

Recollections of J.B.S. Haldane, with special reference to Human Genetics in India

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This paper is a brief account of the scientific work of J.B.S. Haldane (1892–1964), with special reference to early research in Human Genetics. Brief descriptions of Haldane’s background, his important contributions to the foundations of human genetics, his move to India from Great Britain and the research carried out in Human Genetics in India under his direction are outlined. Population genetic research on Y-linkage in man, inbreeding, color blindness and other aspects are described.

Key words: Color blindness, deaf-mutism and digital anomalies, Haldane, Human Genetics, inbreeding coefficient, Y-linkage

anthropometric research was located at the Indian Statistical Institute (ISI) in Calcutta under the direction of P.C. Mahalanobis and C.R. Rao. However, after we initiated systematic human genetic research at the ISI in Calcutta, this field received much encouragement in India. The eminent scientist J.B.S. Haldane, who left Great Britain to live in India and work at the ISI, deserves much credit for this change in the status of human genetic research in India. The seeds planted by Haldane bore fruit eventually.

Introduction

This paper is partially based on my lecture to the Royal Society in London on October 4, 2011, in which I have recalled memories of working with J.B.S. Haldane.

At the time of Haldane’s move to India in 1957, there was no Indian Society of Human Genetics and no Indian Journal of Human Genetics. There was no university department or teaching in Human Genetics. One active group was led by V.R. Khanolkar and L.D. Sanghvi in Bombay, which was carrying out research on human blood group gene frequencies and cancer epidemiology in different castes. Another center of blood group and

Background

John Burdon Sanderson Haldane (JBS or Jack) was fond of emphasizing his historical roots. From both sides of his family, he inherited a combination of aristocratic self-assurance, physical and intellectual bravery, integrity

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Figure 1:

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of character and occasional magnanimity. He descended from a family of distinguished Scottish intellectuals and politicians.

J.B.S. Haldane (or JBS) was a polymath, Greek: polymathes (“having learned much”). He was a man of great learning whose intellect was not limited by the traditional boundaries between scientific disciplines. Haldane made important contributions to physiology, genetics, biochemistry, biometry, statistics, cosmology and other subjects, all without ever possessing an academic qualification in any branch of science. Haldane was the son of Oxford University physiologist, John Scott Haldane, who taught his son the fundamentals of science from an early age and involved him in legendary and daring physiological experiments. Both father and son acted as their own “guinea pigs” in experiments testing the physiological effects of poisonous gases and safety conditions in diving experiments, which caused much pain, convulsions and even death.^[1] Quite appropriately, their family motto has been called “suffer” and they lived up to it.

Haldane was born in Oxford, England, on November 5, 1892. He was a precocious child. By the age of 3 years, he already acquired some familiarity with scientific terminology. On one occasion, when he fell down and injured his forehead, a doctor came to treat his wound. Upon seeing his blood, young Haldane asked the doctor, “Is this oxyhemoglobin or carboxyhemoglobin?” It is not unusual to hear or read such stories from his childhood. From a young age, he assisted in his father’s experiments. In 1901, when JBS was only 8 years old, his father took him to a lecture by A.D. Darbishire on the newly rediscovered Mendel’s laws. That lecture made a deep impression on young Haldane’s mind, creating a lasting interest to find out more about genetics. Haldane was educated at Eton and Oxford University, graduating in classics with honors in 1914. He excelled in mathematics, which earned him a Fellowship to attend Oxford University where he switched from mathematics to classics.^[2]

