Contributions of R. A. Fisher to genetics

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With J. B. S. Haldane and Sewall Wright, Fisher formed a troika, in whose differences of opinion population genetics thrived.

RONALD Aylmer Fisher, later Sir Ronald, was born on 17 February 1890. He was trained in mathematics and physics at Cambridge, although he excelled in biology in school. His interest in biology began early. He won many prizes in school and often chose books on biology as his prizes. The most significant of these was his choice of the thirteen-volume set of the complete works of Charles Darwin as a prize in his last year in school.

Fisher worked as an applied statistician at Rothamsted Experimental Station, as Galton professor of eugenics at the University College London, and as Arthur Balfour professor of genetics at Cambridge University. He moved to Adelaide in 1959.

Although Fisher's first paper was published in 1912, he read a paper on heredity, comparing methods of biometry and Mendelism, in 1911 at the second undergraduate meeting of the Cambridge University Eugenics Society. This paper was never published in a scientific journal, but is now available as a book[1]. Many of the concepts and methods that later became trademarks of R. A. Fisher, e.g. maximum likelihood, synthesis of biometry and Mendelism, are contained in their rudimentary forms in this paper. Fisher's contributions to genetics are many and varied. In this article, I briefly describe some of his contributions that have had significant impacts in the field of genetics. (Fisher also wrote a great deal on eugenics—the framing of deliberate policies for the genetic improvement of the human race. However, these writings have not had a lasting influence in genetics, and, in fact, Fisher did not write on eugenics in his later life).

Darwinism, biometry and Mendelism

Darwin was a believer in gradual and continuous evolutionary change. He believed that variation was a fundamental property of any species. He realized that for evolution to occur by natural selection some of these variations had to be heritable. Under this mechanism of evolution by natural selection, characters are expected to change very rapidly over generations. Therefore a mechanism for retaining uniformity of characters was needed. Darwin propounded 'blending inheritance' in 1842, under which characters of offspring were supposed to be derived by a 'blending' of parental characters, e.g. the apparent blending of skin colour in offspring of whites and blacks. In 1868, although he modified this to the 'provisional hypothesis of pangenesis', the concept of blending was retained. Darwin's view of gradual and continuous evolutionary change was strongly criticized by his staunchest supporters and admirers—Thomas Henry Huxley and Darwin's half-cousin Francis Galton. On the basis of certain investigations into heredity, they thought that evolution might proceed by discontinuous leaps. They also claimed that their view of discontinuous evolution fitted better with the fossil record, in which intermediate forms between species were often not observed. Further, Galton suggested that hereditary qualities were embedded in the reproductive organs and the germ plasm, which was passed on from one generation to the next with little alteration. Thus, unlike Darwin, Galton emphasized that variation caused by environmental effects were not heritable. These ideas were synthesized by him in his book *Natural Inheritance*[2] published in 1889. In this book and earlier, Galton had worked out correlations of metrical characters for various pairs of relatives—parent–offspring, grandparent–grandchild, etc.—and formulated, in a preliminary form, a law that later came to be known as 'Galton's law of ancestral heredity'[3].

Ideas on variation and inheritance similar to those of Galton, but more concretely framed and stated, were published by Hugo de Vries in 1900 in his book *Mutationstheorie*. In the same year de Vries, along with Carl Correns and Erich von Tschermark, rediscovered Mendelism. The rediscovery of Mendelism intensified the conflict between the biometricians, who believed in the Darwinian view of gradual and continuous evolution, and those who concurred with Huxley's and Galton's view that evolution proceeded by discontinuous leaps. Mendelism proposed particulate inheritance, which was assumed to imply discontinuous evolution.

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Karl Pearson and W. F. R. Weldon led the biometrical school, and William Bateson, and to a lesser extent R. C. Punnett, were the most vocal proponents of Mendelism. Apart from the main conflict between the two schools regarding graduality and continuity and discontinuity in evolution, the biometricians also criticized Mendelism because of its complete 'neglect of ancestry'. Mendelian laws imply that the genotypes of offspring are completely determined by the genotypes of the parents; given the parental genotypes other ancestral genotypes are irrelevant. Both biometricians and Mendelians agreed that 'Galton's law of ancestral heredity' (which takes into account hereditary contributions of all ancestors of an individual) and Mendel's laws of heredity were incompatible. However, in 1902, G. Udny Yule showed[4] mathematically that under certain conditions, viz. complete dominance, there was no incompatibility. Soon Karl Pearson claimed[5] to have shown mathematically that the phenotypic correlations between various types of relatives expected under Mendelian laws were well below those empirically observed. Thus he claimed to have proven the inconsistency between Mendelism and biometry. Yule[6] rebutted Pearson's calculations, and showed that Pearson made certain tacit assumptions that had led to his incorrect inferences.

