PROFILE

Profile of Brian Charlesworth

Jennifer Viegas
Science Writer

National Academy of Sciences foreign associate Brian Charlesworth has been at the forefront of evolutionary genetics research for the last four decades. Using theoretical ideas to design experiments and experimental data as a stimulant for the development of theory, Charlesworth investigates fundamental life processes. His work has contributed to improved understanding of molecular evolution and variation, the evolution of genetic and sexual systems, and the evolutionary genetics of life history traits. In 2010, Charlesworth retired from his faculty position as professor at the University of Edinburgh's Institute of Evolutionary Biology but actively continues to inspire students and conduct research.

An Early Love of Nature

Until age 8, Charlesworth lived near the English seaside in Hove, East Sussex. There, he explored marine life in rockpools, studied snails collected from a bombsite, admired a giant tortoise that lived in a garden behind his apartment, and went on walks with his parents in the Sussex countryside. His family later moved to London, but Charlesworth's interest in nature remained.

At age 11, he entered the private Haberdashers' Aske's Boys' School, which he attended on a local government scholarship. "It had well-equipped labs and some very good teachers," Charlesworth says. He read extensively, visited London museums, and attended public lectures at University College London. His early role models were physics and biology teacher Theodore Savory and biology teacher Barry Goater. He says, "The notion of discovering how the natural world works, purely from observation and reasoning, thrilled me from an early age and continues to do so."

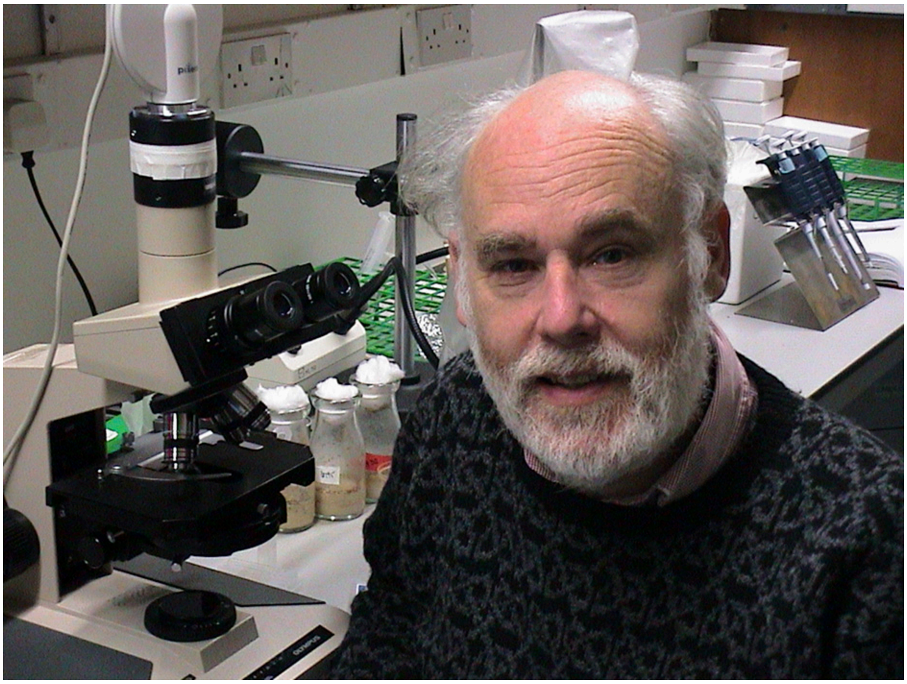
Applying Mathematics to Evolutionary Genetics

In 1966, Charlesworth earned a BA in natural sciences with honors at the University of Cambridge. During his final year at the university, he studied genetics and soon became interested in evolution and the application of mathematics to evolutionary genetics. "I met my future wife, Deborah Maltby, there. We owe a huge amount to each other intellectually, and much of my best work has been done in collaboration with her," says Charlesworth.

Charlesworth continued his studies at Cambridge, earning a PhD in genetics in 1969. This was followed by 2 years of postdoctoral work at the University of Chicago, where Richard Lewontin served as his adviser. "He was a wonderful role model, with a penetrating intellect and a readiness to argue about almost everything," Charlesworth says. "I have probably learnt more about how to do science from him than anyone else." Population genetics pioneer James Crow was another guiding influence.

Charlesworth's first teaching position, from 1971 to 1974, was as a lecturer in genetics at the University of Liverpool. His research at the time primarily involved modeling how natural selection works in populations with age structure (1), in which mating occurs among individuals of different ages.

The models provided a foundation for evolutionary theories of life history patterns, especially aging, which he explains is a consequence of the weakened efficiency of selection on genetic variants whose effects on survival or reproduction are expressed late in life. The work stimulated much empirical research, including the pioneering experiments of his later student Michael Rose on selection for extended lifespan in the fruit fly *Drosophila*.



Profile photograph of Brian Charlesworth. Image courtesy of Xulio Maside.

