Professor Sir Ronald Fisher, FRS

Cyril Clarke

"If it's significant it hits you in the eye; if it doesn't it isn't." This was spoken by a distinguished surgeon and has cheered up multitudes of hard working clinicians, suggesting to them that they need not after all understand the intricacies of statistical language. But they ought to know about the basic techniques for unless they do the danger is that they will just give the statisticians their data and be unable to take part in any discussions.

Early days

Ronald Aylmer Fisher was born in February 1890, and I have written this summary of his life to show how his brilliance was of great help to medicine. Interestingly, it was a medical disability, severe myopia, which was turned to his advantage. Because of this his mathematics teacher at Harrow taught him without pencil or paper so that Fisher was increasingly able to solve problems in his head resulting later in other statisticians criticising him for using intuition.¹

At Caius College, Cambridge, Fisher developed strong biological interests and became keenly interested in evolutionary problems, particularly eugenics, and we can edge into his scientific eminence by quoting one of his views (not easily proved mathematically) in which he isolates a single cause for the deterioration of civilisations including our own. It was, as shown by the 1911 census in the United Kingdom, the result of a strong inverse relation between fertility and social position. He argued that this showed that the upper classes owed their status to the advantages of small families and that this would lead to the mating of ability with infertility with long term disastrous results. Interestingly, his parents may have held the same view as they tried to combat the trend: Fisher was the youngest but one of eight children, and he and his wife Eileen (née Guinness) lived up to the theory by producing eight offspring.

Fisher the statistician

Fisher was appointed statistician of the Rothamsted Research Station in 1919 with the remit to see whether he could show the usefulness of statistics to practical men, such as giving them advice on how to produce the best crops by studying the mass of data at the station, which went back 67 years. Fisher was easily able to correlate the crop yields with different types of fertiliser and rainfall. There were, however, unexplained variations between years, which appeared to confound these inferences. Fisher produced an original explanation for these. He dug down into the records and found that in the 1850s a great deal of hand weeding had been done by boy labourers, but 30 years later the education acts had stopped this workforce and back came the ubiquitous slender foxtail grass.²

While at Rothamsted, when he was writing (among much else) *Statistical Methods for Research Workers*, a famous party took place. Fisher poured a cup of tea

Professor Sir Ronald Fisher

from the urn for one of the staff, Dr Muriel Bristol. She declined it, saying that she preferred a cup into which the milk had been poured first. "Surely it makes no difference," said Fisher, but she maintained that of course it did, and an experiment was set up by Fisher and her fiancé to test her statement. It consisted of mixing eight cups of tea, four in one way and four in the other, and presenting them for judgment in a random order to see whether the subject could allot them correctly by taste. The details of this experiment took pride of place some years later when Fisher (by this time Galton Professor of Eugenics at University College London) wrote his classic *The Design of Experiments*,³ but he does not mention that Dr Bristol did allocate the cups correctly—though this was claimed for her by Fisher's daughter Joan Fisher Box in her biography of him.² (My technician thought that Dr Bristol should have been blindfolded.)

The analysis of a single experiment such as this and the conclusions that could be drawn from it interested Fisher greatly as opposed to the assembly and analysis of a varied collection of experiments. For instance, his deduction from Doll's and Hill's published results on smoking and lung cancer that those who inhaled were less at risk than those who did not was a striking demonstration of how conclusions could be turned upside down, and his example from twin studies seemed to show that smoking habits were strongly genetically controlled. He never tried to review the later evidence, however, but the suggestion that his arguments lose value because he was employed as a consultant to the tobacco firms is unjust—he always

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disliked and mistrusted puritanical tendencies of all kinds. Nevertheless, it must be admitted that he greatly enjoyed his pipe. One of his letters exemplifies the rigorousness of his approach⁴:

There is nothing to stop those who greatly desire it from believing that lung cancer is caused by smoking cigarettes. They should also believe that inhaling cigarette smoke is a protection. To believe either is, however, to run the risk of failing to recognise, and therefore failing to prevent, other and more genuine causes. [These might not be amenable to the computer—for example, unhappiness—CC.]