Thus, around the time when Fisher read his 1911 paper, the scenario was that Mendelians and biometricians were engaged in a bitter conflict over (i) the nature of evolution—discontinuity vs continuity, (ii) factors governing direction of evolution—mutation vs natural selection, and (iii) observed and expected correlations between relatives for metrical characters. In this paper Fisher described the reasons why he thought that biometrical observations, especially those pertaining to correlations between relatives, were not incompatible with Mendelism. He quantified his ideas and provided statistical results in his 1918 paper[7], which remains a landmark in the annals of genetics and actually gave birth to 'biometrical genetics'. The crux of Fisher's paper[7] was that inheritance of continuous variation could be explained by Mendelian particulate inheritance. Fisher postulated that a large number of Mendelian 'factors' jointly control the character under study, and that each factor contributes a certain amount to the overall quantitative phenotypic value of that character. Using this model he derived the correlations for pairs of relatives that are expected for a quantitative character, and showed that these agreed with empirical observations. In particular, he pointed out that the correlation for a pair of siblings may be higher than that for a parent–offspring pair if there is dominance. The idea of analysis of variance was also introduced and greatly developed in this paper. Fisher partitioned the total phenotypic variance into its heritable and non-heritable components, and further partitioned the

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heritable component into components due to additive gene action, dominance effects and genic interaction (epistasis). He performed a detailed reanalysis of the data that were initially collected and analysed by Pearson and Lee[8]. From their analyses Pearson and Lee had claimed to have shown the inadequacy of Mendel's laws in explaining continuous variation, e.g. of stature. From his reanalysis Fisher, however, concluded that stature was determined primarily by many Mendelian factors and not by environmental factors. The 1918 paper is also remarkable in terms of the systematic exploration of the effects of the various factors on the components of variation. Starting with a set of simplified assumptions—random mating, independence of the Mendelian factors, etc.—Fisher relaxed his assumptions one by one and studied the consequences of assortative mating, linkage, and so on. The paper laid to rest the apparent conflict between Mendelians and biometricians, and remains as Fisher's most celebrated paper in genetics.

Two historical facts concerning this paper are worth mentioning. First, Fisher completed this paper in 1916 and submitted it for publication to the Royal Society of London. The paper was reviewed by Karl Pearson and

R. C. Punnett, who were bitter opponents in the biometry–Mendelism controversy. Both gave unfavourable reviews, and 'it has been said that this was the only time that the two ever agreed'[9]. Pearson wrote, 'I do not think in the present state of affairs that the paper is wide enough to be of much interest from the biometric standpoint...', while Punnett wrote, '...whatever its value from the standpoint of statistics and population I do not feel that this kind of work affects us biologists much at present'. Further details on the review of this paper are given in Norton and Pearson[10]. The paper was finally published by the Royal Society of Edinburgh, with financial help from Major Leonard Darwin, Charles Darwin's son. Secondly, the paper makes difficult reading. Several attempts have been made by others to explain the contents of various sections of the paper more lucidly. The most successful of these attempts is by Moran and Smith[11], who comment on the paper section by section.

Having settled the conflict between Mendelians and biometricians regarding the interpretation of observed correlations between relatives for a continuous character, Fisher turned his attention to evolutionary problems. In 1922 he wrote a paper entitled 'Darwinian evolution by mutations'. Between 1922 and 1930 he wrote several other papers on evolution of dominance, mimicry, etc., which culminated in the production of his book *The Genetical Theory of Natural Selection*[12] in 1930.

The Genetical Theory of Natural Selection

The central issue in the Mendelism–biometry conflict concerned the process of evolution. In the first chapter of *The Genetical Theory of Natural Selection*, Fisher clearly outlined the problems with both the Darwinian and the Mendelian views of evolution. He showed that, in the absence of a high correlation between mates, the Darwinian view implied that the heritable variance was approximately halved in each generation. Therefore maintenance of variability over generations must imply a steady input of variability in each generation, and, therefore, impossibly high mutation rates. On the other hand, the assertion of the Mendelian school that the direction of evolutionary change was actually governed by the direction of mutations was also impossible since available data suggested that most new mutations were disadvantageous or lethal. Thus Fisher concluded that, while inheritance of characters was governed by Mendelian laws, and mutations infrequently introduced variation into the population, natural selection was the only agency by which species could be modified to any appreciable extent.