Foundations of Human Genetics

Haldane’s early research in genetics was on linkage

and mapping function. He discovered the first case of linkage in mammals.^[3] In his paper on mapping function, Haldane^[4] suggested the term “centimorgan” or cM as a unit of map distance. He was one of the few pioneers (along with F. Bernstein, R.A. Fisher and L. Hogben) who devised methods for human pedigree analysis.^[5] His most important genetical contributions were a series of mathematical papers on the effect of natural selection, which were summarized in his book, “The Causes of Evolution.”^[6] This work became the foundation for “population genetics” along with the works of R.A. Fisher^[7] and Sewall Wright.^[8] Haldane devised methods to estimate the probability of gene fixation in a population,^[9] to estimate the human mutation rate^[10] and to measure the impact of mutation on a population (genetic loads).^[11,12] He prepared the first human gene map between the loci for hemophilia and color blindness on the X chromosome.^[13] Furthermore, he made important contributions to the analysis of gene/environment interaction^[14] and the genetic effects of radiation.^[15] These early advances in human genetics were summarized in Haldane’s Croonian Lecture for the Royal Society of London in 1949,^[16] which was one of the foundations of human genetics.

Haldane introduced the important idea that immunity to infectious diseases played an important part in human evolution^[17] and that the individuals heterozygous for thalassemia (and sickle cell polymorphism) may possess greater resistance to falciparum malarial infection.^[18] He emphasized the importance of ethical considerations in evaluating eugenic programs and the impact of *in vitro* fertilization.^[19] Haldane’s contributions to human genetics were summarized in my book: Foundations of Human Genetics,^[20] and many of his papers in human genetics and population genetics were reprinted in my book: Selected Genetic Papers of J.B.S. Haldane.^[21]

Haldane was a Fellow in Physiology at New College, Oxford, when he pursued his early research in genetic linkage and mapping function while conducting physiological research at the same time. In 1923, he accepted the position of Readership in Biochemistry at Cambridge University and remained in that position for 10 years. That was his most productive period scientifically; in addition to his important work in theoretical population genetics, he derived the law of steady-state kinetics in

enzyme chemistry, he tested the physiological effects of breathing carbon monoxide and carbon dioxide employing himself as his own “guinea pig,” predicted later developments in molecular and reproductive biology in relation to eugenics and started his successful career in scientific popularization. From 1933 to 1937, he was Professor of Genetics and from 1937 to 1957 Professor of Biometry at University College, London. In July 1957, he moved to India and became an Indian citizen. He died of cancer in Bhubaneswar on December 1, 1964.

Arrival at the Indian Statistical Institute

During the 1950s, Haldane became increasingly dissatisfied with the political situation in Great Britain. He was drawn to India because of its politics under Nehru and its cultural and philosophical foundations. Haldane was interested in the biological diversity and the human genetic variation of India, which offer much scope for research. Consequently, when the Director of the ISI, P.C. Mahalanobis, offered him a professorship, he was only too glad to accept it. Another attraction was a similar offer of employment for Mrs. Haldane (Dr. Helen Spurway), who was a geneticist, at the same institute. Since he first visited India in 1915 to recuperate from wounds received in the First World War, Haldane made up his mind to live in India after independence. He made brief visits in the 1950s to attend the Indian Science Congress and to visit the ISI in Calcutta.^[22]

I first learned of Haldane’s move to India from a newspaper report in New Delhi in the summer of 1957. When I contacted him for a research fellowship, Haldane replied immediately to test my knowledge of genetics and to invite me to come and meet with him at the ISI in Calcutta. This was a big surprise to me because famous and important individuals in India do not answer letters from young unknown students, let alone invite them to come and meet with them. I did not know much about Haldane at that point except that he was a very famous and important scientist whose name often appeared in books and newspapers. As a young student in genetics at Agra University, I read his brief biography in Pears’ Encyclopedia and saw some references to his papers in a textbook on genetics.

Research with Haldane

I joined Haldane’s group at the ISI by the end of 1957. The Head of our Division was the distinguished statistician, C.R. Rao, who was Director of the Research and Training School and later Director of the ISI. The research programmes of our group ranged over many topics, from plant breeding and animal behavior to population genetics and plant physiology. In this paper, I will summarize our early beginnings in human genetics.

Besides conducting my research, which initially started with plant breeding, my duties included teaching a course in genetics. Those who received my instruction at the ISI included statistical trainees Jayaraman and Suresh Jayakar, and many others.

Y-Linkage in Man

The first project in human genetics was concerned with the possibility of Y-linked inheritance in the human species. Until then, that possibility was considered to be quite negligible because of the dearth of Y-linked genes in the fruit fly *Drosophila*.

