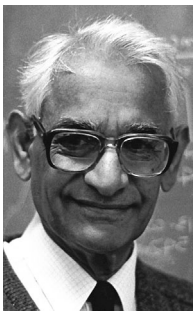
Har G. Khorana

Har Ghobind Khorana (1922–2011)

"In the years ahead, genes are going to be synthesized. The next step would be to learn to manipulate the information content of genes and to learn to insert them into and delete them from the genetic systems. When in the distant future all this comes to pass, the temptation to change our biology will be very strong."

H. G. Khorana, *Pure Appl. Chem.* **1968**, *17*, 349.

A giant of bioorganic chemistry and a visionary who paved the way for some of the most important developments in modern biology decades ago has died on November 9, 2011 in Cambridge (USA). Science has lost a brilliant mind and a humble human being.

The career of H. Ghobind Khorana reads almost like a fairy tale storyline that is only rarely encountered today. Khorana was born in 1922 as the youngest of five children on a date that was not exactly recorded in a small village in the Punjab where his father was the only literate person. Based on his good performance in school, the young Khorana was able to move with a fellowship to the Punjab University in Lahore where he finished his M.S. degree in 1945. With an overseas fellowship from the Indian government to study applied pesticide chemistry, he obtained a PhD in organic chemistry from Liverpool University focusing on basic indole chemistry. In 1948/49 Khorana spent one year in the laboratory of Professor Vladimir Prelog for a postdoctoral fellowship at the ETH Zurich to analyze the constitution of alkaloids. After having to return to India without a position, his former colleague G. W. Kenner arranged for Khorana to join Lord Todd in Cambridge in 1950. It was in the Todd laboratory where Ghobind Khorana encountered the challenge of carbohydrate phosphorylation and where he applied carbodiimides as condensing agents in aqueous organic media. These were key reagents for his later ester and amide syntheses. In 1952 Khorana married Esther Sibler, with whom he had three children.

The British Columbia Research Council hired the thirty year old as a group leader of organic chemistry to Vancouver with plenty of freedom and little funding. Sugar diesters, nucleotides, and coenzymes that were just being discovered provided attractive synthetic challenges for a bioorganic chemist. The systematic synthesis of pure oligonucleotides provided a basis to examine nucleases as potential tools for analysis as well as synthesis.

In 1960, at the height of the work on the oligonucleotides, Khorana was invited to join the famous Institute for Enzyme Research in Madison (Wisconsin). The 1960s were a fruitful decade establishing the field of polynucleotide and nucleic acid biochemistry. The combined chemical and enzymatic synthesis of all possible trinucleotides provided the necessary tools required to elucidate the genetic code. This work was honored with the Nobel Prize for Medicine or Physiology together with R. W. Holley and M. W. Nirenberg in 1968.

The explorations into oligonucleotide chemistry laid the foundation for the coupling chemistry and protective groups required to make longer sequences. In a heroic effort, the Khorana team prepared the first synthetic gene to be reported in 1970. The series of articles following in 1972 are a masterpiece of the systematic approach of a team of chemists developing novel methods to meet the challenges posed by one of the most complex molecules ever made—even if the synthetic organic chemists of the time did not consider oligonucleotide chemistry part of their discipline that focused much on alkaloids and terpenes. In a comment in *Nature*, the first synthesis of a gene was described as *"…perhaps the greatest tour de force organic and biochemists have yet achieved. Like NASA with its Apollo program, Khorana's group has shown it can be done, and both feats may never be repeated…"*. Well, only ten years later one of the members of the Khorana team, M. H. Caruthers, developed a new strategy for oligonucleotide assembly that was amenable to solid-phase assembly and is the basis for the synthesis of not only entire genomes but also many millions of primers for the polymerase chain reaction (PCR) every year. Incidentally, in their work on DNA polymerases, Khorana and Kornberg discovered the principles of PCR in the 1960s.

In 1970, Khorana was appointed Alfred P. Sloan Professor for Biology and Chemistry at MIT and switched research areas, as he did every ten years. Using synthetic probes prepared by chemical and enzymatic means he began to study the biological membrane. Starting in the 1980s, the question as to how integrating membrane chromoproteins insert cooperatively into the bilayer was studied on bacteriorhodopsin, which led to the final big questions Khorana took on. The coupling of G-protein cascades for the regulation of signal transduction processes and amplification and adaptation were studied for almost fifteen years until his retirement from active research.

The loss of his wife Esther after a bout with cancer brought on a tuberculosis infection that must have been lying dormant since his youth in India. For this reason, in his mid-eighties Ghobind Khorana had to stop doing active research and break with his life-long habit of ten-hour work days interrupted by his daily swim in the MIT pool.

Ghobind Khorana won many of the highest awards that can be bestowed upon a scientist; in

addition to the Nobel Prize, he received the National Medal of Science of the USA and the Lasker Prize, to name just a few. He was a fierce pacifist and used his fame to promote peaceful research and human collaboration. Ghobind Khorana, a glowing example of how cutting-edge synthetic chemistry can be used to understand some of the most complex biomolecules and biological systems, has left us. What remains are his many former co-workers that have made outstanding contributions in their own right in the many fields that Khorana often pioneered. The methods he developed with them remain with us for many years to come. As his "chemical grandson" I remember a scientist in a white lab coat sitting in his office at MIT in December 1999, asking me some of the toughest questions I have ever faced about oligosaccharide assembly while he was eating a bowl of rice for his lunch. Maybe this memory of a modest man with immense scientific insights is common to many of us lucky enough to have known H. Ghobind Khorana.

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