The object of chapter II of the book was 'to state the principle of natural selection in the form of a rigorous mathematical theorem, by which the rate of improvement of any species of organisms in relation to its environment is determined by its present condition'. For this purpose, using actuarial techniques, Fisher devised a measure of fitness, i.e. the extent to which persons of a given age contribute to the ancestry of future generations, of a population and of specific genotypes, which he termed 'the Malthusian parameter of population increase'. He then derived that 'the rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time', and called it the 'fundamental theorem of natural selection'. Put differently, the fundamental theorem states that the rate of increase in fitness that is attributable to changes in gene frequency under natural selection is equal to the additive component of the total genetic variance. There has been a lot of criticism and debate about the truth and interpretation of this theorem, begun by Wright[13] in his review of the book, and continuing to this day[14]. Be that as it may, it is generally agreed that the fundamental theorem captures the essence of the way natural selection works[15]. Having quantified the role of natural selection, Fisher considered the nature of adaptation. He viewed adaptive impovement as a process involving interaction between the genetic make-up of the organism and its environment. He concluded that adaptation involved a large number of small evolutionary steps. Thus Fisher's description of evolution is one of gradual change, in agreement with the Darwinian view.

In the book, Fisher also consolidated his studies on the evolution of dominance and mimicry. The bases of his studies on these aspects were the existence of modifier genes and the operation of weak selection pressures on these genes. He therefore viewed the genome not as a set of independent loci or groups of loci, but as an interacting system. Fisher's view of evolution of dominance has, however, been criticized by both Haldane and Wright.

Fisher devoted two chapters in the book to quantitative assessment of the consequences of natural selection, mutation and finite population size on genetic variation in populations. In 1922 he had first derived[16] the probability that a favourable mutation would be fixed in a population, i.e. attain a frequency of 1. He used a branching-process method for this purpose. In this paper Fisher first introduced the idea of treating gene frequencies as random variables. He viewed the genes in generation $t + 1$ as having been derived by sampling with replacement from the genes of generation t. Thus the frequency of an allele was viewed not as the result of a deterministic process but as the result of a stochastic process over generations. Using diffusion methods for the first time in genetics, he obtained approximations to probability distributions of allele frequencies. He showed that asymptotically the gene-frequency distribution becomes uniform and decays at

the rate of $1/4N$ per generation in a randon-mating population of size N with no mutation or selection. However, Wright later pointed out a discrepancy, which led Fisher to discover an error in the diffusion equation in his 1922 paper that had arisen owing to his neglect of a small term. Fisher corrected the error in the book and showed that the asymptotic gene-frequency distribution was still uniform but the rate of decay was $1/2N$, instead of $1/4N$, per generation. Using methods introduced by Fisher[16], Haldane[17] derived the simple formula $P = 2s$, where P denotes the fixation probability of a gene whose heterozygote selective advantage is s. In the book Fisher extended this result to a finite population of size N. He also made detailed examinations of the equilibrium and stability properties of various genetic models.

The remaining portion of the book is largely devoted to the application of his genetical ideas to human populations. Fisher asserted that all human traits, including mental and moral traits, had evolved by natural selection. Thus he insisted that genetic variation must be seriously considered in studying the evolution of man and human society.

Reception of the book at the time of its publication was mixed. Punnett[18], in the opening paragraph of his review in *Nature*, stated, 'Probably most geneticists today are somewhat skeptical as to the value of the mathematical treatment of their problems....' However, both Haldane and Wright hailed the book enormously. In *Eugenics Review*, Haldane[19] wrote, 'No serious future discussion, either of evolution or eugenics, can possibly ignore it...; during the next generation any discussions of the problem of gradual evolution which are likely to be of permanent value will take the form of a development, discussion, and, perhaps in some cases, a refutation of the arguments stated in the book....' Wright[13] described the book in *Journal of Heredity* as 'a book which is certain to rank as one of the major contributions to the theory of evolution'.

Serology

Fisher's interest in serology is evident from a note he prepared as early as in 1924 for *Eugenics Review* 'to bring to the attention of the Ministry of Health the urgent desirability of establishing a Chair of Human Heredity in relation to disease...' (cited in Box[20]). He pointed out in this note that the factorial basis of the isoagglutinins of human blood (the ABO blood-group system) had recently been successfully elucidated (in 1900 by Landsteiner), and that similar Mendelian analysis of the hereditary complex should be continued. Later, in 1947, he clearly stated why he considered blood-group studies to be of importance[21]. His reasons were: (i) they provide markers for linkage studies, (ii) they are important in making blood transfusions, (iii) they are useful for forensic recognition of individuals, and (iv) they are useful in ethnographic studies because of the frequency differences observed among different human races.