The reasons for the relative “inertness” of the human Y chromosome are mentioned below.

Stern^[23] summarized this field in 1957 and concluded as follows: “An analysis of the evidence concerning sixteen traits formerly regarded as possibly or presumably being due to completely Y-linked genes and a new trait of similar inheritance leads to the conclusion that some pedigrees must definitely be excluded from complete Y-linkage...final decision must await further data.”

In 1959, a distinguished geneticist from Chicago, Dr. Herman Slatk, visited our group at the ISI and drew our attention to the paper by Stern.^[23] He commented that the question of Y-linkage in man was not resolved and we have an opportunity in India to study the inheritance of hairy ears, which is one of the disputed traits. With the support of Haldane and the ISI, I started my investigation of Y-linkage in man.^[24-27] The largest and most investigated pedigree was of my own family. I travelled widely by myself, and occasionally with Mrs. Haldane (who was also known as Dr. Helen Spurway,

a scientist in *Drosophila* genetics), to collect family data and sometimes photographic evidence. These data were published at that time and raised the possibility of discovering other genes located on the Y chromosome. This was an important consequence of my research.

We have come a long way in recent decades. The question whether the human Y is genetically “inert” (except for the SRY) is still being discussed in the light of new technologies and methods. In humans, the Y chromosome has about 58 million base pairs and represents approximately 2% of the total DNA in a male cell. The human Y chromosome contains 86 genes, which code for only 23 distinct proteins. It is unable to recombine with the X chromosome, except for small pieces of pseudoautosomal regions at the telomeres. The human Y chromosome has lost 1,393 of its 1,438 original genes over the course of its existence. With a rate of genetic loss of 4.6 genes per million years, the Y chromosome may potentially lose complete function within the next 10 million years. Degeneration may simply be the fate of all nonrecombining sex chromosomes due to three common evolutionary forces: high mutation rate and inefficient selection, lack of recombination and genetic drift.

Inbreeding

Among other studies, research on inbreeding in the populations of Andhra Pradesh was initiated by me in 1959. It was supported by Haldane who at once provided both scientific advice and financial assistance from his own pocket. He was particularly helpful in designing the questionnaires and the Forms for recording the data. Prof. C.R. Rao provided valuable advice and support.

I recruited several volunteer-helpers who assisted me to contact schools and a hospital in the Visakhapatnam area. They included P. Meera Khan who was a second year medical student at that time at the Andhra Medical College and the King George Hospital I in Visakhapatnam, as well as M.R. Shastry and P. Srihari Rao and several others who helped in recording the data. Both Prof. Haldane and Dr. Spurway (Mrs. Haldane) accompanied me to the project initially to make sure that the data were being collected with sufficient care and accuracy.

Some of my associates later had successful careers in human genetics, such as P. Meera Khan in Leiden University and Ajit Kishore Ray in the University of Toronto, who received early training with the famous Anthropologist, Normal Kumar Bose in Calcutta.

There were two different sources of data: hospital inpatients and their families from King George Hospital in Visakhapatnam, and parents of schoolchildren from local schools. The total number of marriages included in the study was 2,177. Of these, 16.6% were between first cousins, 7.2% with maternal uncles and 6.7% with distant relatives such as first cousins once removed and second cousins. In total, 666 marriages or 30.6% were found to be consanguineous, with the mean coefficient of inbreeding being 0.02093 [Table 1].^[28,29]

These initial data on inbreeding in Andhra Pradesh came as a big surprise to many population geneticists from other countries. Such high inbreeding rates are normally expected in “isolated” island populations, whether the isolation is due to physical barriers or cultural differences (e.g., Amish in the USA). Populations of coastal Andhra Pradesh do not fall under this category. Caste and subcaste traditions have placed restrictions on marriage patterns in the past; however, the resulting endogamous groups still had large enough populations to avoid consanguinity if so desired. Consequently, it was argued that the reasons for high rates of inbreeding in Andhra Pradesh were due to cultural traditions,^[29] not because of small size of the population.

