J.B.S. Haldane (1892–1964)

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In view of the leadership of J.B.S. Haldane, the chief architect who formulated the "malaria hypothesis," it is of interest to review his contributions to genetics briefly, especially to the aspects of evolution and human genetics. He was a remarkable scientist. He possessed no formal academic qualification in science, yet he became one of the twentieth century's most influential scientists. He was a polymath whose intellectual versatility covered many disciplines, including physiology, genetics, biochemistry, biometry, statistics, cosmology, and philosophy, to name a few. Furthermore, he was a most skilled and prolific popularizer of science whose articles in the popular press covered even more disciplines. The following account is a brief summary of Haldane's contributions to genetics. His important work in physiology, biochemistry, biometry, and other fields is not included here.

He was the author of over 400 research papers (for most of which he was the sole author), 24 books, numerous popular articles, book-reviews, and political speeches. His intellectual productivity was even more remarkable when we consider that the computer and the word processor did not even exist during his lifetime.

Haldane not only understood several scientific disciplines, but he also made fundamental contributions to many of them. In many fields, his ideas, concepts, and methods shaped the course of a given field, often transforming it profoundly and introducing a rigor that did not exist before. He frequently made connections between disparate fields of science, which others (so-called professional scientists in those disciplines) had missed, thereby introducing new points of view and opening whole new fields of science. Examples include the connection between malaria and thalassemia (Haldane 1949a,b), and the connection between anaerobic environment and the origin of primitive life (Dronamraju, 1968).

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John Burdon Sanderson Haldane (1892–1964), or "JBS" as he was widely known was the only son of an Oxford University physiologist, John Scott Haldane (1860–1936), who was distinguished for his contributions to respiratory physiology. His distinguished ancestors included his uncle Lord Haldane who was Chancellor of the Exchequer and his great uncle, Burdon Sanderson, who was the first Waynflete Professor of Physiology at Oxford University.

The younger Haldane was groomed by his father from his childhood to follow the scientific tradition. J.B.S.'s intellectual precocity was legendary. At the age of 3, when he was wounded in a fall and was bleeding, he was reported to have asked the doctor whether his blood contained oxyhemoglobin or carboxyhemoglobin. Before he was 10, he used to accompany his father into coal mines to collect air samples and on one occasion, readily calculated a set of log tables when asked to do so by his father who had forgotten to bring his own. He was educated at Eton and Oxford University, graduating in Classics in 1915. But, while he was a student at Oxford he had already published two physiological papers in collaboration with his father and also an important paper on one of the first cases of genetic linkage in the vertebrates (Haldane *et al*., 1915). He possessed a brilliant mind and prodigious memory and was fond of quoting, in his later years, extensive passages from Greco-Roman classics, Hindu epics (e.g., *Ramayana* and *Mahabharata*), and excertps from psalms and various other religious texts, during international scientific conferences.

During his long career, Haldane was successively identified as a physiologist, biochemist, geneticist, biometrician, and a statistician, among others. He was a Fellow in physiology at New College, Oxford during the years 1919–1922. He was appointed as the Sir William Dunn Reader in the Biochemistry Department at Cambridge University by Sir Gowland Hopkins in 1923 and served with distinction for 10 years when he resigned, in 1933, to accept the Chair of Genetics (1933–1937) and later Biometry (1937–1957) at University College, London. In July 1957, he moved to India when offered a Research Professorship at the Indian Statistical Institute in Calcutta. Haldane directed research in India in several disciplines but especially in human genetics. He continued his mathematical investigations in population genetics. This period of Haldane's life was discussed in detail in my book: *Haldane: The Life and Work of J.B.S. Haldane with special reference to India* (Dronamraju 1985).

Haldane contributed original ideas, concepts, and methods to almost all aspects of genetics. The following account touches upon only a few highlights of his many important contributions to genetics. A fuller account can be found in various biographical accounts (Dronamraju, 1985, 1987, 1990, 1992a,b, 1993, 1995, 1996, 2004).