Fisher set up a blood-grouping department in the Galton Laboratory in 1935. Before the outbreak of World War II, this department was engaged in trying to detect linkage of particular blood groups with various diseases, but was without positive results[22]. After war broke out, the department moved to Cambridge; in 1943, Fisher himself moved to Cambridge as professor of genetics.

Fisher's major contribution to serology was the elucidation of the genetic system underlying the rhesus (Rh) blood groups. His major paper[21] on the Rh factor, published in 1947, was titled 'The rhesus factor: A study in scientific method'. Indeed, this paper clearly represents Fisher's view of the 'scientific method'—the making of theoretical deductions from empirical data. The Rh groups were discovered in 1940 in the United States. Fisher hypothesized the genetics of the Rh system on the basis of data available towards the end of 1943 (see table). Fisher observed that antiserum-1 and antiserum-4 gave antithetical reactions. He hypothesized that the corresponding genes were allelic and called them C and c. Since antiserum-2 and antiserum-3 did not produce antithetical reactions, and their reactions also did not bear any resemblance to the reactions produced by antiserum-1 and antiserum-2, he hypothesized that the corresponding genes were at separate loci and called them D and E. He predicted that D and E would have corresponding alleles d and e. With three loci (C, D, and E) each with two alleles (C, c, D, d, E, e), eight chromosomal types are expected. However, at that time the CdE type was not observed. This type and anti-e were found shortly afterwards; anti-d has not yet been found.

Data on the rhesus factor available to Fisher in 1943

Antisera	Antigen and chromosomal type							
	R_1 *CDe*	R_2 *cDE*	r *cde*	R_0 *cDe*	R′ *cdE*	R″ *Cde*	R_z *CDE*	R_y *CdE*
1. Anti-C	+	−	−	−	−	+	+	+
2. Anti-D	+	+	−	+	−	−	+	−
3 Anti-E	−	+	−	−	+	−	+	+
4 Anti-c	−	+	+	+	+	−	−	−
5. Anti-d	−	−	+	−	+	+	−	+
6 Anti-e	+	−	+	+	−	+	−	−
Approx % frequencies in the English population	43 61	12 80	37 90	3 05	0 61	1 70	0 13	0 005*

Note Only the portion of the reaction data presented within the box were available to Fisher On the basis of these data he drew inferences on the genetics on the Rh system

*This chromosomal type was not observed at that time, Fisher inferred that its frequency was probably less than 0 005

Fisher then considered the frequencies of the chromosomal types in the English population. These are presented in the last row of the table. Noting that three of the chromosomal types were quite frequent, and the others rare, he hypothesized that the three loci were linked, and the rarer types produced by recombination. For example, types *cDe* and *CdE* could be produced by a recombination between *C* and *D* in *CDe/cde*. As recombination probability is small, the frequencies of the proposed recombinant types are expected to be low. The puzzling absence of *CdE* was also explained by Fisher. This type could be produced by a recombination between *C* and *E* loci in *cDE/Cde*. But *Cde* is itself a product of recombination, the frequency of which is, therefore, low. Hence *CdE* would predictably be extremely rare. By further detailed consideration of the frequencies of various chromosomal types, Fisher also deduced that the order of the three loci on the chromosome was *D–C–E*. He applied his maximum-likelihood method to obtain maximum-likelihood estimates of the Rh chromosomal types. He later commented[23] that elucidation of the rhesus system 'has been of service not only in making the medical profession to some extent genotype-conscious but in demonstrating the genetic complexity of the regions of the germplasm responsible for the blood-group polymorphisms'.

Although Fisher is remembered for making the Rh system understandable, he also clarified a confusion that persisted in respect of the P blood-group system. The presence of weak reactors often led to a misclassification of P^+ individuals as P^- unless a powerful anti-P serum was available. There was confusion over whether there were other alleles at this locus or whether genes at other loci interacted with the genes at this locus. Fisher[24] made a very thorough analysis of family data and showed that the difference in reactivity was due to some P^+ individuals being of the *PP* genotype and the others (the weak reactors) being of the *Pp* genotype. This is now an accepted fact. Fisher also devised statistical methods for analysing blood-group data from families, and laid out standard calculations for doubtful parentage, twin zygosity, etc., using blood-group gene frequencies.

