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Har Gobind Khorana (1922–2011) — A Pioneer Nobel Laureate in Molecular Biology

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One of the great chemists of the 20th century, a pioneer at the dawn of the age of molecular biology and the father of chemical biology.

Har Gobind Khorana (known as "Gobind" to all) was born in a Hindu family in Raipur, a little village in Punjab (now in Pakistan). His date of birth is shown as January 9, 1922 in all documents but there is misgivings to his exact date of his birth. Amongst four siblings (three brothers and one sister) he is the youngest in the family. Although a *patwari* (a village agricultural taxation clerk in the British Indian system of government), his father was committed to educating his children with his meager earnings. Gobind was taught at home by his father till high school.In a village of about 100 people, their family was practically the only literate one.

As a child, Gobind would wake up early to go out into the village, to look for a house with smoke coming out of the chimney, and then to request for a bit of ember to take home to light the cooking fire. Later he used to sit on the steps of the post office and transcribe letters for illiterate villagers. Who would know then that the boy who helped his mother every morning to light up the fires for cooking, would one day light up the world of knowledge as Father of molecular biology!

Gobind earned his B. Sc. (1943) and M. Sc. (1945) from Punjab University, Lahore (now in Pakistan). In 1945 he went to the University of Liverpool with a fellowship from the Government and received a Ph. D (1948) working on the chemistry of melanins under Roger Beer. His introduction to Western civilization and culture began at the University of Liverpool.

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He did his postdoctoral studies in Zürich (1948–1949) with Professor Vladimir Prelog at Eidgeno¨ssische Technische Hochshule in Zurich. Here he worked for 11 months on alkaloid chemistry without any funding and had to sustain himself on his poor savings living essentially in the laboratory and surviving on rice and unpasteurized milk. However, an instant and long-lasting bond established with his legendary mentor, Prelog greatly influenced Gobind's approach to work and his scientific integrity.

At that time he rediscovered from the German chemical literature a little-known synthetic reagent, carbodiimide, which Gobind later applied in his work to create a revolution in biochemistry.

He returned to India in 1949 and found that due to the partition of India his ancestral village had ended up in Pakistan and his family had dispersed. After spending a fruitless year looking for a job, Gobind, at the age of 27 years, sailed to England when his extended family could pull together the fare for a journey by ship.

Gobind got a fellowship to work for 2 years (1950–52) with Professor G. W. Kenner and Lord A. R. Todd in the Cambridge University on peptides and nucleotides. Since then he became interested in both proteins and nucleic acids. This association tremendously influenced his thought and philosophy towards science, work, and effort.

In 1952, he went to the University of British Columbia, Vancouver with a job offer with limited facilities but immense freedom to do what he would like to do. He stayed here for about eight years (1952-60), and during his stay there, a group began to work in the field of biologically interesting phosphate esters and nucleic acids.

In 1960, he moved to the University of Wisconsin, Madison and worked here for about 10 years (1960-70) as the Director of the Institute for Enzyme Research.

In 1970, Gobind became the Alfred Sloan Professor of Biology and Chemistry at the Massachusetts Institute of Technology where he worked until retiring in 2007.

Gobind married Esther Elizabeth Sibler, of Swiss origin, in 1952. They had three children: Julia Elizabeth (born May 4, 1953), Emily Anne

(born October 18, 1954 died in 1979) and Dave Roy (born July 26, 1958). Esther brought a consistent sense of purpose into his life at a time when, after six years' of absence from the country of his birth, Khorana "felt out of place everywhere and at home nowhere". He became a naturalized citizen of the United States in 1966. Gobind was shattered when Esther died in 2001 and his health began to deteriorate quickly since then.

Landmark Contributions

In Vancouver Gobind used carbodiimides to initially synthesize the deoxy- and ribotriphosphates and coenzymeA (Khorana, 1954) for which he received considerable international recognition. These syntheses provided Gobind an entré into the use of chemistry to solve biological problems.

Eugene P. Kennedy's group synthesized cytidine diphosphate (CDP) choline, the intermediate in phosphatidylcholine synthesis using the carbodiimide reaction, the "elegant procedure of Khorana"(Kennedy &Weiss, 1955). Chemically synthesized CDP- choline was tested for biological activity even before it had been isolated from natural sources. This work acted as a great catalyst that promoted the general awareness of Gobind's chemical methods among the biochemical community.

Contemporary great biochemists (Paul Berg, Arthur Kornberg, Leon Heppel, Saul Roseman, Irving Goldberg, Herman M. Kalckar, Rollin Hotchkiss, and others) began to visit Gobind's laboratory in Vancouver to learn how to prepare and use the new carbodiimide reagents to make nucleotides of potential biological interest. The course of Gobind's career was greatly influenced by his contact with these great biochemists at the dawn of the age of molecular biology.

