Perspectives

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Centennial: J. B. S. HALDANE, 1892–1964

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REMARKABLY, three years, 1889–1892, saw the birth of six men who dominated genetics in its pre-molecular days: C. B. BRIDGES, 1889; SEWALL WRIGHT, 1889; R. A. FISHER, 1890; H. J. MULLER, 1890; A. H. STURTEVANT, 1891; and J. B. S. HALDANE, 1892.

By far the most broadly knowledgeable of these pioneers was HALDANE, "probably the most erudite biologist of his generation, and perhaps of the century" (WHITE 1965). Yet, whereas each of the others is known for at least one path-breaking accomplishment, HALDANE is not. Why? I think the answer lies in the very breadth of his knowledge and interest. He did too many things, he had too many distractions, he was too eclectic, he was too interested in the work of others, and he was too open-minded to push specific ideas. His name is now regularly associated with only two phenomena, HALDANE's rule for interspecies hybrids and the BRIGGS-HALDANE equations for enzyme kinetics. Yet, his influence was felt throughout genetics and considerably beyond.

JOHN BURDON SANDERSON HALDANE was the son of a distinguished physiologist, JOHN SCOTT HALDANE. He actively aided his father in his respiratory experiments, frequently as an experimental subject, and being mathematically precocious, often did calculations and derivations. He was educated at Eton, which he hated, and Oxford, which he loved. He studied maths and won a prize, then switched to classics and graduated with a first in "greats." He never ceased to enjoy quoting poetry in Greek, Latin and the several other languages in which he was fluent. In his sixties in India, he complained that it was no longer easy to learn a new language. He had no graduate degree in science; if you know as much as HALDANE you don't need one. As a student he intended to follow in his father's footsteps and go on to graduate work in physiology, but World War I intervened and he spent four and half years as a bombing officer in the Black Watch. Amazingly, despite being injured twice, he found the whole bloody experience exciting, even exhilarating.

Returning to Oxford in 1919 he became a fellow in physiology. In 1923 he became a reader in biochemistry at Cambridge under F. GOWLAND HOPKINS. After 10 years he moved to University College, London, remaining until 1957. He then migrated to India, first to the Indian Statistical Institute in Calcutta and eventually to Bhubaneswar, Orissa. Changes of locale were usually precipitated by a disagreement, followed by a characteristic Haldanian denunciation and a highly public resignation. In particular, his move to India was the result of increasing dissatisfaction with England, and the Suez crisis in particular. He seized the opportunity to say that he could not continue to live in a criminal police state dominated by a foreign power. He also said that he was increasingly uncomfortable with not being able to understand all the latest technology, particularly electronics, and preferred to move to a country whose technology he could fully understand.

Associating with HALDANE was always stimulating, but not easy. His students admired him, but feared his unpredictability. He could be excessively friendly, but also prickly. He was often insulting, but claimed to be impartial by insulting everyone. Yet he enjoyed conversation and could be completely charming. CLARK (1969) called him a "cuddly cactus."

Biology, especially genetics: In 1901, when HALDANE was 8 years old, his father took him to hear a lecture by DARBISHIRE on the new Mendelian theory. He found it "interesting, but difficult," and his interest in the subject never ceased. A decade later he found evidence for reduplication (as linkage was then called) in some of DARBISHIRE's mouse data. He was advised by PUNNETT not to publish until he did experiments of his own, which he started with a friend A. D. SPRUNT and his gifted younger sister, NAOMI (MIT-

CHISON). They soon confirmed the results, but not until HALDANE was in the battlefield. The paper, I suppose the most important science article ever written in a front-line trench, was finally published in 1915. SPRUNT had already been killed. HALDANE always regretted not publishing the work sooner, for he would then have been contemporaneous with MORGAN.

HALDANE soon developed a much deeper insight into linkage, and was the first to derive a mapping function. The widely used KOSAMBI formula is a particular solution of HALDANE's differential equation. Later, he demonstrated interference by chiasma distribution and measured linkage in polyploids, finding the values roughly the same as in diploids. He also contributed substantially to the theory of polyploid segregation.

During the early twenties he formulated the empirical generalization, now known as HALDANE's rule, that in interspecies hybrids if one sex has reduced viability or fertility, it is the heterogametic sex. He changed his mind at least once about the explanation and the genetic basis is still in dispute, as attested by a flurry of recent articles–see, for example, COYNE and ORR (1989), FRANK (1991), and HURST and POMIANKOWSKI (1991).