Detection of linkage, and chromosome mapping

By the time Fisher turned his attention to the statistical detection of linkage, i.e. whether genes at a pair of loci cosegregated in families, Haldane had already published papers in this area. Fisher's first paper on this topic[25] was written with Bhai Balmukand in 1928 (although he had written a paper[26] on gene localization by means of cross-over ratios in 1922), and dealt with estimation of linkage from data on offspring of selfed heterozygotes. In this paper, five methods of estimation, including maximum likelihood and minimum chi-square, were compared, and the maximum-likelihood method was shown to have distinct advantages over the other methods. It may be mentioned that it was Haldane[27], not Fisher, who in 1919 first applied the maximum-likelihood method to estimation of linkage. In 1934 Haldane wrote a major paper[28] on detection of linkage, which seems to have prompted Fisher to study this problem in great detail. In the same year Fisher published two papers, in which he developed the scoring method for linkage problems, and extensively studied the relative information content of various types of families. The next year (1935) he published two major papers[29,30] dealing with detection of linkage separately for dominant and recessive abnormalities. In these papers, Fisher developed a simpler alternative method of scoring, and, using the method of generating functions, obtained the sampling distribution of the new test statistic that he proposed. Now, with the increasing realization that extended pedigrees are much more informative than nuclear families for detecting linkage, and with the increasing availability of computers, the simpler method suggested by Fisher is no longer used.

Linkage heterogeneity, i.e. the possibility that a disease may be linked to a genetic locus in some families and unlinked in other families, indicating thereby that the disease may be aetiologically heterogeneous, is a routine concept now. Efforts are still being made to devise efficient statistical tests to detect linkage heterogeneity. Fisher[31] was perhaps the first to introduce this concept and to devise a test for this purpose in 1936. He applied his test to detection of linkage heterogeneity between Friedreich's ataxia and the *ABO* blood groups, and showed, in his data set of 12 families, that there was significant heterogeneity. One of the families showed strong evidence of linkage; the others did not. It is of interest to note that the ABO blood-group locus has now been mapped to chromosome 9 at q34, while Friedreich's ataxia has been mapped to the same chromosome in region q13-21.1.

Fisher's interest in linkage prompted him to initiate breeding experiments with mice. Between 1934 and 1936, at the Galton Laboratory, an extensive linkage test was carried out under Fisher's statistical supervision. Fisher applied and further developed the statistical methods that he had devised for detection of linkage on the data thus generated. Although some linkage groups were identified, little of profound biological importance came out of these experiments, except for an indication of recombination values exceeding 50% between the loci for dilute pigmentation (*d*) and wavy hair (*wv*)[32]. This was evidence for chromatid interference, i.e. the nonrandom assortment of the four strands in crossing-over at successive chiasmata. On the basis of this observation Fisher[33] developed a quantitative theory of genetic

recombination and chiasma formation, which he read at the First International Biometric Conference in 1947. Fisher's theory implied that genes near the ends of the long chromosome arms would characteristically show recombination values exceeding 50%. This, in turn, implied that chromatid interference was a common phenomenon, which was contrary to observations in *Drosophila*. In the face of protests, Fisher curtly stated that his model did not deal with the relation among the four strands of the bivalent but was based on consideration of only single strands. Knowledge of the actual biological process of recombination and chiasma formation is far from complete, but, as Mather[34] noted, '... there can be little doubt that the assumptions in Fisher's mathematical treatment do contain—and conceal—the postulate of chromatid interference'.

Fisher speaking at a farewell to him at the Indian Statistical Institute in Calcutta, 16 March 1959. Also in the picture are J. B. S. Haldane (centre), and C. R. Rao (left) and P. C. Mahalanobis, India's best-known statisticians.

Segregation analysis

Statistical modelling of inheritance patterns makes use of a parameter called the segregation ratio, which is the conditional probability of an offspring having a particular phenotype/genotype given the parental phenotypes/genotypes. The segregation ratio is estimated from family data. However, for purposes of enriching a data set for individuals possessing the phenotype of interest, family data are often gathered nonrandomly, e.g. by looking for the presence of at least one affected offsping in the family. This procedure of sampling obviously introduces a bias, called ascertainment bias. At the estimation stage this sampling bias needs to be corrected for obtaining valid parameter estimates. Haldane[35] studied this problem, and Fisher[36] reconsidered it in much greater detail and obtained many general results and estimators. In particular, Fisher emphasized that biases of ascertainment could lead to incorrect inferences, and developed methods of handling missing observations. These methods were later used by him in analysing family data.

