American, British, and Japanese genetics would not have been eclipsed by those of Cambodia and Nigeria about A.D. 2000.'' I have tried in this essay to ward off such a verdict.

Meanwhile, I have retired to a one-storied ''ivory tower'' provided for me by the Government of Orissa in this earthly paradise of Bhubaneswar and hope to devote my remaining years largely to beanbag genetics.

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Commentary: Haldane and beanbag genetics

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We are all unique; but for Haldane the word seems pallid. A grizzly bear of a man, he seemed larger than life. He was a multidimensional outlier.[1]

JBS Haldane (1892–1964) was arguably the most erudite biologist of his generation. I think he was also the most interesting. He was fluent in Latin and Greek; he once said that as a pre-school child he had already 'written erotic poetry in two dead languages'. Remarkably, he had no advanced degree in biology; at Oxford, he majored in 'greats'. Late in life, after moving to India, he became proficient in Hindu languages as well as the lore of that country. Blessed with a near-perfect memory, he did not need to save the paper after doing extensive algebra. He could quote large passages from Shakespeare, Dante, the Bible, the Koran, and who knows what else? As a child, helping his physiologist father with respiratory experiments, he learned to speak while inhaling as well as exhaling, thereby being able to speak continuously and rendering himself immune to interruption. He was one of the best of science popularizers; he had a rare gift of simplifying without distorting the meaning. His breadth of knowledge was astonishing. He wrote on such diverse subjects as: Marxist philosophy, enzyme kinetics, astronomy, economics, chemical warfare, relativity, respiration, probability, statistics, embryology, immunology and of course genetics and evolution. All together he wrote 23 books and more than 400 scientific articles, plus an even larger number of essays and popular articles.

Another Haldane trait was a willingness to experiment on himself. This was particularly evident in his

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wartime experiments on rescues from submarines, which involved exposure to high atmospheric pressures and frequent unconsciousness. He suffered an injury to his spinal cord that gave him intermittent pain the rest of his life.

Haldane's political views were definitely leftist and he did not keep his opinions to himself. For a time he was active in the communist party and wrote several hundred articles for the 'Daily Worker', usually while commuting to work. These affiliations caused later problems in the United States. In the 'Beanbag' article,[2] Haldane said that he was writing this essay instead of presenting it orally, since he was ineligible for a visa.

He finally got one. In a footnote he added that he was not permitted to lecture in North Carolina because of refusing to answer a question that he found offensive. (According to my recollection, when he was asked if he had ever advocated the forceful overthrow of the United States government, he answered that had indeed done so and 'I still do'.) This was duly reported in the ever-reliable New York Times, whereupon I seized the opportunity and got my University to invite Haldane to move his lecture to Wisconsin, where no such question would be asked. He accepted with alacrity and gave four fine lectures.

'A Defense of Beanbag Genetics' is vintage Haldane—spirited, sprightly, witty, irreverent, insulting and erudite. Ernst Mayr had criticized population genetics for being overly simple, analogous to drawing different coloured beans from a bag. In his words:

> The Mendelian was apt to compare the genetic contents of a population to a bag full of colored beans . . . To consider genes as independent units is meaningless from the physiological as well as the evolutionary viewpoint . . . These authors [Haldane, Fisher and Wright] although sometimes disagreeing with each other in detail or emphasis, have worked out an impressive mathematical theory of genetical variation and evolutionary change. But what, precisely, has been the contribution of this mathematical school to evolutionary theory, if I may be permitted to ask such a provocative question.

Haldane was spot-on in his characterization of the reaction from Mayr's targets. Fisher indeed 'preferred attack to defense' and Wright was indeed 'one of the gentlest of men'. Wright was indeed gentle, but there were two exceptions. One was RA Fisher. Their differences over the importance of random drift became bitterly personal. The other was Mayr, because of being classified as a beanbag geneticist. After receiving the prestigious Balzan Prize, Wright told me that he was honoured to receive the award, but its value was substantially diminished when he discovered that Ernst Mayr had won it the year before. So, with the other two targets not likely to respond, Haldane took it upon himself to provide a defence.

