and see if hybridisation gave a better explanation of the origin of species than transmutation, and not to search for a general theory of heredity.

On reading de Vries's *Berichte* paper,[5] Bateson, who was fluent in German, searched out Mendel's paper[6] and gave it a fall citation in the printed text of his RHS paper[1] in 1901. In this he also made comment on de Vries's two papers,[3,5] but merely named the other publications[7,8,9,10,11] of 1900 by de Vries, Carl Correns (1864–1933) of Tübingen and Erich von Tschermak-Seysenegg (1871–1962) of Vienna, that also discussed Mendel's work. A translation of Mendel's paper appeared in the Royal Horticultural Society's journal[6] later in 1901, as well as being published with modifications in Bateson's *Mendel's Principles of heredity: A Defence,* Cambridge, 1902. Soon after this, Bateson and Saunders[12] published the results of experiments on crossing poultry, and Lucien Cuénot (1866–1951)[13] on mice, each of which showed that Mendel's theory applied to the animal kingdom. Bateson's book *Mendel's Principles of Heredity*[14] (again with the translation of Mendel's paper) followed in 1909.

Bateson's recognition of the importance of Mendel's work has more significance than mere questions of priority in the publications of 1900. What genetics now has are two laws—the law of segregation and the law of independent assortment—both derived from Mendel, that summarise part of his paper. In fact, they were not named until long after his death.

## Mendel's studies on hybridisation of the garden pea

The first use of *Pisum sativum* in the study of hybrids began in 1787. It was reported[15] to the Royal Society in 1799 by Thomas Andrew Knight (1759–1838) in experiments initially designed to see whether it was possible to confer characters on apples by artificial pollination. Knight crossed two varieties of peas and (to use today's Mendelian terms) discovered dominance in the first hybrid generation. He backcrossed the hybrids to the recessive parent and found both dominant and recessive types in the progeny. In 1822, John Goss[16] and Alexander Seton,[17] working independently (and with their results verified by Knight[18]), reported crossing different varieties of peas and discovering dominance in the first hybrid generation and the reappearance of both types in the second generation. Goss found three types in the third generation, the recessive, the heterozygous dominant (which produced some recessives as segregants) and the homozygous dominant that bred true. As noted by Conway Zirkle,[19] all of Mendelism had, in fact, been recorded except the independent inheritance of separate factors (itself described by Augustin Sageret[20] in melons in 1826), and a definite numerical ratio in the second generation (described by Johann Dzierzon[21] in bees in 1854).

Mendel chose *Pisum sativum* because its seed and plant have striking characteristics that are easily and reliably distinguishable, because it yields fertile hybrids and because the pollinated flower can easily be protected from crosspollination. He crossed varieties differing from each other in one definite character and studied discontinuous variation of seven pairs of characters. He read his paper in two parts on 8 February and 8 March 1865 to 40 members of the Naturforschender Verein (Natural Science Society) of Brünn, Austria, now Brno, Czech Republic. When asked to publish the text, Mendel only handed it over after he had re-examined his "records for the various years of experimentation, and not having been able to find a source of errors"[22]. It was published in the Transactions of the Society[6] in 1866.

In its analysis of the inheritance of particular characters, Mendel's paper was entirely unlike all that had gone before. The aims of the hybridists and breeders were quite different. None of Mendel's audience were horticulturists or theoretical biologists, but, although the volume containing his work was only the fourth of a new publication, it was widely distributed by exchange arrangements with 115 universities, academies and scientific societies in Europe and the United States, so that every prominent biologist of the mid-nineteenth century had access to the paper[23]. The copy read by William Bateson was easily available to him from Cambridge University Library, as a copy possibly received on publication (and perhaps by exchange) was bound there in 1881.[2] However, though present as recently as 1985, it is now missing from the library.

Mendel ordered 40 offprints of his paper to distribute on New Year's Day of 1867, of which 8 have been traced.[22] Two are in Brno, and two others, one in Indiana University, Bloomington and one in Mishima in Japan, came from Brno in about 1921. One, now in Graz University, was sent to the botanist Franz Unger (1800–1870), who had been one of Mendel's teachers in Vienna (but was by then in retirement), and it remained unread. One went to the botanist Anton Kerner von Marilaun (1831–1898) at Innsbruck, who took a cynical view on laws of heredity and did not bother to read it, and one to another botanist, Carl Wilhem von Nägeli (1817–1870) in Munich, who lost no time in slitting open the pages, but whose behaviour towards the "amateur" Mendel was patronising and unhelpful.[23]

