Har Gobind Khorana

(1922–2011)

Chemical biologist who helped to establish the genetic code.

Har Gobind Khorana, who died on 9 November 2011 at the age of 89, was a pioneer and a visionary. That someone with such a humble background could rise to become an icon of molecular biology is a testament to his extraordinary drive, discipline and striving for excellence.

His background was in chemistry, but his interests lay in applying chemistry to problems in biology. By doing so, he started the field of 'chemical biology'. For his work on uncovering the genetic code, Khorana was awarded the Nobel Prize in Physiology or Medicine in 1968.

Khorana's chemical synthesis of the first gene in 1970, followed by his synthesis of a related gene and demonstration in 1979 that it was functional in a bacterium, was a landmark in genetics. This work ushered in the era of recombinant DNA and underlies the *in vitro* assembly of whole genomes from shorter DNA strands.

Khorana was born in Raipur, a small village in the Punjab province of what is now Pakistan, but was then India. His father, an agricultural taxation clerk, believed in education; and Khorana and his siblings were the only literate children in the village. Despite poor educational facilities, Khorana completed high school and went on to receive bachelor's and master's degrees in chemistry from University of the Punjab in Lahore. In 1945, Khorana moved to the University of Liverpool, UK, under a Government of India Fellowship. He was slated to study insecticides and fungicides, but because of lack of space was asked to pursue organic chemistry. It was there that he obtained a PhD in 1948 working on the chemistry of melanins with Roger Beer.

Having seen much German scientific literature, Khorana wanted to do postdoctoral research in a German-speaking country. So he went to the Swiss Federal Institute of Technology (ETH) in Zurich, where he worked for 11 months on alkaloid chemistry with Vladimir Prelog. His stay was short — he received no stipend and had to sustain himself on savings. Fortunately, in 1949, he received a fellowship to work with Alexander Todd at the University of Cambridge, UK, on peptides and nucleotides.

In 1952, Khorana moved to Vancouver to start his own research group at the British Columbia Research Council. The council's director, Gordon Shrum, had come from Canada to interview him and said: "You can have all the freedom to do what you want", but we don't have much in terms of facilities. Shrum said candidly that he wanted to hire an organic chemist because they were cheap — needing only test tubes to do research. Undaunted, Khorana accepted the offer, and established an outstanding research programme.

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In 1960, he moved to the University of Wisconsin–Madison, where he worked on the genetic code and chemical synthesis of a transfer RNA gene. In 1970, he moved to the Massachusetts Institute of Technology in Cambridge, where he switched to working on membranes and signal transduction, problems on which he worked for more than 30 years until his retirement in 2007.

A DEEP THINKER

Much of Khorana's early work used a class of reagents called carbodiimides, which he had come across in Zurich while translating papers from German to English. In Vancouver, his use of these reagents led to the synthesis of nucleotide coenzymes and oligonucleotides, and brought him into contact with biochemists Arthur Kornberg, Paul Berg, Saul Roseman, Jerry Hurwitz, Fritz Lipmann, Charles Dekker and Leon Heppel, many of whom spent summers in his lab.

Khorana was a pioneer. Spanning chemistry, biology and physics, he was doing interdisciplinary research before the current trend. In 1968, he wrote about gene manipulation before individual genes from any organism had been characterized. And in 1971, he wrote about the need to amplify the synthetic gene, using a series of steps that looks eerily similar to the technique for this now known as PCR.

A deep thinker, Khorana put much thought into choosing a problem to work on. He was not influenced by its difficulty or the time needed to solve it, as long as it was of fundamental importance. He often said: "If you want to get far, you have to travel alone." Yet he was always well prepared, making "pilgrimages" to work in laboratories — ranging from Stanford University in California to the National Cancer Center of Tokyo — before undertaking new projects.

As a mentor, Khorana set high standards. He was loyal to the people who helped him and to the institutions at which he worked. He could be demanding, but he was no more so of others than he was of himself. One associate said: "He showed us what excellence in science was and we learnt to recognize it."

Gobind was modest, humble and avoided publicity. He loved music, swimming and long walks, and had a curiosity that lasted until the end. Three days before he passed away, I was by his hospital bed and we talked about glucose and the brain.

Gobind used the solitude of hiking to think about scientific problems, and always carried a pen and notecards to write down his thoughts. On the day of his Nobel prize announcement, he was among the last at the university to hear about it. As he often did, he had gone to a rented cottage by a lake outside Madison with no telephone or radio, to write papers. His wife Esther had to drive over to give him the news. At the celebration, I remember him enthusiastically explaining his latest work on the blackboard to two professors holding glasses of champagne. Gobind was at heart an experimental scientist. With him gone, we have lost an extraordinary man. ■

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