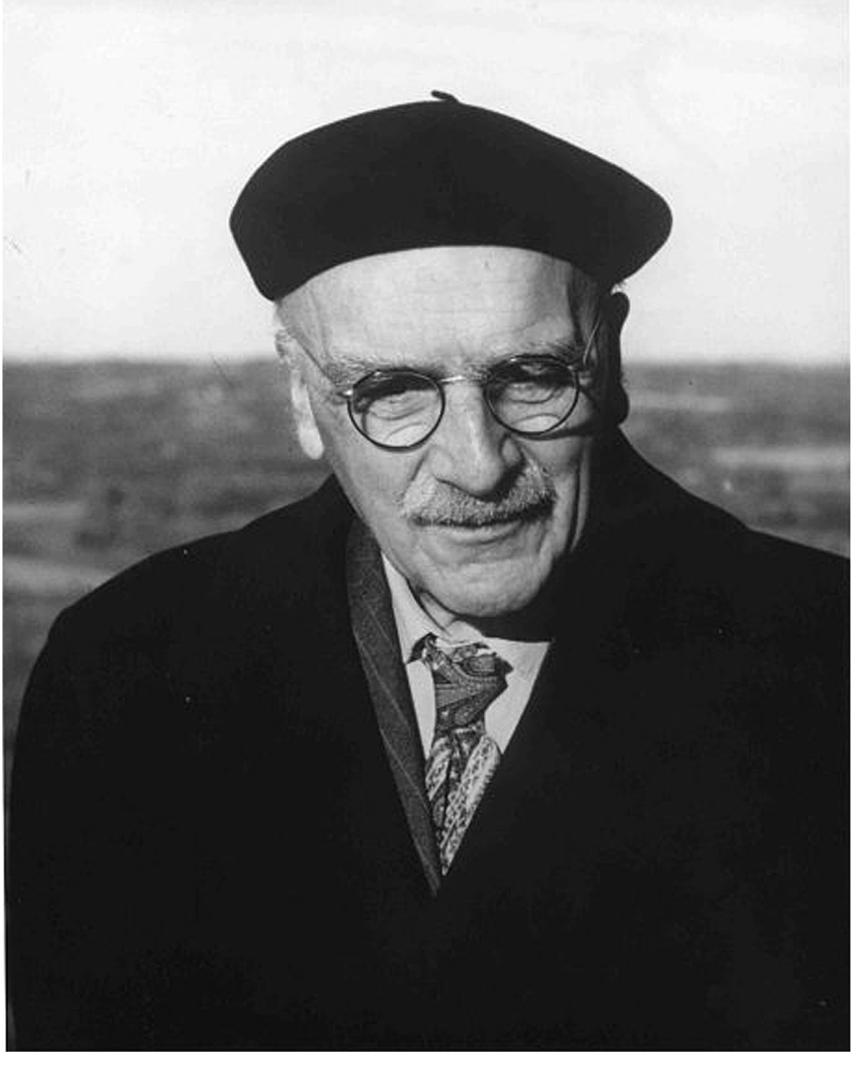

Photo of J.B.S. Haldane taken in Madison, Wisconsin, shortly before his death in 1964. (Photo was taken by Dr. Klaus Patau.)

1. Population Genetics

Haldane served in the Black Watch during World War I, and soon after returning to civilian life, published an important paper on the estimation of linkage between loci based on recombination, later known as "mapping functions." In the same paper, he proposed the term "centimorgan" or *cM*, which is still used today (Haldane, 1919). But his major interest during the 1920s was the development of an extensive mathematical theory of natural selection. In a series of mathematical papers on a quantitative theory of natural selection, Haldane derived equations to examine the consequences of selection and mutation under several hypothetical genetic circumstamces, such as inbreeding, outcrossing, dominance, recessivity, partial penetrance, epistasis, and linkage, etc. For instance, he showed that for a dominant gene with a selective advantage of 0.001, a total of 6920 generations is required to change the gene frequency from 0.001 to 1%, a total of 4819 generations is required to change from 1 to 50%, a total of 11,664 generations is required to change from 50 to 99%, and a total of 3,09,780 generations is required to change from 99 to 99.999%. He also examined the consequences of selection for quantitative traits and very rare characters. Haldane's investigations during that period (1924–32) were summed up in his book *The Causes of Evolution* (Haldane, 1932). His work laid the foundation of what later came to be called *population genetics* to which Fisher (1930) and Wright (1931) also contributed independently. However, unlike Fisher and Wright, Haldane contributed to the foundations of human genetics quite extensively. His knowledge of demographic genetics, biochemical genetics, and several other branches of genetics was far greater than that of his contemporaries.