The Theory of Inbreeding

In 1949 Fisher wrote a small book on inbreeding[37] and worked out in detail the loss of genetic varration under various systems of mating between biologically related individuals. This book has been used very widely. In this book Fisher applied the techniques of matrix algebra extensively in his analyses of mating systems, including sib mating in diploids and tetraploids, double-first-cousin mating, and so on. (It may, however, be mentioned that many of the mating systems considered by Fisher had been studied earlier by Bartlett and Haldane[38]. Fisher evidently was unaware of this paper since he did not cite it in his book.) Fisher introduced, for the first time, a method to compare a pair of mating systems. He did this by studying how many generations were required by the two systems to achieve the same reduction in heterozygosity. He showed that this could be done elegantly by considering a ratio of appropriate eigenvalues corresponding to some matrices that arise naturally in the analysis of mating systems. The book also has one section (section 14, pages 49–61) in which Fisher put forward what he called the 'theory of junctions'. He later expanded on this theory in two papers[39,40] published in 1954 and 1959. Not much attention has been paid to this theory so far, but with the increasing emphasis on tracing phylogenies of genes, and on understanding identity by descent of chromosomal regions rather than of individual loci, this theory may turn out to be very important and useful.

Fisher, Haldane and Wright

The works of the three founders of population genetics were complementary in a broad sense, but also differed markedly. Throughout their lives they differed in their views of the evolutionary process. Had the three founders not differed in their opinions as strongly as they did, perhaps population genetics would not have advanced as rapidly as it has. Fisher and Haldane agreed on their views regarding the importance of natural selection in the process of evolution. Although they recognized—and in fact Fisher was the first to bring this to light—that stochastic factors play an important role in the determination of the fate of genes in populations, they essentially dealt with large population sizes and deterministic models because in

large populations the effects of the stochastic factors are relatively minor. Wright, on the other hand, placed much greater emphasis on the role of stochastic factors in the evolutionary process. Both Haldane and Wright strongly criticized Fisher's theory on the evolution of dominance; Haldane's and Wright's reasons for criticism were, however, very different. Although Haldane and Fisher agreed that natural selection was the major driving force of evolution, they disagreed on the quantitative aspects. While Fisher considered weak selection pressures over long periods of time to be important, Haldane considered that strong selection pressure caused by a single-gene effect in a natural population was more important. Further, in spite of recognizing interactions among loci, Fisher essentially developed his theory by considering single alleles at individual loci because he thought that interactions between loci rapidly declined owing to recombination. Haldane and Wright, on the other hand, emphasized genic interaction. Another point on which Haldane and Wright agreed, and Fisher differed, was the role of migration and admixture in the evolution of natural populations. These differences of opinion led to rapid advancement of deterministic models by Fisher and Haldane, and also to rapid advancement of stochastic models by Wright. Population genetics thrived, but personal relationships deteriorated. Haldane seems to have remained more or less equidistant from both Fisher and Wright, but, in their later years, the relationship between Fisher and Wright 'had deteriorated to the point that neither wanted to see the other'[15].

Epilogue

Fisher's contributions to genetics have been fundamental and far-reaching. Whether he was primarily a statistician or a geneticist is a moot question. His daughter aptly called him a 'scientist'[20]. Fisher was a strong supporter of Mendel. Yet, in the true spirit of a scientist, he reexamined Mendel's data and wrote a critical article entitled 'Has Mendel's work been rediscovered?' in 1936. In this article Fisher statistically analysed the results of Mendel's different experiments — the monofactorial, the bifactorial, the trifactorial and the gametic ratio — and obtained an overall goodness-of-fit chi-square value, which turned out to be highly improbable because the corresponding P value was 0.99993; i.e. Mendel's results are expected to be realized only seven times in 100,000 trials. On the basis of this, and another, similar observation, Fisher concluded that 'the data of most, if not all, of (Mendel's) experiments have been falsified so as to agree closely with Mendel's expectations'. Fisher, of course, did not believe that Mendel himself had adjusted the data but suggested that some assistant who knew Mendel's expectation tried to please him. Fisher's interpretation of Mendel's results has been criticized[41,42], but his accusation has not been refuted[43]. This example illustrates the true scientific spirit of R. A. Fisher; on the basis of scientific evidence he did not quiver to criticize even that individual whom he regarded in the highest esteem.

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