



Har Gobind Khorana



Raipur, India, 9 Jan. 1922 - Concord, USA, 9 Nov. 2011

Nomination 17 Apr. 1978

Field Biochemistry

Title Professor, Nobel laureate in Physiology or Medicine, 1968

Commemoration – Har Gobind Khorana had his roots in India, where he was born on 9 January 1922, in Raipur, Punjab where he also received his basic education. His wide scientific interests were strengthened by his studies at Punjab University, Lahore, where he obtained his B.Sc. in 1943 and his M.Sci. in 1945. He then emigrated to Europe for advanced studies at the University of Liverpool, where he obtained his Ph.D. in 1948. During his postdoctoral training at the ETH Zurich in 1948/49 he became acquainted with his future wife. He then spent another two years at Cambridge University before leaving in 1952 for the University of British Columbia in Vancouver.

Khorana's essential contributions to research in organic chemistry and synthesis strongly benefited from his broad interests in biological problems and they received wide recognition by the scientific community. By the 1950s his laboratory had already been studying energy-rich phosphate esters including polynucleotides. He thereby developed methods for their synthesis. He continued this work after moving to the University of Wisconsin, Madison, USA, in 1960. This then led him to fundamental investigations on the genetic code that serves living organisms as language in the biosynthesis of protein gene products. Carrying out this research with several quite different organisms he came to the conclusion that a particular genetic code is used by all studied organisms and that this code is thus most likely to be of a universal nature, used by all living beings. This fundamental contribution to scientific knowledge found its well merited recognition with the attribution of the Nobel Prize in Medicine in 1968, jointly with Robert Holley and our late Academician Marshall Nirenberg, who had also made essential contributions to the understanding of protein synthesis.

In 1970 Khorana accepted an Alfred Sloan Professorship for Biology and Chemistry at the Massachusetts Institute of Technology in Cambridge, USA, where he worked until his retirement in 2007. On 17 April 1978 he was appointed to our Academy, where he became an active and highly estimated member. Following the elucidation of the universal genetic code, he paid particular attention to the total synthesis of polynucleotides, including genetic information in the laboratory. We can consider him to be an early pioneer of synthetic biology by developing underlying methodology and concepts. His interests also led him to studies of biological membranes, in particular of membrane proteins that transduce light, such as bacteriorhodopsin and essential functions for photoreception and energy transfer in living organisms.

Har Gobind Khorana died on 9 November 2011, after a rich life, leaving very valuable contributions to novel fundamental scientific knowledge. Our Academy is grateful to him for his appraised contributions to its activities.

Werner Arber

Most important awards, prizes and academies

Awards: Dannie-Heineman Preiz, Göttingen, Germany (1967); Louisa Gross Horwitz Prize (1968); Lasker Foundation Award for Basic Medical Research (1968); Nobel Prize in Physiology or Medicine (1968); William Gibbs Medal of the Chicago Section of the American Chemical Society (1974); Gairdner Foundation Annual Award, Toronto, Canada (1980); M.I.T. School of Science Distinguished Service Award (2000); Centennial Honorary Degree, Rockefeller University (2001). **Academies:** National Academy of Sciences, Washington, DC (1966); American Academy of Arts and Sciences (1967); Deutsche Akademie der Naturforscher Leopoldina,

Halle/Saale, Germany (1968); Foreign Member, USSR Academy of Sciences (1971); Foreign Member, Indian Academy of Sciences (1978); Pontifical Academy of Sciences (1978); Foreign Member, Royal Society, London (1978); Foreign Member, Royal Society of Edinburgh, London (1982).

Summary of scientific research

With his background as an organic chemist and interest in biology, he always attempted to attack current biological problems by chemical approaches. In the fifties, his laboratory was interested in studying energy-rich phosphate esters, e.g. ATP and coenzyme A and related compounds, and general methods for their synthesis were developed. This was followed by investigations of the chemistry of nucleic acids and especially the synthesis of polynucleotides containing specific sequences. The methods thus developed made possible definitive studies of the genetic code by the synthesis of defined messenger RNAs. Following elucidation of the genetic code, he then became interested in the problem of the total synthesis of genes in the laboratory. These studies carried out in the sixties and early seventies led to simple and general methods that have now led to the synthesis of large numbers of genes in different laboratories. His interests then turned to studies of biological membranes. In his final years he was particularly interested in membrane proteins that transduce light. Thus, Bacteriorhodopsin uses light energy to pump protons and the membrane potential thus generated is used by the organism for the synthesis of ATP. Vision in vertebrates and invertebrates depends on light transduction by photo receptors in the rod cells. These were the topics he was engaged in up to his death.