Haldane's contribution to population genetics differed from those of Fisher and Wright in several respects. He considered both the statics and the dynamics of evolution, and much of his early work on gene frequency changes was deterministic. In one of his papers on the mathematical theory of natural selection, Haldane (1927a) dealt with a stochastic problem, investigating the probability of fixation of mutant genes. Haldane showed that the probability that a single mutation (with selective advantage k) will ultimately become established is only about $2k$ if dominant and only about $\sqrt{k/N}$ if completely recessive, where N is the population size. Although this analysis was greatly extended by the later works of Fisher, Wright, and Kimura, Haldane was the first to tackle this aspect of population genetics.

In another important investigation, Haldane (1931) anticipated Wright's shifting balance theory. His paper on "metastable populations" contained an elegant demonstration that mutant genes, which are harmful singly, may become advantageous in combination. He then showed that, for *m* genes, a population can be represented by a point in *m*-dimensional space. He argued that the process of speciation can result from a rupture of the metastable equilibrium and that such ruptures may be more likely to occur in small isolated communities. During his later years in India, he returned to many of these problems in population genetics, some in collaboration with Jayakar, investigating the conditions for polymorphism under selection of varying direction (Haldane and Jayakar 1963), the elimination of double dominants in large random mating populations, polymorphism due to selection depending on the composition of a population, and solutions to some problems in population genetics that were first considered by Haldane long time ago. One of his last papers with Jayakar, gave in a very elegant form the conditions for stability of an intermediate gene frequency at a sex-linked locus. These are summarized by Dronamraju (1985).

2. Beanbag Genetics

Towards the end of his life, Haldane (1964) wrote a remarkable essay, entitled "A defense of beanbag genetics," justifying the value of theoretical population genetics, which was founded by him, R.A. Fisher, and Sewall Wright. Evolutionary biologist, Ernst Mayr (1963), had earlier questioned the importance of theoretical population genetics and its relevance to evolutionary biology. Haldane (1964) responded by saying that a mathematical theory may be regarded as a kind of scaffolding within which a reasonably secure theory expressible in words may be built up. He stated further that only algebraic arguments can be decisive in some situations and adequate field data were not forthcoming to test the theoretical models. Haldane wrote that he made certain simplifying assumptions, which enabled the framing of biological questions in a form that would suit mathematical analyses. He added that the mathematical methods employed by himself, Fisher, and Wright would not impress professional mathematicians as they were simple by mathematical standards.

3. Terminology

There are at least three instances of Haldane's contribution to the terminology of genetics and evolutionary biology. He introduced the term *centimorgan*, or *cM*, as a unit of chromosome map distance, deriving a relationship between the distance (*mapping function*) between two loci and their crossover value (Haldane, 1919). A second instance was his introduction of the terms *cis* and *trans* into genetics from biochemistry, replacing the terms first introduced by his mentor William Bateson—*coupling* and *repulsion*, which were in vogue until then (Haldane, 1941a). Haldane's (1949a) contribution to the terminology of evolutionary biology included the term *Darwin* as a measure of evolutionary rate on the basis of changes in tooth size in fossil horses. For example, it can be an increase or decrease of size by a factor of e per million years, or an increase or decrease of 1/1000 per 1000 years. The horse rates would range around 40 millidarwins. Haldane wrote that the unit for the character may be a unit increase in the natural logarithm of a variate, or alternatively one standard deviation of the character in a population at a given horizon. Haldane's paper was written at the invitation of Ernst Mayr, who, as the first editor of Evolution, was then soliciting papers from eminent evolutionary biologists.

4. Human Genetics

During the period, 1930–1964, Haldane published numerous papers on all aspects of the genetics of man, laying the foundation for what later came to be called "human or medical genetics." His methods were mathematical and statistical. Haldane's analysis and insight moved the field of human and medical genetics forward in the era of premolecular-biology. The subjects covered by Haldane include: the formal analysis of human pedigrees, especially his maximum likelihood method of estimating the true proportions of affected offspring in families with recessive hereditary diseases (Haldane 1932a), the first human mutation rate (for hemophilia) (Haldane 1932b, 1935), the first human gene map for hemophilia and color blindness on the X chromosome (Haldane and Bell 1937, Haldane and Smith, 1947), relation of modifying genes to age-at-onset variation (Haldane, 1941b), analysis of heredity–environment interaction (Haldane 1946), the role of infectious disease in evolution (Haldane, 1949b,c), and the measurement of natural selection (1954). Other papers of interest include a study of the impact of inbreeding on the spread of sex-linked genes in human populations (Haldane and Moshinsky, 1939) and the dysgenic effect of induced recessive mutations (Haldane, 1947). In his later years in India, he took special interest in the genetics of human populations of that region (Dronamraju and Haldane 1962, Haldane and Jayakar 1962).

