

Govindachari Rajagopalan (1938–2020)

Dr Govindachari Rajagopalan, known to many as Rajagopalan and as 'Raj' to his close friends and family, a pioneer in drug metabolism/pharmacokinetics and one of the most distinguished scientists of India passed away on 20 February 2020 at the age of 82 in Chennai.

Rajagopalan, the eldest child of Prof. T. R. Govindachari and Rajamani, was born on 28 July 1938. He studied at Sri Ramakrishna Mission School in Chennai, where his inherited deep faith in God grew into a humane and spiritual vision. In 1960, he received his M.Sc. degree in biochemistry from the University of Madras. Then he went to the US and for his Ph.D. at Duke University (1960–1963) with Prof. William Byrne. Duke had a great reputation in the discipline of biochemistry.

Rajagopalan joined The Rockefeller Institute as a postdoc (1963–1966) with Nobel laureates Stanford Moore and William H. Stein. Moore wrote on Stein, 'Stein, throughout his life, in his generous manner, took a special interest in facilitating the careers of scholars whose sojourns in the laboratory made possible the exploration of many facets of the researches. A number of enzymes were the subjects of studies of specific aspects of protein structure and function'¹. Raj too learnt this warm and encouraging attitude towards the career of his colleagues. In this same article Moore refers to Rajagopalan's outstanding research on 'Pepsin and pepsinogen – preparation and properties' published in the *Journal of Biological Chemistry*².

In 1972, the Nobel Prize in Chemistry was awarded to Christian B. Anfinsen 'for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation', and to Stanford Moore and William H. Stein 'for their contribution to the understanding of the connection between chemical structure and catalytic activity of the active centre of the ribonuclease molecule'. In their Nobel lecture, Moore and Stein have gracefully acknowledged Rajagopalan's work that helped in their research, particularly the esterification of carboxyl groups at the active centre of pepsin³. The exposure to some of the best protein and enzyme chemists at Rockefeller, made an indelible impact on Raj's mind for lateral

thinking and innovative ideas throughout his distinguished career. With his unassuming nature, Rajagopalan hardly ever mentioned his work with Moore and Stein. At the CIBA Research Centre, Basle, Switzerland which he joined later, there were several of us who belonged to the lineage of Nobel Prize-winners. Indian science, in general, remained unaware of the excellent pool of 'reverse brain drain' that had constituted that group⁴.



Rajagopalan also had a small stint at the Indian Institute of Science (IISc), Bengaluru. But he soon realized that the milieu in India, then, was not suitable for striving for excellence in basic sciences. He took a momentous decision to join pharmaceutical research and development, just like his illustrious and renowned father, Prof. T. R. Govindachari, who left his leading academic position as the Principal of Presidency College in Chennai and accepted the Directorship of the new CIBA Research Centre⁵. What was a loss to IISc was a major gain for the fledgling Indian efforts for new drug discovery from medicinal chemistry and natural products. CIBA's top management considered that having a Nobel laureate's student, at Basle, was a golden opportunity.

Raj spent four years (1967–1971) at CIBA R&D in Basle, in the outstanding Drug Metabolism and Pharmacokinetics Laboratory, with Heinrich Keberle and Walter Riess. A protein chemist par excellence, he switched over imperceptibly to metabolism and kinetics of new drugs like oxprenolol and ludiomil^{6,7}. At Basle, he gained much expertise in drug metabolism, gas chromatography (GC) and high performance liquid chromatography

(HPLC). He was one of the first among scientists who brought such expertise and technology that greatly facilitated phase 1 and 2 clinical trials with new molecules developed in India.

During his tenure at Ciba-Geigy Research Centre in Mumbai from 1971 to 1982, Rajagopalan complemented R. K. Maller and B. S. Anjaneyulu, who had earlier established radioactively labelled drug studies in animals, by creating a new drug metabolism and kinetics laboratory with GC and HPLC methods. After my advanced training in clinical pharmacology at Yale, USA, I had joined the Ciba-Geigy Research Center in 1970, with a clinical ward at Seth G. S. Medical College and KEM Hospital, Mumbai, under Prof. U. K. Sheth. We were handicapped, until Raj's arrival, to conduct phase 1 and 2 studies with new chemical entities, without human pharmacokinetic data.