Table 1: Hospital inpatients and their families

Category	Percentage consanguineous
Hospital inpatients	39.3
Parents of inpatients	5.1
Children of inpatients	33.8
Parents of school children	5.9

Table 2: Coefficients of inbreeding in some populations (from the 1960s)

Population	Coefficients of inbreeding
Andhra Pradesh	0.02093
Hiroshima and Nagasaki	0.00372
Navaho Indians (USA)	0.00660
Dinka tribes	0.00153, 0.00096, 0.00049
Brazil (Blacks)	0.04800
North-east Brazil (General)	0.00230
Croatian village isolate	0.04900
Amish isolate (USA)	0.02296

In western countries, inbreeding rates are usually very low in the main population. However, certain isolates still exist where the small size of the community results in higher rates of inbreeding. One such isolate is the Amish community in Pennsylvania and Ohio, where some very high rates of inbreeding are recorded [Table 2]. These rates are comparable to those of coastal Andhra Pradesh.^[28]

Color Blindness

One of our research investigations dealt with a study of color blindness in Andhra Pradesh and Orissa.^[30-32] The frequencies of color blind individuals and those with different types of color blindness are in general agreement with those reported for other nontribal communities in various countries. However, the frequencies in the tribal communities of Orissa were found to be lower than among the nontribal communities of Andhra Pradesh. This observation is consistent with other studies elsewhere, such as those of Post (1982) in Michigan, that selection relaxation in urban nontribal populations has resulted in higher frequencies of color blindness. The total frequency of alleles producing the red color vision deficiencies are roughly estimated to have increased from 0.005 to 0.02 in European populations during about 120 generations; the green, from 0.015 to 0.06, supporting the assumption that selection at both loci has been completely relaxed during this time.

Short Fourth Metatarsal

Haldane and Ray^[33] studied the genetics of families with a short fourth metatarsal (short fourth toes) on one or both feet. Two hundred and six individuals have been studied in 61 pedigrees in West Bengal and Orissa. Pedigree analysis indicated an autosomal-dominant inheritance with about 27% penetrance. Similar observations were reported from Japan and Mexico.

Multifactorial Anomalies

Later, research on multifactorial anomalies such as cleft lip and palate and deaf-mutism, continued in Orissa.

Recessive deaf-mutism^[34] was noted in the smaller inbred community of Bengali Kayastha settlers in Orissa. Studies of both deaf-mutism and cleft lip and palate continued afterwards in association with fetal mortality, resulting in my book: "Cleft Lip and Palate: Aspects of Reproductive Biology."^[35]

Other Activities

Haldane spent several hours each week writing popular scientific essays that are published in popular magazines and newspapers. Several of these dealt with topics in human physiology and human genetics and evolution. They often dealt with scientific subjects but, occasionally, included politics or social issues. A book containing these collected essays was published recently.^[36] Haldane's exchange with the Harvard biologist Ernst Mayr regarding the value of mathematical applications in evolutionary biology is discussed in my most recent book.^[37]

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References

1. Behnke AR, Brauer RW. Physiologic investigations in diving and inhalation of gases. In: Dronamraju KR, editor. Haldane and Modern Biology. Baltimore, MD: Johns Hopkins University Press; 1968. p. 267-75.
2. Dronamraju KR. Haldane: The Life and Work of JBS Haldane with special reference to India. Aberdeen, UK: Aberdeen University Press; 1985.
3. Haldane JB, Sprunt AD, Haldane NM. Reduplication in mice. *J Genet* 1915;5:133-5.
4. Haldane JB. The combination of linkage values and the calculation of distances between the loci of linked factors. *J Genet* 1919;8:299-309.
5. Haldane JB. A method for investigating recessive characters in man. *J Genet* 1932a;25:251-5.
6. Haldane JB. *The Causes of Evolution*. London: Longmans Green; 1932b.
7. Fisher RA. *The Genetical Theory of Natural Selection*. Oxford: Clarendon Press; 1932.
8. Wright S. Evolution in Mendelian populations. *Genetics* 1931;16:97-159.
9. Haldane JB. A mathematical theory of natural and artificial

