J B S Haldane[1]

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Vidyanand Nanjundiah obtained his bachelor's degree in physics and mathematics at St.Xavier's College, Mumbai. He continued to study physics and got his PhD at the University of Chicago. He then moved to biology and has been working on the developmental biology of cellular slime moulds (social amoebae) ever since. He is also interested in evolutionary theory.

Few biologists of this century have done as much, and in as many areas, as John Burdon Saunderson Haldane. Known primarily for his path-breaking contributions to our understanding of how evolution works, Haldane was also a first-rate geneticist and biochemist. He devoted a great deal of his time to the popularization of science, believing that to be at least as important as carrying out original research. Many people who do not know exactly what he did as a scientist nevertheless know of him through the stories associated with his name. Perhaps the best-known is his supposed response to being asked if he believed in God: *"I do not know if God exists, but if He does, He must be inordinately fond of beetles"*. (The point being, that of all the groups of animals in this world, there are more species of insects – and among insects, of beetles – than that of any other animal.)

J B S Haldane was born on 5 November 1892. His father, John Scott Haldane, was a physiologist and a recognized expert on respiration. Young JBS soon started serving as a guinea pig in his father's experiments. Some of these concerned the effects of deep-sea diving and so were potentially hazardous. Physical courage and a willingness to take risks remained characteristic of him throughout his life. An aggressive attitude, along with a fondness for underdogs, were also long-lasting traits. He seems to have been a precocious child and was gifted with an excellent memory. In later years his powers of recollection were such that he had no need to go to a library to look up the correct citations when he wrote something up for publication. His formal education involved a preparatory school followed by the famous 'public' school of Eton – which he disliked intensely – and university study at Oxford. His primary interests during this phase were Greek and Latin, philosophy and mathematics; not

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biology, in which he never took a degree and was largely self-taught. He served in the first World War and was seriously wounded. After the war he went into formal teaching and research and worked at many academic institutions. The last of these were the Indian Statistical Institute in Calcutta and the Genetics and Biometry Laboratory in Bhubaneshwar; Haldane and his wife had migrated to India in 1957. He died in Orissa in 1964. (For more on Haldane's Indian sojourn, see the accompanying article by Majumder). His wife, Helen Spurway, a distinguished student of genetics and animal behaviour in her own right, later moved to Hyderabad and survived her husband by 12 years.

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If we discount the experiments in which he assisted his father, the earliest important contribution that Haldane made to science came when he was a schoolboy of 16. It all began from his dissatisfaction with the interpretation of some results in a paper concerning mouse breeding. The author of the publication, a scientist named Darbishire, had not noticed that his results appeared to disobey a rule formulated by Mendel, the founder of genetics. The rule was that various inherited traits behaved as if they were passed down from parents to offspring independently of each other, so that the joint occurrence of two traits was simply a matter of chance. This is exactly what Mendel had found to be true in the case of his peas, and subsequent work on other plants, mice and poultry had confirmed the rule. What Haldane noticed about Darbishire's data was that some traits appeared to associate with each other more frequently than one would expect on the basis of chance alone. Together with the help of his younger sister (who, under the name Naomi Mitchison, became a famous novelist and social worker and encouraged many young scientists), he repeated the experiments himself. The original finding was confirmed, and Haldane realised that the association of traits could have exciting implications: perhaps it meant that genes, the particulate 'carriers' of those traits, were also associated with each other, this time physically – like beads on a string. This was the first discovery of what we now call

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linkage. Linkage is explained by saying that groups of genes are indeed physically situated on string-like entities known as chromosomes. The hypothesis could not be published immediately because of Haldane's involvement with the war, and when it eventually was, T H Morgan and his group in Columbia University had already reported linkage in the fruit fly *Drosophila*.

Haldane first hypothesized that genes may be physically linked "like beads on a string" but could not publish this idea due to the turmoil of World War I. In the meantime, linkage was discovered by T H Morgan and co-workers in the USA.