Some mathematical details

Karl Pearson invented the χ^2 test, which is used to test the goodness of fit of actual numerical observations to expectations, but it can be used only when the samples are large. Fisher, realising that workers are often restricted to small samples, modified this test to use in these cases. He did this by introducing randomisation into experimental designs so that the laws of chance would allow statistics to provide unbiased quantitative estimates due both to environmental conditions and to the variability of the material being tested. In addition, a probability figure in the form of a percentage could be attached to the error estimate. For example, a statement that an error is at the 5% level of significance would mean that the results could be trusted to include the true figure 95 out of 100 times.

One of the most generally applicable procedures Fisher invented for the testing of small samples is the analysis of variance, which gives us the F (Fisher) ratio; this uses the entire population of the experiment and can be used on groups of unequal size. For example, if you take three different families and look at the height of the brothers (all adult and all Englishmen) to see whether height really does run in families the F ratio shows that the variance (the variability around the mean) within families is much less than between them.

Fame as a geneticist

In the early part of his career Fisher was greatly intrigued by the controversy on the hereditary determination of continuously variable characters which had raged between the Mendelian geneticists and the Darwinians. Big variations (the Darwinians thought) were due to heredity and the small ones to the environment. Fisher was in no doubt that Mendelism

Professor Sir Ronald Fisher's handwritten solution of Rh blood grouping

and Darwinism must fit together, and he showed by statistical methods that the properties of continuous variation were compatible with many small differences being explained by Mendelian inheritance provided the effects of many small genes were additive.

The experimental proof of Fisher's explanation was tested on *drosophila*, and Kenneth Mather showed that though the effects of "minor" genes might not be recognisable on their own, where their effects were additive and formed a system their behaviour was Mendelian, as predicted by Fisher. Thus "neo-Darwinism" solved the controversy, and the reconciliation was complete in Fisher's *The Genetical Theory of Natural Selection*.⁵

Fisher's fame as a geneticist is also borne out by his theory of the evolution of dominance, with which he begins this great book, but the concept is not easy to understand and has been the subject of great controversy, particularly with Sewall Wright.⁶

The general theory is that when it first appears a mutant is nearly always completely recessive. Fisher, however, pointed out that genes have more than one effect, that some of these will be dominant, and that this dominance is particularly likely to increase if there are modifying genes increasing the dominant effect if this is favourable. As such modifiers accumulate the gene will become completely dominant—that is, the homozygote will be indistinguishable from the heterozygote.

A good example of the evolution of dominance is in mimicry in butterflies, where the effects of modifiers can be indisputably shown, and the whole idea is a splendid example of Fisherian brilliance. (How we enjoyed showing him the swallowtail butterflies in Liverpool.) But as doctors we see trouble; diseases such as achondroplasia, tuberous sclerosis, and Huntington's chorea are all considered dominant diseases, but they seem highly disadvantageous—as does the medionigra form of the scarlet tiger moth, which no sooner appears (the story goes) than it starts to disappear. The excuse made for the diseases in man is that we cannot call them proper dominants because the homozygote has never been seen, though this does not apply to the moth, and the human argument seems a bit weak and irrelevant. We can conclude that the fundamental Fisher discovery is that dominance can evolve.

Clarification of Rh blood groups

Undoubtedly, Fisher's greatest contribution to medicine was his clarification of the Rh blood groups. Wiener and Levine had discovered the Rh system and its importance in haemolytic disease of the newborn. The excitement of the discovery, however—that there was not one antigen but several (by 1943 Wiener had defined six)—led to great bewilderment and as Box

The Bun Shop, Cambridge

writes: "The symbolism was chaotic with upper and lower case Rh, Hr, primes and subscripts."² The genes of Wiener appeared as composite reacting molecules instead of each having its own specific antigen and antibody so that in Wiener's view, for example, anti-Rh1 serum recognised antigens for both Rh1 and Rh2 and anti-Hr recognised both Rh2 and Rh. Despite changes made by Wiener the terminology remained hopelessly confused. Fisher brought order out of chaos in a remarkable article on the Rhesus factor⁷ (first presented during his visit to the United States in 1946). He introduced the unfamiliar story to American scientists as it had unfolded itself to English workers during the war years.

