P. R. Mahadevan

Perurmadom Ramaiyer Mahadevan or PR, as he was affectionately referred to, was born on 20 May 1928 in Cochin, Kerala. He died after a brief illness on 27 April 2003 in Hyderabad. He was elected a Fellow of the Indian Academy of Sciences (IAS), Bangalore in 1973. He leaves behind his wife Sita, two sons and two daughters. Behind this brief description lies the life and science of one of our leading biologists who was the earliest in discovering the power of a multidisciplinary approach to investigating biological phenomena, be it the cell wall of a fungus or the complex pathogenesis of a human disease, leprosy.

PR moved with great facility between microbiology, molecular biology and immunology, networking the essential features of each of these disciplines to reach the core of the problem. In this era of 'nonhypothesis-based' approaches, he stands tall as an integrator of diverse approaches towards a meaningful whole. He was critical of reductionist methodoligies that were treated as an end in themselves and insisted that these had to be integrated into the physiology of the system. He was ahead of many biologists who, having gone 'molecular', are now using the term of functional genomics as the new mantra. He saw the need for integration of function with biochemical and genetic findings, even as the genetic code was unfolding its power.

PR began his studies in botany at the Madras University and went to Banaras Hindu University to obtain the Master's degree in 1955. Like many Indians of that era, he went to USA for his doctoral degree with Bruce Eberhart at Princeton University. His research career can be thought to have begun during the sixties, when he started his doctoral thesis. Subsequently, he went on to join the Nobel Laureate E. L. Tatum at the Rockefeller University, an experience and contact that he cherished and maintained even after his return to India. It was during this period that he used *Neurospora crassa* as a model to understand the basic phenomenon of morphological changes that fungal species undergo both *in vitro* and *in vivo*. Fungi are notorious for changing shape from thread-like filaments to branching ones, as well as becoming rod-like, circular or conoid. The changes in shape are observable at microscopic as well as colony level, when they grow in culture media or in the tissues of plants or animals. He was particularly interested in the genetic regulation of the enzymes of this fungus that would influence the cell-wall constituents and thereby permit the fungi to take on different shapes. In a landmark discovery, he showed that a single gene was the dominant regulator for the enzyme aryl β-glucosidase and it altered the ratio and composition of the cell-wall polymers. Later on, while working in India,

he also showed the relationship of other enzymes to cell-wall constituents and their effects on the morphology of the fungal colonies. He also demonstrated the localization of the structural polymers in the cell wall, which were responsible for the morphological changes. More significantly, he established a chemical method for studying the cell-wall constituents which began to be used routinely by other laboratories.

During the mid-sixties, he returned to India to lead a group in biochemical genetics and molecular biology in the Biomedical Division at the Bhabha Atomic Research Centre (BARC), Mumbai. During the next seven years his group continued the cell-wall studies, dissecting further the nature of the genetic control. They went on to show the level of genetic control and how hydrolytic enzymes were associated with the cell walls and how they hydrolysed the cell walls at the branching points. PR concluded that the distribution and hydrolytic activity of these enzymes were the determining factors for the total pattern of branching and appearance of the fungus. Of interest and significance was the demonstration of the presence of long-lived mRNA and the presence of an inhibitory protein that regulated transcription in the *Neurospora* species. These studies encompassed the finest biochemical and genetic approaches of that time, to understand a basic problem that had long fascinated microbiologists.

It is not clear to me as to why he found it necessary to shift fields and leave the ambience of BARC for the remotely situated Indian Drugs and Pharmaceuticals Ltd (IDPL) in Rishikesh. He was perhaps attracted by the challenge to build new laboratories (a recurring pattern in his life) in a public-sector undertaking and bring new knowledge into the area of antibiotics and fermentation technology. I have heard him talking about these years with nostalgia. He came to IDPL as Chief of Research and Development (R&D) Laboratory at a time when there was a national need to be self-sufficient in producing antibiotics for the health needs of India. We had not signed the Paris Convention Treaty which would have bound us with patents, and it was during those years from 1972 to 1978, that PR contributed his knowledge for improvement of antibiotic strains and helped to make improved microbial products. He applied genetic approaches to industrial fermentation technologies and thereby helped create better strains and improved methodologies for tetracycline and streptomycine production. It is a matter of history that the early pioneers in chemical engineering and industrial microbiology provided India with cheaper drugs and antibiotics, which helped revolutionize healthcare. The trials and tribulations of PR in these early years can be easily imagined when one realizes that he was isolated in a scenic but poorly connected town, far from the academic environments that drive research. Yet, he was happy because he was involved in a challenging job, both academically and managerially. Moreover, he made the transition from esoteric research to one with practical application with ease and grace.