The name of J B S Haldane is most widely associated with that branch of evolutionary biology known as population genetics. This field depends on a combination of mathematical modelling and experimentation. Its aim, roughly speaking, is to analyse the spread of genes within populations and to describe populations in terms of their genetic structure. The basic assumption on which population genetics depends is that one can associate something called fitness with a gene or group of genes. Fitness is more properly the property of an individual, but in a loose but useful sense one may define the fitness of a gene as the relative contribution made by that gene to the reproduction of an individual carrying it. To take an example, suppose that there are two sorts of animals within the population of some species, tall and short, and that the difference between these sorts has to do with two different variants of the same gene. Then, on average, if a tall animal has more (or fewer) children than a short one, the 'tall gene' may be said to be more fit (or less fit) than the 'short gene'. Obviously, in the course of time the 'tall gene' will spread (or be eliminated) through the population.

That much is easy to understand. But there are other aspects of the situation, and understanding them is not such a straightforward matter. How is the fitness differential related to the rate at which a gene becomes more frequent or less frequent? What happens when – as is true with most multicellular creatures such as the higher plants and animals – each gene comes in two copies, and one of them can mask the effect of the other? (In technical language, one copy is said to be dominant over the other.) Under what circumstances can a number of genes co-exist so that the population exhibits a steady level of genetic diversity? How do mutations, which change genes and keep occurring at random all the time, affect the outcome of evolution? How is the spread of a gene affected if population sizes are small? (In small populations the average outcome may not be representative of what happens: accidental events, such as the failure of an individual to reproduce – for reasons having nothing to do with his or her genes – become important and chance begins to play an important role in evolution.) The mathematics which Haldane used to answer such questions was often developed *ad hoc* and was not always elegant, but was nevertheless effective. A popular book in which he summarised his early work was *The Causes of Evolution* published in 1932. The book has recently been issued in a new and partially updated edition, but it inevitably lacks a great deal of what Haldane did in population genetics and evolutionary theory after 1932.

Haldane was the first to assert that genes influenced the rates of chemical reactions in cells by encoding catalytic activities. This notion later become famous in genetics as the 'one gene, one enzyme hypothesis'.

Questions such as the ones mentioned above were attacked by a number of persons more or less at the same time, soon after the re-discovery of Mendel's laws of inheritance around the beginning of this century. The reason was simple. Mendel had shown that the carriers of hereditary traits were particulate entities (what we today call genes). This meant that their mathematical analysis was straightforward, at any rate in principle. In addition, it was fairly obvious that an essential difference between the different species of plants and animals that inhabit the earth must lie in their hereditary traits: elephants have baby elephants and ants have baby ants, so to speak. Therefore, it appeared that an understanding of the manner in which changes occur in hereditary traits might be both possible and capable of yielding insights into the evolutionary process. Four names are associated above all with that first attempt to apply mathematics to the study of evolution: S S Chetverikov in the USSR, S Wright in the USA and R A Fisher and J B S Haldane in Britain (for a more detailed description of these early years of population genetics, especially the contributions of R A Fisher, see *Resonance* Vol.2, No.9, pp27–31). In parallel with these theoretical studies, a number of scientists carried out equally pioneering empirical research on fossil records, genetic variation in nature and geographical diversity. By about 1930, there was general agreement that a satisfactory understanding had been achieved of the principles of evolution by natural selection as first enunciated by Darwin and Wallace. The one major advance that has occurred since then has been mainly due to the Japanese evolutionist Motoo Kimura. This was the realization that completely random variations in gene frequencies are more important than had been thought possible. Indeed, at the level of the genetic material (DNA) itself, they may be far more frequent than changes occurring due to natural selection. Today the picture we have of evolution is that it is a process that may be thought to operate at two levels. At the level of the anatomy, physiology and behaviour of individual organisms, Darwinian natural selection is likely to be the dominant force in evolution. On the other hand, only a small fraction of the changes that occur in DNA sequences are thought to be due to natural selection, most of them occurring purely by chance, as one mutant gene or the other becomes more common in different populations.