The successful explanation came as the result of Fisher's move to the chair of genetics in Cambridge in 1943, where after a day's work he used to meet Rob Race and Ruth Sanger at the Bun Shop, a small public house close to the pathology department, and almost every evening they would be found there drinking beer and talking over the tangle of the emerging Rh results. One evening the latest results were given to Fisher and in about two hours' thinking time after dinner he produced the solution.

This was that there were three loci each with their own allelic forms and that the rarer genotypes could be accounted for by crossing over. He noticed that two of the antibody reactions were antithetical and that the antigens recognised by these two antibodies could be allelic. He called them C and c. The actions of the remaining two antisera were not antithetical so he supposed that there were two further antigens each at another locus on the same chromosome and he called them D and E, each with its allele d and e. There were, therefore, three loci and these could account for the observed antigen-antibody reactions. Walter Bodmer recalls that Fisher had suggested to him that the CDE solution was influenced by the Swiss geneticist Ernst's interpretation of the incompatibility system of the primrose.⁸ This perhaps makes our story that a study of butterfly mimicry led to a method of preventing Rh haemolytic disease seem not too far fetched.

There is a story about Rh factors which shows how geniuses like Fisher must sometimes bow to the specialised knowledge of a technician. In the days of group O duodenal ulcer a highly significant new association was reported by workers in the United States between this disease and R1R2 and MN, and this was the talk of the town at the International Congress of Human Genetics in Rome in 1961. Fisher and other great men were most impressed but I, though I had no explanation, thought that the story

was complicated and that it might be an example of the too good to be true syndrome. At home our blood group technician, Mr W T A Donohoe, solved the problem in 30 seconds. "Sir," he said (remember this was 30 years ago), "this is the result of a blood transfusion." And so it was. All the patients with ulcer had received transfusions because of haemorrhage and had picked up temporarily Rh and MN antigens from the blood donors. When patients who had not received transfusions were tested the association vanished.

Civilised controversy is the backbone of scientific advances, and although at times human frailty causes the participants not to be totally impartial, on the whole the battle between Fisher and Sewall Wright has done nothing but good. It has had stimulating effects on the younger generations, and the natural selection versus drift arguments are still not settled—not least because the factors operating for or against selection are often mere guesswork.

His great legacy

Although he made mistakes, Fisher vastly improved the investigation of statistical problems in genetics, and his great legacy to medicine (not always followed these days) was how to design experiments and how to assess a bewildering mass of recalcitrant data.

Fisher died unexpectedly in 1962 of a pulmonary embolus during colectomy and, as his daughter writes: "His memorial is in the minds and hearts of the scientists over several generations who had been his students."

Interestingly, his faith was in the tradition of the Church of England and "he saw it as a quality very like courage which makes one hold fast to that which is good irrespective of all the encouragement, slander, intimidation, etc, which Christians have learned to expect in their pilgrimage."² A splendid compromise between science and religion.

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Iatrogenic suction cup injuries

A 30 year old orthopaedic registrar was entertaining his 15 month old daughter with a toy car phone. To amuse her further he stuck the rubber base of the phone on to his forehead with the phone attached. The suction base remained on his forehead for several minutes while his daughter tugged it. Only with extreme difficulty did the rubber base peel off. An immediate 6 cm diameter bruise was imprinted on the registrar's forehead. The bruise took just over a week to disappear; ice packs did not help.

The next day the registrar's consultant accused the registrar of fighting and wanted to know where and how he had got his "Glasgow kiss." These toy car phones should have a warning that they should not be stuck to skin. —C W OLIVER, *orthopaedic tutor, General Infirmary, Leeds LS1 3EX* and R J NEWMAN, *senior lecturer in orthopaedics, St James's University Hospital, Leeds LS9 7TF*