As a physiologist and biochemist he quantified his father's theories about blood pH and alkaline reserve. He followed his usual practice of experimenting on himself and found that drinking ammonium chloride gave symptoms of severe acid poisoning. Ammonium chloride turned out to be an effective treatment for babies whose fits were caused by excess blood alkalinity. As a result of his experiments on respiration he learned the trick for which he later became famous. This was to speak, harmonica-like, while inhaling as well as while exhaling–amusing, but sometimes exasperating to those who might have wished to interrupt his continuous flow of words. Another consequence of his knowledge of respiratory physiology was his subsequent life-saving wartime work, again with himself and friends as guinea pigs, on life at high pressures, such as were encountered in submarines and escapes therefrom.

Also during this period he did fundamental work on enzymology, culminating in a classic book (HALDANE 1930). It was reprinted in the last year of his life. The most important result was the BRIGGS-HALDANE relationship which added realism and specificity to the MICHAELIS-MENTON equation. The form of the equation remained the same, but the MICHAELIS constant, K_m, now became a ratio of different velocity constants and no longer a simple dissociation constant. Somewhat later HALDANE, in his association with the John Innes Horticulural Institution, instigated several studies on the biochemistry of flower colors, in some ways anticipating modern biochemical genetics. He organized human enzymatic pathways in a highly influential book *New Paths in Genetics* (HALDANE 1942). Among a number of original touches in this book, he purloined the words *cis* and *trans* from chemistry and introduced them in their now-familiar genetic context.

As a human geneticist, HALDANE, along with FISHER, pioneered in developing methods for segregation and linkage analysis. He was the first to measure a human recombination value, that between hemophilia and color-blindness. He worked out the equilibrium relationship between mutation and selection and used this to measure the rate of mutation of the hemophilia gene. Remarkably, he discovered that the male rate is an order of magnitude higher than that in females. This was doubted at the time, but is now abundantly confirmed. This led to the idea, for which there is now strong evidence, that neutral molecular evolution in primates is male-driven (MIYATA *et al.* 1990).

HALDANE was a prophet ahead of his time in suggesting that abnormal hemoglobins were maintained at high frequency by heterozygote resistance to malaria. He also noticed the polymorphism at the *Rh* locus in Europeans and their derivatives, when the equilibrium should be unstable. He argued for infectious disease as a major selective factor in human evolution.

Finally, I should mention one of HALDANE's most influential thoughts. As early as 1924 he foretold the current heterotrophic theory of the origin of life. (He and OPARIN apparently arrived at this independently.) HALDANE was much impressed by MULLER's analogizing viruses and genes. He noted that the primitive atmosphere contained little or no oxygen, hence more UV impinged on the earth. To quote: "Now, when ultraviolet light acts on a mixture of water, carbon dioxide, and ammonia, a vast variety of organic substances are made, including sugars and apparently some of the materials from which proteins are built up . . . In this present world such substances, if left about, decay–that is to say, they are destroyed by microorganisms. But before the origin of life they must have accumulated till the primitive oceans reached the consistency of hot dilute soup. Today an organism must trust to luck, skill, or strength to obtain its food. The first precursors of life found food available in considerable quantities, and had no competitors in the struggle for existence."

Evolution theory: HALDANE's best known work is his mathematical work in evolution. He, along with WRIGHT and FISHER, founded the subject of population genetics. In a series of papers starting in 1924 he made a systematic study of the kinetics of selection. His tables giving the rate of change of gene frequen-

cies under selection are found in one textbook after another. He showed the relationship between intensity of selection and the change in a quantitative trait, fundamental to selection of such traits. His paper on metastable equilibrium anticipated much of WRIGHT's work. A striking result was his calculating, as early as 1927, that the probability of ultimate fixation of a new mutation with heterozygous selective advantage s is $2s$, a relationship later extended by FISHER, MALÉCOT, and especially KIMURA who used it in developing his neutral theory. HALDANE also discussed the evolution of cooperation and of altruism by what is now called kin selection. In this context I recall a famous retort attributed to him. He was asked if he would follow the biblical injunction and lay down his life for his brother. He answered that he would not, but he would consider it for two brothers. Simple kin-selection arithmetic!

HALDANE's most famous papers are "The effect of variation on fitness" and "The cost of natural selection." In the first he showed that the impact of mutation on the population is given by the mutation rate, not by the severity of effect of the individual mutations. This principle, now called mutation load, has been greatly extended and used for quantifying the impact of mutation on the population, for analyzing the effect of inbreeding in the human population, and for developing ideas about the evolutionary advantages of diploidy and sexual reproduction. The second paper showed that the amount of selection required to fix a gene depends on its initial frequency rather than the selection coefficient. This was used by KIMURA in his initial argument for neutral molecular evolution. These two papers are vintage HALDANE. Both show that a factor that might be thought to be essential for the calculations, the selective intensity, cancels out in such a way as to permit a very strong conclusion without knowing this difficult-to-measure quantity.