Indeed elementary expositions of population genetics often fit Mayr's description. But his criticism of the three pioneers was badly misdirected. All of them took linkage, dominance and epistasis into account. One of Fisher's greatest accomplishments was to show that natural selection, despite dominance and epistasis, acts on the additive component of variance, assessed by least squares, and is therefore quite effective;[3] nature discovered least squares long before Gauss. Somewhat later, Kimura showed that under most circumstances, even with linkage disequilibrium, epistatic variance, since it is cancelled by the linkage disequilibrium variance, makes hardly any contribution to the transmissible variance.[4] Wright's emphasis on epistasis was even greater; complex interactions were the very essence of his shifting balance theory.[5–8] Haldane was justifiably critical of Mayr's 'genetic cohesion', 'integrated gene complexes' and 'the coadapted harmony of the gene pool', which lack predictive value and add little to our understanding of the basic mechanisms of evolution. And I would add 'genetic revolution', as another vague and misguided Mayr concept. As Haldane pointed out, models are necessarily simplified, but only by simplifying can testable predictions be made. A good model simplifies while revealing some aspect of reality. And if the model does not predict well, it is open to improvement.

In one respect the beanbag model is particularly in tune with later developments. Drawing coloured beans from a bag forces one to attend to random processes, which play such a large role in recent theories of molecular evolution. As models become more complex and realistic, the bean-pool may change, but the essential randomness remains. Only by postulating infinite populations and deterministic evolutionary forces, all unrealistic, can we ignore the random element.

In his 'Defense', Haldane cited one example after another where beanbag genetics has provided deeper insights into evolutionary problems. Although, he was scrupulously fair to Fisher and Wright, Haldane was not inhibited by false modesty. Many of the examples are taken from his own work. Here are two that I particularly like: First, he showed that selection against haemolytic disease in newborns does not lead to a stable equilibrium of Rh+ and Rh− alleles. He suggested that the current European population is the result of a recent hybridization of original Europeans (Rh−) and migrants from the East (Rh+). Supporting evidence came from the Basques, thought to be the nearest descendants of the original Europeans. Sure enough, they have an excess of Rh− genes.

The second example is what has been called industrial melanism, the replacement of spotted white moths by darker forms in the coal-burning regions of England during the nineteenth century. As tree trunks darkened, the darker forms became more protectively coloured. Haldane took advantage of the historical record and the fact that this moth reproduces annually to determine the number of generations involved, and concluded that the selective intensity was about 50%. This was the first instance in which the intensity of selection had been measured for evolution in nature.

Haldane also justified the use of mathematics, both in evolution and in the physical sciences. For example, he gave a justification for the inverse square rule of gravitational attraction. Among other things he considered the disastrous consequences if there were an inverse cube rule. On another subject, it has almost been forgotten that he worked out the mathematics of enzyme kinetics and wrote what was once the standard book on the subject. Haldane was justifiably proud of his mathematical skill and enjoyed complex calculations, which he did by hand. He once solved an inbreeding problem that involved 22 simultaneous equations. At the same time, he was studiously honest and ready to credit others. At the 1956 International Genetics Symposium in Japan, I overheard an interview with a reporter who asked Haldane if he were a good mathematician. Haldane replied that indeed he was a very good mathematician, but 'your man Kimura is better'.

How well has Haldane's analysis stood up? It has been more than four decades since his article was published. Beginning with the Watson-Crick model of DNA structure, the subject of genetics has been revolutionized. Gene action is much better understood and the important role of regulation, with the constant discovery of new mechanisms, has taken over from the earlier emphasis on transcription and translation. But strikingly, and perhaps paradoxically, as our understanding of what used to be called physiological genetics has increased, the importance of beanbag genetics has also increased.

The main reason for the increased usefulness of beanbag genetics is that molecular techniques have provided an abundance of data. Classical population genetics had a beautiful theory, probably the best in biology. But there was a dearth of reliable data. Molecular genetics has reversed this. There is an abundance of data, and the theory has not always kept up. The unit of observation is no longer confined to the gene, usually vaguely inferred from phenotypes, but may be as small as the nucleotide, which can be observed accurately and its variability measured with precision.

What is contemporary beanbag genetics? It is such things as molecular clocks, nucleotide diversity, coalescence and DNA-based phylogenetic trees, along with holdovers from the classical period: mutation, selection, migration and random drift. Evolution rates at the nucleotide level can be measured and compared among populations and among species. And something that to classical eyes was utterly amazing, but is now so commonplace that it is rarely mentioned, is this: it used to be that genetic differences between populations could be measured only by hybridization. Geneticists could not really *prove* that generic differences were genic. Many specific differences, so say nothing of genera and higher orders, could not be measured because the groups were not crossable. Now we think nothing of comparing DNA similarity in tulips and turtles, and assessing the time since they diverged. Although there is nothing surprising in principle, the extreme conservation of some genes is nevertheless remarkable. To mention one more example: the 'out of Africa' concept in human ancestry depended on beanbag genetics, since the most important evidence came from nucleotide diversity.