"In 1954, Haldane proposed a measurement of the intensity of selection, $I = \ln s - \ln S$, where s is the fitness of the optimum phenotype and S is that of the whole population." By applying Karn and Penrose's (1951) data on human birth–weight distribution, Haldane found that 58% of all deaths were selective on the sole criterion of weight, and the intensity was $I = 0.0240 \pm 0.004$. The effect of this natural selection on population was to increase the mean birth weight from 7.06 to 7.13 pounds, or about 1% but to decrease the standard deviation of the birth weights by 10%. The effect of selection in decreasing the variance was far greater than its effect in increasing the mean.

Among Haldane's ideas that had a significant impact on the growth of genetics, were his early emphasis that the biochemical interpretation of gene action is more fundamental than was the practice until then. His paper on the genetic basis of human chemical individuality must be regarded as a milestone in human–biochemical genetics and as a connecting link between the early work of Archibald Garrod (1909) on human–biochemical disorders and the later work of Harris (1953) and others on human biochemical genetics (Haldane, 1937b). He was among the early geneticists who enunciated the gene–enzyme concept, "The chemist may regard them (genes) as large nucleoprotein molecules, but the biologist will perhaps remind him that they exhibit one of the most fundamental characteristics of a living organism: they reproduce themselves without any perceptible change in various different environments . . . in some cases we have very strong evidence that they produce definite quantities of enzymes, and the members of a series of multiple allelomorphs produce the same enzyme in different quantities" (Haldane, 1920).

5. Genetic Load Theory

The general idea of genetic loads is based on a paper by Haldane (1937), "The effect of variation on fitness." He showed that the effect of mutation on population fitness depends mainly on the mutation rate and not on the deleteriousness of the individual mutants. Several years later, Muller (1950) discussed the problem under the title: "Our load of mutations". The theory of genetic loads was chiefly developed by Crow (1958) and Crow and Kimura (1965). Haldane's (1937a) paper gave the first basis for assessing the impact of mutation on the population. It also showed that any increase in mutation rate would have an effect on fitness ultimately equal to this increase. This principle provided a basis for various assessments of the genetic effect of radiation at a time when the question first became one of social and political importance.

6. Immunogenetics

An important contribution of Haldane (1933) was the clarity he introduced into transplantation and immunological genetics. He suggested for the first time that the transplantation factors for tumors identified by C.C. Little and George Snell at the Jackson Laboratory in Bar Harbor were simply antigens controlled by genes that are present and active in both tumors and normal tissues. Haldane's contributions to immunogenetics were summarized by Mitchison (1968). The maintenance of heterozygosis for genes controlling antigens was of great interest to Haldane. He examined the expected rate of approach to homozygosis in inbreeding (Haldane 1936, 1956) and during backcrossing that was specially designed to produce co isogenic strains of mice (Haldane and Snell 1948). He foresaw correctly that inbreeding will not produce complete genetic uniformity as was demonstrated by later work on skin grafts among inbred mice.

Among other ideas was Haldane's (1944) suggestion that the Rhesus polymorphism lacked any satisfactory explanation and was therefore of recent origin. His analysis of maternal–fetal incompatibility showed that the rhesus factor could be in unstable equilibrium when the gene frequency was 1/2, however, most populations would tend to become either Rh-positive or Rh-negative (Haldane 1942). Following the discovery of the genetic basis of human fetal erythroblastosis by Landsteiner and Wiener, Haldane pointed out that the modern populations of Europe were the result of crossing between populations who possessed a majority of Rh-positive genes and populations who had a majority of Rh-negative genes. Furthermore, two populations—one in Switzerland and another in Spain—were discovered to have a majority of Rh-negative genes.

Haldane suggested that the Rh + genes come from Asia and Rh- from Europe. Thus finding thats the Basques, which are thought to be the closest descendants of the original Europeans, and high frequency Rh- alleles supports the idea.

Haldane suggested that a high rate of mortality in their offspring would indicate that such differences would constitute a barrier to crossing, and play some part in preventing hybridization between mammalian species (Haldane 1964). On the other hand, he suggested that such common diseases as amaurotic idiocy, microcythemia, and sickle cell (which are too frequent to be attributed to mutation) might be due to selection in favor of heterozygotes leading to stable equilibria (Haldane 1949c).