Nägeli suggested that Mendel should confirm his findings using hawkweed *Hieracium* hybrids, but this plant, which reproduces asexually, gave utterly disappointing results and led Mendel to doubt his original findings and to discontinue his botanical experiments by 1869.[24,25] Another reason for abandoning his work was that two years after the publication of the *Pisum* paper he had been elected abbot of the Augustinian monastery at Brünn and found he had little time for experimenting (besides complaining in a letter to Nägeli in 1867 of increasing girth limiting his botanical activity).[22]

Sometime before 1889, the eighth offprint, still in Amsterdam, reached the Dutch biologist Martinus Willem Beijerinck (1851–1931), who knowing Hugo de Vries was studying hybrids, sent it to him in 1900 at the time he was about to publish the results of his experiments.[26] De Vries's *Berichte* paper[5] (which mentioned the work of Mendel) was sent off to Berlin on 14 March and published on 25 April 1900.[2] De Vries followed this by sending a short summary[3] of it (albeit with no mention of Mendel) to *Comptes Rendus,* which was published in Paris before 21 April and got to Bateson by 7 May. This reached Carl Correns earlier than the paper published in Berlin, and as a result Correns[8] made the accusation that de Vries had been dishonest in delaying to make reference to Mendel in his writings.

De Vries, Correns and Tschermak studied different problems of plant hybridisation: each thought of himself as an innovator and each began to write the report on his experiments without knowing of Mendel's work. Even when they referred to it, they failed fully to understand it. Despite the wide impression given that all three rediscovered Mendel by independent search of the literature, both Correns and certainly Tschermak appear to have completed their reports after seeing de Vries's Berlin paper, where the reference to Mendel had been made from the reprint sent to de Vries by Beijerinck. No wonder that the identity of the rediscoverer of Mendel has been somewhat indecisive. It is, in any case, historically less important than the enthusiasm with which William Bateson hailed the significance of Mendel's work "with a kind of triumphant gladness".[4]

There were thirteen references to Mendel's *Pisum* paper in the literature between 1866 and 1900, most of them slight. They included mentions in the German botanical journal *Flora* in 1866, 1867 and 1872; the *Proceedings of the Viennese Academy of Science* in 1871 and 1879; the thesis of C.A.Blomberg in 1872 for Stockholm University; the thesis of I.F.Schmalhausen for St Petersburg University in 1874; and the Royal Society's *Catalogue of scientific papers (1864–73)* issued in 1879; 4:338.[22] More substantial is the reference in the publication[27] of 1869 by Hermann Hoffmann (1819–1891) on the determination of species and varieties, in which he attempted to refute Darwin's theory of evolution by denying the importance of variations as a basis for the formation of new species. Darwin himself made marginal notes in his copy of Hoffmann's book, but none against the pages in which there was mention of Mendel's hybridisation experiments. He also referred to Hoffmann's book in his *The Effects of Cross and Self-Fertilisation in the Vegetable Kingdom* (1876).

There is mention—but no signs of understanding—of Mendel's pea experiments in the book[28] of 1881 on plant hybrids by Wilhelm Olbers Focke (1834–1922), which was itself cited in two books[29,30] by L.H.Bailey (1858–1954) in 1892 and 1895. Charles Darwin (1809–1882) passed on his copy of Focke (received in November 1880) unread to G.J.Romanes (1848–1894), who then included Mendel's name in the list of hybridists at the end of the section on "Hybridism" in the *Encyclopaedia Britannica*[31] of 1881–1895 without any comment or apparently having read the pages in which reference is made to Mendel's experiments. Only in 1958 in his memoirs[32] did Tschermak state that in the winter of 1899–1900 he had found and used the reference to Mendel in Focke's book (thus belatedly reclaiming his priority in the rediscovery of Mendel in his paper[11] of 1900).

## Darwin and Mendel

Mendel planned and began his experiments on *Pisum* two to three years before the publication of *On the Origin of Species* in 1859, before he could have heard of Darwin's theories. He knew no English and only bought and annotated the second German edition[33] of *On the Origin of Species* when it was published in 1863, though he must have heard of it earlier. Indeed, Alexander Makowsky (1833–1908) delivered a paper, "Ueber Darwin's Theorie der organischen Schöpfung" ["Theory of organic creation"], on 11 January 1865 to the Brünn Natural Science Society (*Sitzungsberichte,* vol. IV 1865, pp. 10–18) a month before Mendel gave his first paper, though there is no evidence that Mendel was present at the meeting.[22]

Mendel visited England in 1862 as a member of a delegation to the Great Industrial Exhibition in London. However, he could not have gone to Down House and met Darwin that week as, after an attack of scarlet fever in the family, all the Darwins were away.[34] In any case, the Church authorities in Austria would scarcely have condoned an excursion to Downe, and any visit there by a Catholic priest would have caused much local comment.