Gobind's group in the Institute for Enzyme Research at the University of Wisconsin, Madison worked round the clock double shifts to synthesize all the possible triplet tri-nucleotides, thus providing a firm basis to establish the Genetic code.

At the age of 46, Gobind shared the Nobel Prize for Physiology and Medicine in 1968 with Robert W Holley and Marshall W. Nierenberg for contributions towards elucidating the genetic code – one of the greatest scientific achievements ushering in the age of the molecular biology.

Gobind began his researches in chemical biology on "January 5, 1955" when Kennedy's group chemically synthesized CDP- choline using carbodiimide (Kennedy &Weiss, 1955). After the confluence of the contemporary great biochemists in his laboratory in Vancouver, his line of thinking was clearly outlined in 1960 i.e. use of chemistry to solve biological problems, and this clearly cemented his designation as the Father of Chemical Biology (Khorana, 2000).

In 1972 Gobind's team, at the Massachusetts Institute of Technology, described a monumental achievement in chemical biology- the total chemical synthesis of a functional tRNA gene of yeast (Khorana etal. 1972). Khorana's methods of extension of DNA polymers into synthetic gene (Khorana, 1979), using polymerase and ligase enzymes that link pieces of DNA together as well as methods that anticipated the invention of PCR, are widely used in biology laboratories for sequencing, cloning and engineering new organisms. These are fully automated and commercialized now. In 1976, Khorana's group completed the synthesis of the first fully functional manmade gene in a living cell. The technique they pioneered laid the groundwork for subsequent research on how the structure of a gene influences its function.

Gobind switched from working on polynucleotides and gene synthesis and took up the subject of membrane proteins in the mid-1970s. He chose to work on bacteriorhodopsin. Bacteriorhodopsin is a protein used by Archaea, the most notable one being Halobacteria. It acts as a proton pump; that is, it captures light energy and uses it to move protons across the membrane out of the cell. The resulting proton gradient is subsequently converted into chemical energy. Bacteriorhodopsin was the first integral membrane protein to be sequenced. Gobind then cloned the gene, worked out a heterologous expression scheme, and used site-directed mutagenesis (just invented by his former colleague M. Smith) to elucidate mechanism. Related work on the G protein-coupled receptor (GPRC), rhodopsin (visual pigment), went on essentially in parallel (Ahuja, Crocker, Eilers, Hornak, Hirshfeld, Ziliox, Syrett, Reeves, 2009), and many of the methods pioneered by Gobind's group, including the use of immunoaffinity purification, were used later to advance the structural biology of GPCRs.

As a mentor, Gobind set high standards. He was loyal to the people who helped him and to the institutions where 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”. The Khorana group has always been a tight-knit association of colleagues who interact easily and enjoy one another’s company. All of them know the entire group starting from those in Vancouver to the present. Periodic large meetings of the Khorana group in Cambrigde, UK (1985), Vancouver, Boston (2000), Japan (2004) and Wisconsin (2009) have provided the platforms for interaction of this extended family with their great mentor.

Besides the Nobel prize, Khorana and Nirenberg shared the Louisa Gross Horwitz Prize from Columbia University1968. Other awards include Gairdner Foundation International Award, Albert Lasker Award for Basic Medical Research, and the Padma Vibhushan.

Legacy

Acharya Jagadis Chandra Bose, a harbinger of modern science in India, said -

> “As a candle can only be lighted by another burning candle, a true teacher alone can ignite enthusiasm in his disciples”.

Gobind could ignite hundreds of young minds and train them. Many of the scientists who worked with him, are doing well in many countries throughout the world now. In addition to his incredible scientific contributions, this is the true legacy he left behind.Though unassuming, humble and shy, Gobind was not impersonal. The warmth of his affection has been a guiding spirit for all his associates.

Gobind avoided publicity. On the day of the award of the Nobel prize to him was announced, he was among the last at the university of Wisconsin 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. Esther, his wife, had to drive over to give him the news. He loved music, swimming, long walks, solitude of hiking, and had a great inquisitive mind until the end.

He was greatly influenced by the works of the great poet, T. S. Eliot. The following poem of Eliot often inspired Gobind’s thoughts and works (Khorana, 2000):

"We must be still and still moving
Into another intensity
For a further union, a deeper
communion
Through the dark cold and the
empty desolation,
The wave cry, the wind cry, the vast
waters
Of the petrel and the porpoise. In
my end is my beginning."

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