Genetics of Mimicry and the Origin of Two Sexes

Leading evolutionary biologists Tony Bradshaw, Philip Sheppard, and Arthur Cain were at the University of Liverpool during Charlesworth's time there. "Philip, in particular, encouraged us to work on the theory of mimicry, which stimulated much of our later work on the apparently unrelated topic of the evolution of separate sexes and plant mating systems," he says.

In 1974, evolutionary biologist and geneticist John Maynard Smith recruited Charlesworth for a lecturer position in biology at the University of Sussex. The following year, Charlesworth and his wife authored a seminal

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paper on Batesian mimicry (2), a phenomenon in which a harmless species evolves to resemble a dangerous one. The paper describes a model on how such a system evolves, whereby a new variant that improves mimicry can only enter the population if it is sufficiently close in the genome to a variant that has already entered the population because it confers an imperfect degree of mimicry. The model explains the origin of the close linkage of genes controlling mimicry.

Four years later, Charlesworth and his wife formulated a model (3) that elucidates features of the origin of two sexes from a hermaphrodite ancestor capable of self-fertilization, as is the case for many flowering plants. The model additionally explains how the specialized chromosomes involved in sex determination start to evolve from an ancestral condition in which they are identical in genetic makeup.

Charlesworth returned to the University of Chicago in 1985. He was a professor of ecology and evolution there for the next 12 years. In 1987, he and coauthors Jerry Coyne and Nick Barton investigated how chromosomal location can affect the fates of new mutations (4). Charlesworth explains that, in many species with genetic sex determination, the X chromosome is unusual because its partner in males, the Y chromosome, lacks genes that are present on the X chromosome. In contrast, females carry two copies of the X chromosome.

Charlesworth and his colleagues showed that beneficial mutations often accumulate along an evolving lineage at a faster rate on the X chromosome compared with the autosomes. This phenomenon was later dubbed the "faster-X effect." He says, "This stimulated a large body of research to test for faster-X effects in a variety of species; recent work using whole-genome sequence information suggests that these are indeed quite frequently observed."

Background Selection

In 1993, he and his wife, along with coauthor Martin Morgan, authored an influential paper on the effect that harmful mutations have on genetic variation (5). The paper was a response to a concept known as "genetic hitchhiking," according to which the spread of a beneficial mutation through a population causes the loss of variability at nearby locations in the genome.

Charlesworth and his team proposed an alternative model, background selection, noting that there is a steady input of harmful variants into the population as a result of mutation. "These are mostly destined to be removed from the population by selection; when genetic recombination is rare or absent, this results in the simultaneous removal of other variants located in the same genome," he says. "The observed correlation between variability and the rate of recombination can be explained by background selection, as well as by the hitchhiking of beneficial mutations." The findings have since stimulated substantial research on distinguishing hitchhiking from background selection effects.

Y Chromosome Evolution and Variation in Fitness

In 1997, Charlesworth became a Royal Society Research Professor at the University of Edinburgh. Five years later, while continuing to explore the origin of sex chromosomes, Charlesworth and coauthor Doris Bachtrog showed that an enormous reduction in genetic variability occurred on the newly evolved Y chromosome of the fruit fly species *Drosophila miranda* compared with the homologous genes on its X chromosome (6). Later work on this system, especially by Bachtrog and Carolina Bartolomé, has confirmed and extended the findings. The research provides valuable insights into the early stages of the evolution of the Y chromosome.

Charlesworth's inaugural article, "The causes of natural variation in fitness: Evidence from studies of *Drosophila* populations," applies quantitative genetic studies of the fruit fly to resolve the question of why fitness greatly varies (7). The study reveals the existence of a class of mutations with much larger fitness effects than those inferred from studies of DNA sequence variability. "This class contributes most of the standing variation in fitness within a population," he says. "Variation due to deleterious mutations explains only some of this standing variation, so that processes such as balancing selection (when different versions of a gene are actively maintained in the gene pool) must also contribute."

Continuing Goals

Through his research, faculty positions, lectures, and books (8–10), Charlesworth inspires numerous students and others to learn more about evolution and genetics. For these efforts and his contributions to science, he has received several awards and honors. He was elected to the Royal Society of London (1991), the American Academy of Arts and Sciences (1996), and the Royal Society of Edinburgh (2000). He was awarded the Darwin Medal of the Royal Society of London in 2000 and the Darwin-Wallace Medal of the Linnean Society in 2010.

In his semiretirement, Charlesworth would like to pursue various questions raised by the patterns he and postdoctoral researcher José Campos have observed in data compiled on DNA sequences generated by the *Drosophila* Population Genomics Project. "This would involve extensive computer simulations of hitchhiking and background selection, tailored to the details of the composition of the chromosome regions concerned," he says.

Charlesworth adds, "I also plan to work on various other theoretical projects in population genetics and evolution. My general goal is to try and better understand patterns that we can see in the data provided by genetics and genomics, in the light of reasonably realistic mathematical and computer models based on population genetics."

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