Mendel bought most of Darwin's works, studying them closely and making frequent annotations. When he prepared his 1865 paper, Darwin's work was very much in his mind, and where he reflected upon it he did so objectively and without adverse criticism. He appears to have deliberately avoided opposing Darwin's views on inheritance by never mentioning his name in his lectures or scientific papers and only rarely in his drawn-out correspondence with Nägeli. He was not an adversary of Darwin's theories, but considered that an adequate theory of heredity was lacking from his system.[23,25] He clearly accepted the fact of evolution, and Sir Gavin de Beer[34] suggested in 1964 that he appears to have hoped that his discovery would provide something about evolution that was lacking, an explanation for the origin of a sufficient supply of heritable variation for natural selection to work on.

Darwin never visited Brünn, and his collection of offprints of scientific papers in Cambridge University Library does not include one of those sent out by Mendel in 1867.

Two copies of the Transactions of the Natural Science Society of Brünn of 1866, received in 1867, were available to Darwin in London (at the Royal Society and the Linnean Society), but there is no evidence that he, or other Fellows for that matter, took them from the shelves.[23] A sentence in Hoffmann's book[27] dealing with Mendel:

> He believed that hybrids have the tendency to revert in later generations to the parental species

missed Mendel's important points, such as constant numerical ratios, of dominant and recessive characters and of non-blending hereditary transmission, and was hardly likely to have aroused Darwin's interest sufficiently for him to have consulted the original work.

The difficulty that Darwin had in reading scientific German could be another reason why he failed to perceive the importance of Mendel's laws of heredity for his theory of evolution, but his ignorance of mathematics is far less likely a reason, despite what he wrote in his autobiography[35]:

> I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics; for men thus endowed seem to have an extra sense. But I do not believe that I should ever have succeeded beyond a very low grade.

In *The Life and Letters of Charles Darwin*[36], Francis Darwin (1848–1925) wrote of the great labour his father found in studying German texts and how little he could manage to read at a time. "He was especially indignant with Germans, because he was convinced that they could write simply if they chose….He learnt German simply by hammering away with a dictionary; he would say that his only way was to read a sentence a great many times over, and at last the meaning occurred to him." Between 1860 and 1865 he paid his children's governess, Camilla Ludwig, to translate from the German for him,[37] and laughed "at her if she did not translate it fluently."[36]

## Galton and Mendel

Before mentioning Mendel in his paper[1] of 1901, Bateson wrote that he expected that general expressions capable of wide application would be found that could justly be called "laws" of heredity, although, he added, there had so far been few investigations on the transmission of characters. Such laws had been obtained by statistical methods, and he acknowledged that the first systematic attempt to enunciate them had been due entirely to Francis Galton (1822–1911). Galton, half-first cousin of Charles Darwin (Erasmus Darwin [1731–1802] was the grandfather of both), read *On the Origin of Species* on its appearance and immediately began to consider mankind's future in the light of the theory of evolution. His first work[38] on heredity appeared in 1865 and was followed by *Hereditary Genius*[39] in 1869 (Galton later wished he had used the word "talent" in the title to imply high ability rather than "genius"). In turn, came *A Theory of Heredity*[40] in 1875; *Typical Laws of Heredity*[41] in 1877; *Regression towards Mediocrity in Hereditary*

*Stature*[42] in 1885; and *Natural Inheritance*[43] in 1889. Galton's "Theory of Ancestral Inheritance", derived from "The Law of Regression"[42] of 1885, appeared as "a new law of heredity"[44] in 1897.

His main effort from 1865 was to try to discover laws of inheritance in man. He rejected the idea of L.A.J.Quetelet (1796–1874) that all variation in human physical characteristics was an error about a type, and insisted "that the laws of Heredity were solely concerned with deviations expressed in statistical units". He saw that without variation there was no evolution. Deviation from the average was not an error. The answer, he thought, could be achieved by counting and figuring and by bringing quantitative methods into biology, with his maxim being "whenever you can, count".[45]

In 1877, encouraged by Darwin and with the backing of the botanist Joseph Hooker (1817–1911),[45] Galton began to breed the sweet pea, *Lathyrus odoratus*. He chose it because it had little tendency to cross-fertilise and all the peas in the pods were roughly the same size. He classified the seeds according to weight and gave a set of seven packets, each containing ten seeds of the same weight, to nine friends, including Darwin, to undertake their planting and culture—there is a letter from Downe in September 1877 advising him to "come down and sleep here and see them. They are grown to a tremendous height and will be very difficult to separate."[46] With two failures, the plantings gave the produce of 490 carefully weighed seeds to create what was probably the first bivariate distribution. From this Galton constructed the first regression line (although his own term was "reversion").[41]