Haldane's impact on immunogenetics was evident through his colleagues and pupils (see Haldane 1956, Haldane and Snell 1948). One of them was his nephew N.A. Mitchison who described Haldane's impact on his work in a contribution to the memorial tribute, which I have edited shortly after Haldane's death (Mitchison 1968). Many years ago, in 1933, Haldane recruited Peter Gorer to join his Department at University College, London. That move by Haldane proved to be a very important step in advancing immunogenetics. Gorer at first discovered three blood groups among the strains of mice. One of these was named "antigen II", which later became the H-2 locus, that landmark of transplantation biology.

7. Sociobiology

Of particular interest was Haldane's analysis of socially valuable but individually disadvantageous characters (e.g., as in social insects, such as honey bees and ants). Haldane's analysis of altruism led to the development of sociobiology many years later. Haldane (1932a) stated that socially valuable but individually disadvantageous characters can only spread through the population if the genes determining them are carried by a group of related individuals. The chances of these individuals for leaving offspring are increased by the presence of these genes in an individual member of the group whose individual viability is lowered by these very genes. Haldane (1932a) gave two examples. (a) With respect to the inherited trait *broodiness* in poultry, Haldane stated that a broody hen is more likely to have a shorter life than a nonbroody hen because she is more likely caught by a predator while sitting. However, the nonbroody hen will not rear a family, so genes determining this character will be eliminated in nature. Selection may strike a balance between these two extremes—neither a too devoted parent nor one that abandons her young at the slightest danger would be represented in posterity. On the other hand, one that does so only under intense stimulus will live to rear another family. (b) The other example concerns the devotion and self-sacrifice among social insects that may be of biological advantage. In a beehive, the same set of genotypes is represented in the workers and young queens. Any behavior pattern in the workers ("however suicidal it may be") that is of advantage to the hive, will promote the survival of the queens, and thus tend to be favorably selected. On the other hand, genes causing unduly altruistic behavior in the queens would tend to be eliminated. Haldane concluded that the biological advantages of altruistic conduct only outweigh the disadvantages if a substantial proportion of the tribe behaves altruistically. Many years later, Hamilton's (1964) analysis of sociobiology was based on Haldane's ideas.

8. Daedalus and Eugenics

Haldane was a highly skilled popularizer of science and its social applications. Through his numerous articles in the popular magazines and newspapers he exercised great influence in educating millions of people. But none matched his first book—a slim volume entitled *Daedalus, Or*

Science and the Future, which was first published in London in 1923 and in New York a year later. It was an expanded version of his address to Heretics at Cambridge University which was delivered on 4th Feb 1923. The biological predictions in Haldane's *Daedalus* were in the form of hypothetical essay on the influence of biology on history during the 20th century which will (" it is hoped") be read by a rather stupid undergraduate member of this university to his supervisor during his first term 150 years hence. *Daedalus* was a remarkable statement, which was a prediction of what might happen in science in the far distant future and at the same time an appeal to encourage certain lines of biological research, especially genetic engineering, as well as a warning against possible misuse or excessive zeal in applying science to solve social problems. It was a bold document, which proclaimed what scientific revolution might bring forth in the most private aspects of life, death, sex, and marriage, in an era when even the mention of 'birth control' in public media caused an uproar (see Huxley 1970, p. 151; and Dronamraju 1993a, p. 122). Haldane predicted the widespread practice of eugenic selection, *in vitro* fertilization, manipulation of the human genome, and routine production of offspring with exceptional qualities in music, sports, and virtue. He prophesied the widespread use of psychotropic drugs and numerous other biological and therapeutic interventions to modify the psychological behavioral, as well as the biochemical condition of the human body and mind. *Daedalus* became a sensational bestseller overnight and the American edition was reprinted five times in 1924. Many years later, in 1932, Aldous Huxley's *Brave New World* was published. It was simply a fictionalized version of Haldane's *Daedalus* but without any acknowledgement to the source. In response to *Daedalus*, a contrary point of view was expressed by Bertrand Russell (1924) who argued that science is no substitute for virtue.

Daedalus firmly established Haldane as an outstanding popular science writer (also see Haldane 1993b). Throughout his life, he wrote numerous popular scientific articles, which appeared in the newspapers and magazines in several countries, and were later published in collected volumes, such as *Possible Worlds and Other Essays* (1927b), *The Inequality of Man and Other Essays* (1932c), *Science in Everyday Life* (1940a), *Keeping Cool and Other Essays* (1940b), *Science Advances* (1947), and several other books.

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