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As stated earlier, Haldane's work provided major insights in areas of biology other than evolutionary theory. In formal genetics, he built on his early interest concerning linkage to derive a mathematical formula to describe the relationship connecting the distance between two genes on the same chromosome and the likelihood that they would associate more often than expected. He was one of the earliest to assert that by encoding catalytic activities, genes influenced the rates of various chemical reactions in a cell. This became famous after it was formulated by Beadle and Tatum as the one gene – one enzyme hypothesis. He gave the correct interpretation of the kinetics of the simplest possible enzyme reaction – what is commonly known as Michaelis–Menten[2] kinetics – and wrote an influential textbook on enzymes. Together with Oparin, Haldane was among the first to propose a scientifically plausible theory for the origin of life. In the course of doing so he introduced the

[2] see D N Rao, Kinetics of Enzyme-Catalysed Reactions. *Resonance*, Vol.3, No.6, pp.31, 1998.

phrase 'hot dilute soup' to describe the consistency of the primeval ocean, a term that has stuck. A striking piece of work that he carried out with Helen Spurway was an analysis of the dance language of the honeybee from the point of view of the then – new science of cybernetics. What is amazing is that many of Haldane's original scientific ideas were tossed off in popular writings rather than in professional publications, something hardly thinkable in today's climate of public relations and advertising in science. Two that are especially noteworthy are the notion that it may have been RNA, not DNA, that was the first self-reproducing molecular carrier of hereditary traits, and that if altruistic behaviour had a genetic basis, it would find a better chance of getting established among close relatives than among unrelated individuals. He produced a large number of essays and books for the general reader, assuming that it was one of his duties as a scientist to communicate what was interesting and exciting in science. These pieces are still readable, not least for how much they seem to be anticipatory of future developments; Haldane always tended to see much ahead of his time. One quotation of his has become famous and bears pondering:

... the universe is not only queerer than we suppose, but queerer than we can suppose'.
– J B S Haldane

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There is no end to the number of stories about Haldane. Whether they are always accurately reported is hard to say, because they have been retold so often that some mutations must have accumulated. But everyone who knew him is agreed that he was a character and a quotable one at that. He could be extremely generous with his money and at the same time avoid trying to pay for his tea in the canteen. Physically fearless, he would plunge blindly onto a Paris street carrying heavy traffic with his arms extended because that was similar to the aggressive signal employed by fish. He claimed that the only way he could recognise when the British national anthem was being played was when he saw everyone standing up. Helen Spurway was an interesting personality in her own right. (On the only occasion

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on which I met her, she offered me whisky in a copper bowl from which a wild fox had just then been sipping water; and when she saw my dubious reaction, assured me that the whisky would sterilize everything. Some of my colleagues have more vivid stories.) Between the two of them, they decided that an incident in which she was bitten by a policeman's dog after she stepped on its tail was provocative enough for them to leave Britain and settle in India. Haldanes' strong Marxist leanings made him look upon this major venture as a commitment as much as an act of choice.

Haldane had long been interested in Hindu and Buddhist philosophy, and had early on been attracted by the simplicity and idealism of Islam. The stay in India began well but went on to display elements of tragedy towards the end. He started out by being associated with the Indian Statistical Institute in Calcutta; its director, P C Mahalanobis, was a friend of his. After he fell out with the bureaucratic attitudes in ISI, he went through a farcical year during which he was supposedly working for CSIR as head of a new unit of genetics and biometry. The bureaucracy there was if anything worse: The unit never got properly started. Equally important was the fact that Haldane was a strong rationalist, not to say materialist, accustomed to speaking his mind and able to give second preference to everything other than the carrying out of his scientific activities. For such a person the transition to the hierarchical structure and sycophantic culture of scientific institutions in India, overlaid with the inevitable overtone of religiosity, could not have been a smooth one. On the positive side, a number of young men had the opportunity of working with and learning from the Haldanes at first hand. One of them, Suresh Jayakar, made fundamental contributions to population genetics and evolutionary theory, initially in collaboration with Haldane and later on by himself.

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