Main publications

Khorana, H.G., Carbodiimides. Part V. A Novel Synthesis of Adenosine Di- and Triphosphate and P₁,P₂-Diadenosine-5'-pyrophosphate, *J. Am. Chem. Soc.*, 76, p. 3517 (1954); Khorana, H.G., Studies on Polynucleotides. XLIV. The Synthesis of Dodecanucleotides Containing the Repeating Trinucleotide Sequence, Thymidylyl-(3'→5')-thymidylyl-(3'→5')-deoxycytidine (with Jacob, T.M.), *J. Am. Chem. Soc.*, 87, p. 2971 (1965); Khorana, H.G., *et al.*, Studies on Polynucleotides. XLVII. The in vitro Synthesis of Homopeptides as Directed by a Ribopolynucleotide Containing a Repeating Trinucleotide Sequence. New Codon Sequences for Lysine Glutamic Acid and Arginine, *J. Mol. Biol.*, 13, p. 283 (1965); Khorana, H.G., *et al.*, Studies on Polynucleotides. XLVII. The in vitro Synthesis of a Co-polypeptide Containing Two Amino Acids in Alternating Sequence Dependent upon a DNA-like Polymer Containing Two Nucleotides in Alternating Sequence, *J. Mol. Biol.*, 13, p. 302 (1965); Khorana, H.G., Nucleic Acid Synthesis in the Study of the Genetic Code, *Les Prix Nobel en 1968*, pp. 196-220 (1969); Khorana, H.G., Total Synthesis of a Gene, *Science*, 203, p. 614 (1979); Khorana, H.G., *et al.*, Refolding of an Integral Membrane Protein: Denaturation, Renaturation and Reconstitution of Intact Bacteriorhodopsin and Two Proteolytic Fragments, *J. Biol. Chem.*, 256, pp. 3802-9 (1981); Khorana, H.G., *et al.*, The Bacteriorhodopsin Gene, *Proc. Natl. Acad. Sci.*, 78 11, pp. 6744-8 (1981); Khorana, H.G., *et al.*, Specific Amino Acid Substitutions in Bacterio-opsin: Replacement of a Restriction Fragment in the Structural Gene by Synthetic DNA Fragments Containing Altered Codons, *Proc. Natl. Acad. Sci. USA*, 81, pp. 2285-9 (1984); Reeves, P.J., Thurmond, R.L., and Khorana, H.G., Structure and Function in Rhodopsin: High Level Expression of a Synthetic Bovine Opsin Gene and its Mutants in Stable Mammalian Cell Lines, *Proc. Natl. Acad. Sci. USA* 93:11487-92 (1996); Hwa, J., Garriga, P., Liu, X. and Khorana, H.G., Structure and Function in Rhodopsin. Packing of the Helices in the Transmembrane Domain and Folding to a Tertiary Structure in the Intradiscal Domain are Coupled, *Proc. Natl. Acad. Sci. USA* 94: 10571-6 (1997); Khorana, H.G., Molecular Biology of Light Transduction by the Mammalian Photoreceptor, Rhodopsin, *J. Biomolecular Structure & Dynamics* 11 (R.H. Sarma and M.H. Sarma, eds) Adenine Press, pp. 1-16 (2000); Hwa, J., Klein-Seetharaman, J., and Khorana, H.G., Structure and Function in Rhodopsin: Mass Spectrometric Identification of the Abnormal Intradiscal Disulfide Bond in Misfolded Retinitis Pigmentosa Mutants, *Proc. Natl. Acad. Sci. USA* 98:4872-6 (2001); Cai, K., Itoh, Y., and Khorana, H.G., Mapping of Contact Sites in Complex Formation Between Transducin and Light-activated Rhodopsin by Covalent Crosslinking: Use of a Photoactivatable Reagent, *Proc. Natl. Acad. Sci. USA* 98:4877-82 (2001).