The data showed that seed weight was to some extent heritable and that quantitative traits are normally distributed in successive generations. John Edwards[47] has pointed out that, if Galton had been a better mathematician, his genetic law might have preceded Mendel's law in the scientific world's knowledge by twenty-three years. It was, however, anthropological evidence that Galton wanted and looked for by using pedigree analysis, twin studies and anthropometry. He cared "only for the seeds as means of throwing light on heredity in man".[48]

Bateson wrote to Galton on 8 August 1900, suggesting that he look up Mendel's paper "in case you may miss it. Mendel's work seems to me one of the most remarkable investigations yet made on heredity."[46] However, Galton, by then 78, failed to appreciate its significance and took little part in the controversy that then arose between the Mendelians and those who championed his law of ancestral heredity. Galton stated this law as follows: "The influence, pure and simple, of the mid-parent may be taken as a half, of the mid-grandparent as a quarter, of the mid-great-grandparent as an eighth, and so on."[42] It makes little sense under Mendelism, but follows naturally from Galton's theory of heredity, in which the hereditary particles are equally likely to be patent (expressed) or latent (not expressed). The ancestral model seemed to accommodate continuous variation satisfactorily and was taken up by the biometrician Karl Pearson (1857–1936), who developed the theory of multiple regression from it and generalised Galton's law as a prediction formula. like his fellow biometrician, W.F.R.Weldon (1860–1906), Pearson did not accept Mendelism as the theory of inheritance.

In his paper[1] of 1901 to the Royal Horticultural Society, William Bateson summarised Galton's ancestral law and pointed out that it dealt with populations and with continuously varying characters. Mendel's laws, in contrast, applied to discontinuous variation in individuals. In publicising Mendelism, Bateson, Hurst and the other

Mendelians became involved in a bitter argument with the biometricians, particularly over the inheritance of continuous characters, which did not appear to fit into any simple Mendelian pattern, but was later shown to be explicable in Mendelian terms by R.A. Fisher[49]. It took well over ten years for the arguments to fade and for Mendelian segregation to carry the day.

Archibald Garrod (1857–1936) first wrote on “an inborn error in metabolism” in his 1899 paper, “A contribution to the study of alkaptonuria”[50]. Garrod discussed this with Bateson on the publication of his 1901 RHS paper[1], resulting in Bateson reporting to the Evolution Committee of the Royal Society on 17 December 1901 (published[51] in 1902) on the significance of the excess of first cousin marriages amongst the parents of Garrod’s patients with alkaptonuria, which, he said, gave “exactly the conditions most likely to enable a rare and usually recessive character to show itself.”

Next year Garrod applied Mendel’s law to the human in a further paper[52] on alkaptonuria: “It has recently been pointed out by Bateson that the law of heredity discovered by Mendel offers a reasonable account of such phenomena ….In the case of a rare recessive characteristic we may easily imagine that many generations may pass before the union of two recessive gametes takes place…. There seems to be little room for doubt…that a peculiarity of the gametes of both parents is necessary for its production.” In 1908 Garrod gave his Croonian Lectures at the Royal College of Physicians on inborn errors of metabolism. In them he discussed albinism, alkaptonuria, cystinuria and pentosuria with a strong Mendelian flavour for each one.[53]

Thus Garrod may be considered to have been the first, in 1902, to introduce Mendelism into medical “genetics” (a term coined by Bateson in 1905 in a letter to the zoologist Adam Sedgwick [1854–1913] when they were looking for a term for the study of heredity and variation). The word “gene” first appeared, later still, in German in 1909 in a book[54] of twenty-five lectures by Wilhelm Johannsen (1857–1927), which were based on lectures given at the University of Copenhagen in 1903 and published in Danish in 1905. However, Galton had coined the word “Eugenic” from the Greek *eugenes* in 1883,[55] and the word “pangene” had been created by de Vries[56] for the bearers of the separate hereditary characters in 1889.

This historical introductory chapter to this book is followed by chapters covering the fifty years from when William Bateson first recognised the importance of Mendel’s work and brought Mendelism to the notice of the scientific world in 1901. It was Archibald Garrod who, on reading Bateson’s paper, saw the relevance of Mendel’s laws to human disease, and in 1902 introduced Mendelism to what soon became, in fact, medical genetics. The remaining chapters are more clinical in discussing human genetics from 1950, with a final chapter examining genetics and the future of medicine.

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