Sir R A Fisher and the Evolution of Genetics

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In the realm of science, the twentieth century has been, by and large, a time of ever increasing specialisation. It is hard, and some would no doubt say impossible, to find amongst the scientists of this century, people who can legitimately be considered the founding fathers of more than one distinct field of scientific endeavour. Amidst the many great scientists of our century, however, Sir Ronald Aylmer Fisher (1890-1962) stands out as a glorious exception in this regard. During the first half of this century, Fisher almost single-handedly laid the foundation for much of what we today recognise as the academic discipline of statistics (see accompanying article by Krishnan). Fisher also developed much of the theoretical framework of population and quantitative genetics, a body of work that provides the conceptual underpinnings for fields as disparate as plant and animal breeding and evolutionary biology.

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To truly appreciate the magnitude of Fisher's contributions to genetics, one must start by taking a look at the state of this fledgling science at the turn of the century. When Fisher joined Cambridge as an undergraduate in mathematics in 1909, it had just been a few years since the rediscovery of Mendel's work showing that inheritance was particulate, and that it appeared that differences in discrete inheritable factors (what we now call genes) were largely responsible for observed differences in structure and form among individuals. This view was championed by Bateson, also at Cambridge, and one of the first professors in the new field of genetics. An opposing view-point was held by many geneticists who worked largely on human traits and who believed that most differences among individuals were with regard to traits like height and weight that were continuous rather than discrete, and that, therefore, could not be explained by any theory based on particulate inheritance

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which seemingly could lead only to discrete differences among individuals. This school of thought, labelled the biometrical school, was led by Karl Pearson, the head of the Galton Laboratory of Eugenics at University College, London. This difference of opinion between the biometricians and the Mendelians, regarding the continuous or discontinuous nature of inheritance, soon crystallised into a wide-ranging and bitter controversy in biology. At the heart of this controversy was one of the central issues in biology: *The mechanism of adaptive evolution.*

In the mid nineteenth century, Charles Darwin had proposed natural selection, the differential survival and fertility of some variants that were better adapted to the existing environment, as the major mechanism of evolutionary change. Darwin's emphasis was on differences among individuals that were of a continuous rather than discrete nature, and evolutionary change within populations was, consequently, viewed as being continuous and gradual. The missing link in Darwin's theory was a mechanism of inheritance. For natural selection to work, the differences among individuals had to be heritable. This missing link was finally provided by the rediscovery of Mendel's work in the first few years of the twentieth century. In the decade that followed, the biological world was deeply divided by three mutually opposed views about heredity and the mechanism of evolution. Bateson's school believed that since inheritance was particulate, evolutionary change had to be discontinuous and, therefore, rejected Darwin's views on the mechanisms of evolution. Hugo de Vries, one of the rediscoverers of Mendel's work had worked extensively with mutations that had large effects on structural characteristics. Consequently, he believed that mutation alone was the major agent of evolutionary change, and that natural selection had, at best, only a minor role to play in evolution. Pearson and the biometricians believed that both inheritance and the evolutionary process were continuous, and rejected the viewpoints of both de Vries and the Mendelians. It is difficult to overstate the impact that

this controversy had on biology at that time: as long as the controversy was not resolved in some kind of grand synthesis, any significant advancement of our understanding of evolution, the most important of all biological phenomena, would not have been possible.