We could not get any sedative effect of S. Rajappa's compound, Go.6050 in humans, despite its potent hypnotic effect in animals. With Raj's expertise, it was found out that there was hardly any absorption of Go.6050 in the volunteers, as demonstrated by undetectable plasma levels. Similarly, Rajappa's potent broad-spectrum anthelmintic, Go.13866 would not have received investigational new drug (IND) permission from the Drugs Controller, as the compound was fatal in the rodents due to diarrhoea. H. J. Koticha, a general surgeon of eminence, provided us with an excised human appendix. Rajagopalan conclusively showed that the diarrhoea in rodents was due to inhibition of intestinal acetylcholine esterase. The human enzyme, in appendix, was not inhibited even at high concentrations. The data were accepted by the Drugs Controller General (India) (DCGI) and IND was granted. The compound was proven to be effective in humans and was approved as a new drug.

Rajagopalan had an interest in natural products and Ayurveda too. He examined the bioavailability of L-DOPA from the seed powder of *Mucuna pruriens* in patients of Parkinson's study. This was our trail-blazing study in natural products research⁸. Besides the methods of assaying the new drug candidates and their metabolites, Raj also developed methods of analysis of diethylcarbamazine and primaquine in blood^{9,10}. We showed that

berberine and sanguinarine strongly inhibited pregnancy diamine oxidase (histaminase)¹¹. Raj was not keen to publish many scientific papers. Much of his work at Ciba-Geigy Research Centre has remained unpublished. After Govindachari and later R. S. Grewal retired as Directors, D. Subramaniam was appointed as the Director of Ciba-Geigy Research Centre. Several leading scientists left the Research Centre. Raj too looked for opportunities where he could exercise a leadership role. In 1982, he joined as R&D Head of Richardson Hindustan, taken over in 1985 by Procter and Gamble India Ltd, Bombay. Raj was considered as a great asset by the chief Gurucharan Das. From 1982 to 1998, he studied the safety and efficacy of formulations used by traditional systems of medicine in India, China and Southeast Asia. He worked on the development of products targeted to arthritis, upper respiratory and gastrointestinal diseases. He challenged P&G consultant, Vaidya Narendra Bhatt, to develop Ayurvedic logic for new product development. For the first time ever, a huge database was created in association with Bhatt to provide a logical explanation of Ayurvedic formulations and ingredients. This eventually led to a novel, multi-ingredient, disease-modifying anti-arthritic agent studied clinically with positive outcomes. Such a systematic and logical approach, coupled with reverse pharmacology, can provide the much needed rational guidance to develop new Ayurvedic formulations, natural drugs, Ayurceuticals and phytopharmaceuticals¹². Raj also pioneered the development of a bedside method to evaluate antitussive agents¹³. According to Ronnie de Sales, an earlier senior colleague of Raj, 'Raj created the finest state of the art Ayurvedic Research Centres...'. Later, Raj was Scientific Advisor to Vivex International LLC, at La Jolla, California, USA, a company that was involved with discovery, development and marketing of novel nutritional bioactive compounds.

Rajagopalan has trained many scientists and technologists in GC, HPLC, drug metabolism and pharmacokinetics. Some of his research associates have joined other R&D organizations. He also helped Profs Nilima Kshirsagar and N. B. Desai in setting up the Pharmacokinetics Laboratory at Seth G.S. Medical College and K.E.M. Hospital in Mumbai. He was invited to speak at several national and international conferences on new drug discovery, drug regulatory milieu and research in traditional remedies.

Raj loved solitude and a few selected friends. His major hobby was growing orchids. His interest in orchids originated from his father. He advanced this heritage with a massive collection of over 1000 plants. Marcel Proust wrote 'Let us be grateful to the people who make us happy; they are the charming gardeners who make our souls blossom'. Like such a gardener, Raj had a kind and humane approach to people, particularly to those who are generally neglected by the creamy layer of the society. His recommendation for a tourist guide in Sri Lanka reflects how he cared for people who did their jobs well. He wrote 'I rarely find myself writing a letter of recommendation for a tour guide, but Jagath you were exceptional in a difficult business, so we thank you for our wonderful visit to your country. It was a perfect trip for us and it was made even better by our guide who educated us on the history and culture of the country. Jagath kept his word on every promise'¹⁴. That is quintessential Raj. Though he was born in aristocracy, he had the least tolerance for snobbery of any kind.

Raj, for many years, was a heavy smoker but had given up the habit for a long time. However, cancer of the lung eventually caught up and that too with brain metastases. In the terminal days, his brilliant mind could not even communicate the agony and pain he suffered from. He left this world quietly just as he had liked to live, without any fanfare. He is

survived by his wife Meera, a great support through life, and a son. As I conclude this obituary, I cherish a beautiful golden icon of Varad Hanuman given to us by our friends Raj and Meera. That is our daily connection with Raj in silent prayers.

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