- selection, Part V. Selection and mutation. Proc Camb Phil Soc 1927;23:838-44.
10. Haldane JB. The rate of spontaneous mutation of a human gene. J Genet 1935;31:317-26.
 11. Haldane JB. The effect of variation on fitness. Am Nat 1937;71:337-49.
 12. Crow JF. The cost of evolution and genetic loads. In: Dronamraju KR, editor, Haldane and Modern Biology. Baltimore, MD: Johns Hopkins University Press; 1968. p. 165-78.
 13. Haldane JB, Bell J. The linkage between the genes for colour-blindness and haemophilia in man. Proc R Soc Lond B Biol Sci 1937;123:119-50.
 14. Haldane JB. The interaction of nature and nurture. Ann Eugen 1946;13:197-205.
 15. Haldane JB. The dysgenic effect of induced recessive mutations. Ann Eugen 1946;14:35-43.
 16. Haldane JB. The formal genetics of man. Proc R Soc Lond B Biol Sci 1948;135:147-70.
 17. Haldane JB. Disease and evolution. Ric Sci Suppl 1949;19:68-76.
 18. Haldane JB. The rate of mutation of human genes. In: Proc VIII Intl Cong Genetics. Hereditas 1949;35:267-73.
 19. Haldane JB. Daedalus or Science and the Future. London: Kegan Paul; 1923.
 20. Dronamraju KR. Foundations of Human Genetics. Springfield (IL): Charles C. Thomas Inc.; 1989.
 21. Dronamraju KR, editor. Selected Genetic Papers of JBS Haldane. New York: Garland Publishing Co.
 22. Haldane JB. A passage to India. Rationalist Annual; 1958. p. 124-34.
 23. Stern C. The problem of complete Y-linkage in man. Am J Hum Genet 1957;9:147-66.
 24. Dronamraju KR. Hypertrichosis of the pinna of the human ear: Y-linked pedigrees. J Genet 1960;57:230-44.
 25. Dronamraju KR, Haldane JB. Inheritance of hairy pinnae. Am J Hum Genet 1962;14:102-3.
 26. Dronamraju KR. Y-linkage in man. Nature 1963;201:424-5.
 27. Dronamraju KR. The function of the Y chromosome in man, animals and plants. Adv Genet 1965;13:227-310.
 28. Dronamraju KR. Mating systems of the Andhra Pradesh people. Cold Spring Harb Symp Quant Biol 1964;29:81-4.
 29. Dronamraju KR, Meerakhan P. The frequency and effects of consanguineous marriages in Andhra Pradesh. J Genet 1963;58:387-401.
 30. Dronamraju KR. Frequency of colour blindness in Orissa. Ann Hum Genet 1963;26:315-9.
 31. Dronamraju KR. Reading of Ishihara (1959) Plates 14 and 15: A new X-linked recessive colour vision anomaly? Ann Hum Genet 1963;27:113-7.
 32. Dronamraju KR, Meerakhan P. Frequency of colour blindness in Andhra Pradesh school children. Ann Hum Genet 1961;25:107-10.
 33. Haldane JB, Ray AK. The genetics of a common Indian digital abnormality. Proc Natl Acad Sci U S A 1965;53:1050-3.
 34. Dronamraju KR. A pedigree of recessive deaf-mutism from Orissa. Abstract 15.49, Proc XI Intl Cong Genet, The Hague, 1963.
 35. Dronamraju KR. Cleft Lip and Palate: Aspects of Reproductive Biology. Springfield (IL): Charles C. Thomas Inc.; 1986.
 36. Dronamraju KR, editor. "What I Require from Life: Writings on Science and Life from JBS Haldane", Foreword by Arthur C. Clarke. Oxford: Oxford University Press; 2009.
 37. Dronamraju KR. Haldane, Mayr and Beanbag Genetics. Oxford: Oxford University Press; 2011.

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