This, then, was the stage onto which the young Fisher strode like a colossus. He had been thinking of and occasionally giving talks about attempts to reconcile the biometrician-Mendelian controversy since his undergraduate days, by showing that discontinuous inheritance, continuous variation and gradual and continuous evolution were not only not mutually exclusive, but that this combination was, in fact, how things had to be. This remarkable synthesis was finally achieved in a landmark paper published in 1918. In this thirty-four page paper, Fisher laid out the basics of what would today form the material for an introductory course in quantitative genetics. He showed how a number of discrete Mendelian factors, each with a relatively small individual effect on the trait in question, could generate a continuous distribution of trait values for quantitative traits like height or milk-yield. In one conceptual master-stroke, Fisher was thus able to resolve the greatest controversy in biology in this century. Equally significantly, Fisher in this paper introduced to biology a way of approaching problems that, although well known to mathematicians, was unknown to most practising biologists, even those with theoretical inclinations. The basis of this approach, in Fisher's own words, was to contemplate "a wider domain than the actual", which, he argued, "leads to a far better understanding of the actual". In the preface of his book *The Genetical Theory of Natural Selection*, published in 1930, he illustrated this approach by the following example: "No practical biologist interested in sexual reproduction would be led to work out the detailed consequences experienced by organisms having three or more sexes; yet, what else should he do if he wishes to understand why the sexes are, in fact, always two?"

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Applying this logic to the question of observed correlations between human relatives for a variety of traits, Fisher was able to show that the observed patterns of continuous variation were entirely consistent with Mendelian inheritance. He was also able to consider the effects on these traits of various other modifying factors like dominance, linkage and non-random mating. Moreover, he developed techniques for partitioning the observed variation into components due to environmental effects and effects traceable to different types of genetic phenomena such as additivity, dominance, and epistasis. In their own way, these results have exerted an influence on genetics, which though less well known, is comparable to the influence brought about by Watson and Crick's elucidation of DNA structure in 1953.

During the two or three decades following the landmark paper of 1918, Fisher turned his penetrating insight on a number of problems in evolutionary biology and, indeed in classical genetics. Given the constraints of space, I can do no more than list a few of his major contributions here, and hope this brief account will give the reader some feel for the remarkable breadth of Fisher's contributions to genetics. In this period, Fisher quantified the role of natural selection in altering the genetic composition of populations during adaptive evolution, developed theories explaining the evolution of basic genetic phenomena like dominance and heterosis, and explained why quantitative variation was more likely to contribute to evolutionary change, as compared to variation caused by mutations of major effects. In addition he provided sound explanations for many observed phenomena such as equal numbers of males and females in populations of many species, the ubiquity of sexual reproduction, the evolution of extreme ornamentation (like the peacock's tail), and the fact that species with a widespread geographical distribution are more variable than their close relatives that are less widely distributed. Fisher also did a lot of the work on the genetic consequences of finite population size, and much of the theory of random genetic drift is

actually due to Fisher's work, though this theory is more commonly associated with Sewall Wright, who independently worked on it. In his work on finite populations, Fisher conceptualised the spread of mutant genes in populations over generations as a diffusion process, and used, for the first time, mathematical models from various branches of physics, to describe genetic phenomena at the population level. It was also Fisher, apparently during a conversation in a pub, who first satisfactorily explained the data on inheritance of Rh blood groups by postulating the involvement of three closely linked loci in determining the Rh phenotype of an individual.

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Genius, it has been said, makes itself known early, and this was certainly true in Fisher's case. His daughter, in her biography of her father, tells of the three and a half year old Fisher asking his nurse, "What is the half of a half ?" Upon being told that it was a quarter, he asked, "What is the half of a quarter?", and so on till he was told that the half of one-eighth was one sixteenth. Upon hearing that, Fisher thought seriously for a while and then said, "Then, I suppose, a half of a sixteenth must be a thirty-twoth." The astonishingly penetrating insight that was to baffle and awe generations of population geneticists its reading Fisher's books and papers was evidently present at this very early age. Arthur Vassal, who was Fisher's biology teacher at Harrow, when asked much later to name the ten or so brightest students he had ever had said that on the basis of sheer genius he could divide his students into two groups: one group consisted of Fisher, and the other of everyone else. Ever since I first came to know of Fisher's work when I began to study population genetics, he has remained one of my personal intellectual heroes. I can only hope that this brief outline of his accomplishments will convey to the reader why, for many decades after Fisher's seminal work, the entire field of population genetics was often described as an exercise in 'writing footnotes to Fisher'.

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