I hope I have mentioned enough things to show not only the influence of HALDANE in the past, but the continuing influence of his ideas in current research. The best way to flesh out this skimpy account is to read HALDANE himself. DRONAMRAJU (1990) has assembled many of his best genetical papers.

HALDANE, polymath and curmudgeon: HALDANE's life was a mosaic of contrasts. His erudition and memory were legend. He could (and would) quote endlessly from western classics and Hindu mystics. He could remember mathematical formulas and bibliographic references, which greatly speeded up his paper writing. He carried a pad of paper with him and used spare minutes, such as on train rides, to work on problems or write articles. Sometimes he trusted his memory too far, and minor errors in formulas and bibliographies attest to this. Also, his multitudinous activities and travels sometimes kept him from reading proof, with troublesome but usually only minor consequences. The most amusing is in his classic, *The Causes of Evolution*, in which all his papers are attributed to his wife.

HALDANE often mentioned one deficiency; he was tone deaf. He said that the only way in which he could recognize "God Save the Queen" was by seeing people standing up. He also said, with typical Haldanian absence of false modesty, that this was good; if he had not had a tin ear he would have wasted time listening to music and would have done less research. The world would be the loser.

HALDANE was one of the best popular science writers. In addition to his books, he wrote hundreds of essays. Almost 400 were written for one publication, the *Daily Worker*, during his Communist period. HALDANE had a superb gift for writing simply, yet without losing the essential meaning. His prose style had the terseness and economy of HEMINGWAY with a vocabulary of Basic English. And it was punctuated with witty and quotable epigrams. He also wrote some charming books for children, and at the other extreme, science fiction. His articles are notable not only for their number but for the astonishing variety of subjects. To mention a few: air raid protection, quantum mechanics, animal behavior, dialectics, economics, ecological cycles, astronomy, biochemistry, blood groups, chemical warfare, embryology, on being the right size, bee communication, nuclear energy (he discussed bombs in 1939), relativity, origin of life, origin of the universe, underwater survival, statistics, demography, the taste of oxygen under high pressure, kidney function, effects of hot baths, human races, and heterostyly. In addition to hundreds of popular articles he wrote one on how to write a popular article.

HALDANE must have been a reporter's dream. He could be counted on to answer any question no matter how far out. Not only was he informed on almost any subject, he had an opinion on it, and was uninhibitedly outspoken. Often outlandish, brutally honest, unexpected, irreverent and witty, he was always quotable. And he enjoyed being a character. I'm sure that if he were alive today he would enjoy the stories about himself, and the way they improve with age; indeed, he would be abetting the improvement process.

He was the perfect discussant at a scientific meeting or seminar. (A contemporary rival for this distinction was H. J. MULLER.) Although he could be cutting, much more often his role was to find something interesting about the paper, something that the author had not thought of. His vast knowledge let him see connections with other work that most mortals would miss. Young scientists learned that their work was more important than they had realized. I should like to add that he was remarkably generous regarding

some of my work, which was derivative from his. He played a similarly constructive role for the *Journal of Genetics*, which he edited for many years. His book reviews often displayed HALDANE's unique combination of knowledge, wit and irreverence.

HALDANE also loved to argue. He could be stubborn. He was a Rock of Gibraltar with a voice. There weren't many who could argue with him on equal terms, but he delighted in those who could. During part of World War II he and FISHER were both located at Rothamsted, and their endless arguments are legend. Any subject would do. How I would like to have listened in!

HALDANE was unselfish, especially in citing the work of others and in helping his students and other young scientists, often spending his own money. At the same time he was in constant rebellion against any and all regulations. Every molehill was made into a mountain, and every molecule into a molehill. What others would regard as necessary rules for keeping the machinery oiled or as petty annoyances easier to put up with than to make a fuss over were for him matters of high principle. In most cases his rebellion against rules had little reforming effect and only made life miserable for those, usually low in the pecking order, who were responsible for administering them. And, what a waste of his enormous talents it was.

A low point in HALDANE's genetic career occurred during LYSENKO's powerful and tragic influence over Soviet genetics. HALDANE must have realized that LYSENKO's claims were nonsense. Yet his loyalty to the Communist cause, and perhaps his excessive open-mindedness, led him to equivocate, to find some things in LYSENKO's experiments that might be correct, and to avoid any outright disagreement. Later HALDANE dropped out of the Communist Party and had very little to say about LYSENKO, but the period before this is not a point of light in his life.