Haldane, Fisher and Wright, despite differences of detail, all emphasized natural selection as the guiding factor in evolution. The new beanbag genetics includes Kimura's neutral theory.[9] Kimura should be crowned as the philosopher-king of the neo-beanbaggists. One of the biggest surprises of molecular studies of vertebrates has been the overwhelming fraction of non-coding DNA. Kimura has argued, and I think it is now widely accepted, that most evolution in these regions is driven by neutral mutation, with the fate of individual mutations subject to random drift. This theory has supplied the basis for a molecular clock as well as becoming the accepted null hypothesis for measuring selection. How much of protein evolution is mutation-driven is yet to be determined.

I have no doubt that Haldane, despite his prescience, would be greatly surprised and enormously pleased by the success of beanbag genetics.

Haldane placed great emphasis on the value of mathematical formulation as a way of clarifying problems. The article is rife with examples where verbal thinking was imprecise, incomplete, or misleading. Haldane said that the mathematical theory of evolution was quite primitive. At least it would be so regarded by mathematicians, although biologists who have struggled with Fisher's mathematics might disagree.

Undoubtedly, Haldane would be pleased by the entrance of applied mathematicians into the field, with a consequent increase of breadth and rigour. And where mathematics cannot take us, computers often can. We now have a body of theory that can be mentioned in the same breath as that of the physical sciences. Haldane would be pleased.

In many ways, Haldane's article is dated. One example, to which both Fisher and Haldane contributed, is devising means of extracting information from pedigrees where experimental matings are not possible, as in that genetically recalcitrant species *Homo sapiens*. Molecular techniques have rendered these techniques largely obsolete. I am a bit rueful that these have been eclipsed; some were remarkably clever and fun to play with. Other questions, which were burning at the time, have either been solved, shelved as wrongly formulated, or simply replaced by other questions more easily answered by the powerful new techniques. Haldane, I am sure, would be advocating that such questions not be forgotten, but rather postponed until the techniques become adequate.

Population genetics is more than Mayr's beanbag genetics. The complications that he said were missing in the model are often taken into account. Population models now include multiple factors, linkage, dominance and epistasis. I think that this can be regarded as a natural extension of the beanbag model. In other words, I believe that population genetics can be regarded as an improved beanbag model. Importantly, it preserves the random property of drawing beans from a bag.

I may have given the impression that evo-devo and population genetics are separate, even incompatible fields—in Steve Gould's pomposity, 'nonoverlapping magisteria'. Yet the border between the two areas is leaky. Increasingly, developmental genetics feeds on the advances made in population genetics, and vice versa. One example is QTL mapping. The techniques are those of transmission genetics, but the underlying interest lies in understanding the developmental basis of quantitative traits. This rapprochement is certain to increase.

Finally, a remark on Haldane's closing paragraph. He speaks glowingly of the 'earthly paradise of Bhubaneswar' and of his 'hope to devote my remaining years largely to beanbag genetics'. Alas, he soon encountered the same disagreements and personality differences that he had experienced in England, often because of his own prickly nature. Rather than staying in Orissa, he expressed his dissatisfactions by jumping several times from one dissatisfaction to a new one.

Conflict of interest: None declared.

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Commentary: Growth of beanbag genetics

Newton E Morton

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Half a century ago Ernst Mayr expressed a zoologist's antipathy to mathematical theories of genetic variation and evolutionary change.[1] He later stigmatized them as *beanbag genetics*,[2] for which the relation between genotype and phenotype is fully specified in terms of a small number of parameters. This prompted a spirited defence from JBS Haldane[3] who went beyond Mayr's interest in systematics and the origin of species to include beanbag models of population genetics that are increasingly amenable to observation and experimentation. On the contrary, vague concepts like *homeostasis* and *canalization*[4] do not lend themselves to beanbag models[5] and have not survived into the current century. The most striking failure of a vague model was provided by Lysenko, who sacrificed the validity of his theories and experiments to ruthless ambition that led to fabricated data, death or suppression of genetic and agricultural scientists, and decreasing food production.[6]

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