The next phase in PR's career was to give him a lasting identity in the field of

leprosy and bring him back to Mumbai. The Godrej Foundation decided to institute the Foundation for Medical Research (FMR), whose mandate in the early years was to understand the scientific basis for leprosy and thereby contribute to its elimination. This mandate was both brave and laudatory, as India had a third of the world's population of leprosy patients. The stigma attached to the disease was horrendous and drugs were scarce, but Dapsone had been found useful. PR's knowledge of microbiology made him an appropriate leader in research. Those were heady days. N. H. Antia, a famous plastic surgeon, devoted himself to the treatment and investigation of deformities and had excellent clinical understanding of nerve damage which is the bane of leprosy. The team of Antia and Mahadevan soon attracted brilliant anatomists, neuropathologists and young researchers from India and abroad to this small but beautifully planned institution at the Sea Face Corner at Worli. The then Prime Minister Indira Gandhi gave a clarion call for the elimination of leprosy and India was the first country to institute multiple drug therapy at the national level. Immunologists of the world were fascinated by the disease which seemed to have an immunological basis for the pathogenesis. Human immunology was at its infancy and tools to investigate man were not many. To further add to the challenge was the inability to culture the causative organism by conventional means. Thus, all studies on the pathogen had to be done on those derived from skin biopsies of patients. It is no exaggeration to state that PR was at the centre of this search for new knowledge on leprosy, a search that gave answers to not only this disease, but acted as a model for human diseases caused by organisms that escaped human defence strategies by hiding inside the cells of the host.

With his team of the naï ve and wise, PR drew attention to biochemical defects in the host cells of leprosy patients, that may explain the lack of immunity in the worst affected patients. He showed that there were abnormal changes both in the cell membranes as well as inhibitory factors that were in the cell lysates of macrophages, the very cells that harbour the organism. The latter feature of inhibitory factors was independently found in our laboratory in Delhi. This was not easily accepted by the Western immunologists, who lay the blame for inhibition on a different cell, viz. the T-cell. With the subsequent discovery of cytokines and their network, it is easier now to reconcile the apparent discrepancy in these two interpretations. A major effort of the FMR was to find an easy way to test for the viability of the leprosy bacillus and be able to give an early diagnosis for drug resistance or efficacy of treatment. Both FMR and AIIMS developed *in vitro* methodologies using radiolabelled precursors for DNA and other metabolic pathways used by viable organisms. These assays took a few days compared to the then mouse model which required 6–12 months, air-conditioned facilities and fastidious animal houses which proved a burden for most developing countries. PR was instrumental in screening new drugs being developed in the UK laboratories. Another major contribution of his group is in the understanding of nerve damage caused by the leprosy bacillus, which is the only infectious agent that appears to reside in the Schwann cells. Organized nerve cultures were developed, wherein leprosy bacilli would be maintained.

His penchant for biochemical approaches drew him naturally to investigate the make-up of the leprosy bacillus. The cell wall was his main target. He always maintained that human tissue-derived bacilli were more appropriate than the armadillo-derived ones which were being studied by the Western laboratories, because of the ease in obtaining large amounts of bacilli. PR was able to hone in on a subunit of the cell wall which he felt would have potential as a vaccine. Unfortunately, due to his moving away from FMR, this work did not reach the expected impetus.

Once again, PR moved back to R&D in industry, this time to the Malladi Research Centre in Chennai. He had earlier advised them on technology to improve yields of ephedrine, and they had become the largest producers in the world. PR's dream was to produce natural product-based drugs. Once again, he began building new laboratories, energizing young people and influencing the industrialists to invest in R&D. Unfortunately, the Malladi R&D unit ran into financial problems when the founder died. Unbelievably, PR invested his personal meagre earnings during this period to tide over the temporary problem. Such conviction in other's R&D at one's personal cost is rare to see in today's world. Once the tide had turned, PR was ready to move again. His last move in the year 2001 was to start R&D in a little known new venture called Maanya Biotech in Hyderabad. It was here that he had the first mild heart attack. Though it was treated early, he does not appear to have recovered and complained of weakness and physical debility. During the searing summer of 2003, he was admitted twice more to the hospital and breathed his last on 27 April 2003.

PR would be remembered not just as an advisor to committees in Government agencies such as DST, CSIR, ICMR, private and public establishments/institutions around India, Indo-US programmes, International Societies in Microbiology and IAS, but as a caring teacher whose students are scattered far and wide, as a builder of institutions, as a unique thinker not influenced by current fashions in science and as an integrator of knowledge. His integrity, honesty and transparency will always be remembered. He did not belong to scientist clubs, did not believe in award systems or high offices, owed no loyalty to convenient ideologies, but gave opinions based on merit of the issues. He was modern in the practice of science, but had yesteryear values in the conduct of science.

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