HALDANE was extreme in his reckless disregard for his own health and safety. His war work on surviving at high under-water pressures led to convulsions which produced a back injury that pained him the rest of his life. In 1961 he visited Ceylon and, characteristically, while searching for ancient artifacts broke his leg (Figure 1). "This has seriously diminished my capacity for work," he wrote. That year he was to receive the Kimber Award from the National Academy of Sciences. The injury prevented his making the trip, but despite this and despite the fact that acceptance speeches were not customary, he wrote one, which I quote, courtesy of ERNST MAYR. It's classic HALDANE.

> In thanking the Academy for the honor bestowed on me, I should first like to say that, although I have been awarded several other medals in the past, I have always felt that I would have been still prouder if one or two names had been omitted from the list of my predecessors. For the first time in my experience this is not so today. I am proud to be classed with each one of the previous recipients of the Kimber Medal.

FIGURE 1.—HALDANE (his leg having been broken in Ceylon) is pictured in Calcutta in 1961.

He then went on to describe a number of his recent experiments in India.

He also mentioned as "stop press news" his latest discovery, that the expectations of FISHER's cumulant statistics in a sample are equal to the corresponding parameters in the population. A significant intellectual feat, no doubt, but hardly HALDANE's most lasting achievement.

In the fall of 1963 he gave a series of lectures at the University of Wisconsin after his outspoken revolutionary views prevented this in another state. He was at his charming best. In particular, after a highly laudatory introduction by SEWALL WRIGHT in which

many of HALDANE's accomplishments were cited, he began with a correction, saying that the introduction would have been more accurate if "WRIGHT" were substituted for "HALDANE." He already had the early symptoms of the cancer that was soon to kill him, but he made no mention of it and none of us knew it.

On returning to England for an operation he wrote a remarkable bit of doggerel, entitled (after W. H. AUDEN) "Cancer is a funny thing." Great poetry it wasn't, but there were wit and rhymes worthy of OGDEN NASH. The first two lines go

> I wish I had the voice of Homer
> To sing of rectal carcinoma.

At this time the late PHILIP DALY was starting a project for future generations of filming scientists who had made great accomplishments (including SEWALL WRIGHT and LINUS PAULING). He had the daring idea of asking HALDANE to write his own obituary, which HALDANE accepted with relish. It reads, in part:

> I am going to begin with a boast. I believe that I am one of the most influential people living today, although I haven't got a scrap of power. Let me explain. In 1932 I was the first person to estimate the rate of mutation of a human gene.

It was read on the BBC after his death a few months later. According to DALY, HALDANE originally wrote "*the* most influential person" but thought better of it later.

I find it interesting to think about the similarities and differences between HALDANE and his great contemporary, both friend and rival, FISHER. HALDANE was much more learned and could remember almost everything. His mind, I think, was like that of most other people, except enormously magnified. FISHER, in contrast, had a touch of genius, a kind of mathematical magic. Their differences were qualitative, not quantitative. WRIGHT had less mathematical training than HALDANE, yet solved more difficult problems. KIMURA also has a special gift and extended the work of all three. There is a great difference in style, however, between HALDANE and the three others. He never argued for any particular hypothesis. He was open-minded to a fault. Here lies another HALDANE contradiction: he was completely undogmatic in science, while being highly dogmatic about almost everything else.

How does one sum up the life of such a person? Did he live up to his expectations? Did his breadth of accomplishment make up for his not having developed a few subjects more fully and founding a school? Were his popular writings and political activities as important as the science that he might have done with the extra time? According to WHITE (1965), "The tragedy of his life was that the breadth of his interests and activities precluded the long concentration of effort needed to develop a distinct new field of biology. This fact is certainly connected with [his] openness of mind . . . He was possibly too much interested in the work of others to bother greatly in what directions his own was tending . . . In the history of genetics he will remain a great, sympathetic and yet deeply tragic figure."

I am not so sure. Can a life that full be tragic? Might his breadth not make up for the scatter? Did he not enjoy facing intellectual challenges in many areas? How could a life so interesting to others not be exciting to live? His life was one of almost continuous conflict and petty warfare, but I believe he actually enjoyed it. We are all unique; but the adjective seems to have been invented for HALDANE. The world is enriched by his having been here, and I for one would not want him to have lived his life differently.

I should like to acknowledge my indebtedness to the HALDANE biography by RONALD W. CLARK. Most of the personal details are from this source. I have gotten additional information from SAHOTRA SARKAR. No serious scientific biography of HALDANE exists, but SARKAR is working on one, and I eagerly await it. Finally, I am indebted to KRISHNA DRONAMRAJU for many personal incidents about HALDANE and for supplying the photograph in Figure 1.

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I have listed only the most biological of HALDANE's, 23 books and none of his articles. Nearly complete scientific bibliographies are given by CLARK (1969) and DRONAMRAJU (1985, 1990). As far as I know, no one has undertaken the daunting task of compiling a list of *all* his writings.

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