SCIENCE & TECHNOLOGY

SPEAKING OF SCIENCE / *G.N.Ramachandran*

The prize that missed the master

WHEN A man comes out with one original idea he is called brilliant. When he comes out with two he is thought to be extraordinary but when he comes out with three independent and original ideas he is thought to be a genius. Einstein, Newton, Pauling and Crick are some examples, and I should like to believe that Gopalasamudram Narayana Iyer Ramachandran or GNR as he was affectionately and respectfully called by everybody, belonged to this class. He had at least three independent and original ideas to his credit, each ofwhich moved the field that he was engaged in. His first was the elucidation of the structure of collagen, the protein that goes to make tendons, connective tissues and skin. The triple helical structure that he proposed for collagen explains the function that this protein performs in the body. His second contribution was to show what shapes a protein chain can take on, and what shapes it simply cannot. His third major idea was to show how the three dimensional shape of an object can be reconstructed from a series of flat (or two- D) pictures using methods of convolution, an idea of value in imaging and tomography. On the 7th of April this year GNR passed away, having seen the proverbial one thousand moons at the age of 78 years and six months.

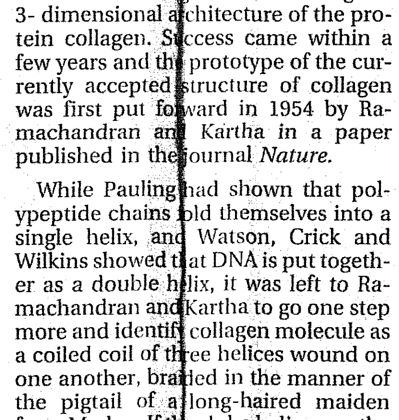
When GNR was born on the 8th of October 1922, it was in an era in India that was fermenting with ideas, vision and hope for the future. The Independence Movement had gathered momentum, education was valued very highly not only for enriching the mind and the soul but also towards enriching the nation itself. Knowledge for its own sake was at a premium. There were scholars not only in science and technology but also in literature, arts, politics, law, medicine and engineering. They all had just one common goal for which they worked, namely, an independent, strong and resurgent India. In many ways the family GNR came from represented the zeitgeist or the spirit of the times. His father, Gopalasamudram Narayana Iyer, was a professor of mathematics and later the Principal of the Maharaja's College in Ernakulum. Gopalasamudram itself is a small village on the outskirts of Tirunelveli in the very womb of Tamilnadu, a place that valued and promoted arts, crafts, language and literature. GNR had his early education there and then in Ernakulam. After his Intermediate degree certificate in the year 1939, he obtained his B.Sc. Honors in physics at the legendary St. Joseph's College, Trichy. He then went to the Indian Institute of Science at Bangalore, and joined the Electrochemical Technology course. Within a few months, however, he was attracted to and by Professor C. V. Raman who was at that time the Head of the Department of Physics. GNR went over and and did his M.Sc. by research and continued on with Raman. Much of his work at that time was in the area of optics, waves and scattering. He then taught for a while at Institute, and had as his colleagues a vibrant group including S. Ramaseshan, Gopinath Kartha, and R. S. Krishnan who was already a Reader at that time in Physics. In 1947 he won the "1851 Exhibition Scholarship", which took him to England where he spent the years 1947 - 49 working in the group of Sir Lawrence Bragg. After his Ph.D. from Cambridge, he returned to the Institute of Science, Bangalore where he taught during 1949 - 1952. It was during this time that the classic review on optics was written by him along with S. Ramaseshan.

The Madras helix

Prof. Ramachandran had by this time decided to work on the structure and shape of biological molecules. The late 1940s and early 1950s were a time of great excitement in biology particularly in the newly developed area called biophysics. The elucidation of the spatial disposition of atoms in molecules became possible, thanks to the method called X-ray diffraction. It was becoming increasingly exciting and challenging with the result that people like the Braggs, J. D. Bernal, W. T. Astbury and others mounted a programme to analyze the molecular structures and three dimensional architecture of molecules as large as proteins and nucleic acids. Across the continent it was Linus Pauling in California who was also very active in the X-ray structure determination of proteins. The idea was to shine X- rays on crystals or fibres of these long biological macromolecules, spot the reflections and diffraction spots on an X-ray film, and back- calculate the structure based on the geometry of the spots. The leading lights in this area were in England, and the man who started the very idea of molecular biology, namely Astbury, had shone X-rays on fibres on animal proteins such as keratin, myosin, epidermin and fibrinogen group of tissues. All these substances diffracted X-rays in a particular manner that he referred to as the alpha form. In contrast to this was the beta form characteristic of other proteins such as fibroins of silk. The first real success came to Pauling and his associates in 1951 when they showed that some of these proteins and polypeptide chains were wound up in a screw- like form that they called the alpha helix. This is a single stranded helical structure, which went to explain not only the structures of polypeptide chains but also of several proteins, including some of the keratins. This was truly a structural tour de force. Pauling's helix was rapidly confirmed by studies of X-ray diffraction by natural protein chains in hair and in synthetic protein chains. There are two aspects to the Pauling structure that are noteworthy. In the first place, the helix is "irrational"; it does not have an integral number of amino acids residues in each turn but 3.6 residues! In having done away with this integral number fixation, Pauling did away with the difficulties and was able to solve the problem in a neat manner. Secondly, it led X-ray crystallographers to study the nature of diffraction by a helical structure in mathematical terms. Such an analysis had an immense influence on further studies of biological structures. A feel for the excitement in the area of structural biology at that time can be had when we see that the double helical structure of the DNA was also unravelled by Watson, Crick and Wilkins in the year 1953, within a couple of years after the Pauling - Corey alpha helix of proteins.

During these eventful years Ramachandran moved from Bangalore to become Professor and Head of the Department of Physics of the University of Madras in 1952, until 1970. It is important to point out here is the offer of help and assistance that was provided to him in abundance by Professor A. Lakshmanaswamy Mudaliar who was the Vice- Chancellor of Madras University at that time. Dr. Mudaliar knew a gem when he saw one and he went all out in his efforts to help, equip the laboratory of Ramachandran, offer him staff positions so that he could recruit young faculty and students, and provide all administrative help and remove all hurdles. In addition Ramachandran also had this wonderful proximity to the Central Leather Research Institute with Dr. Nayudamma, another brilliant and enthusiastic researcher, there. When Ramachandran moved to Madras, a ready source of pure animal collagen was made available to him, thanks to Nayudamma. Set with this and armed with excellent colleagues such as Gopinath Kartha and G. K. Ambadi, Ramachandran set out to meet the challenge of determining the 3- dimensional architecture of the protein collagen. Success came within a few years and the prototype of the currently accepted structure of collagen was first put forward in 1954 by Ramachandran and Kartha in a paper published in the journal *Nature*.

While Pauling had shown that polypeptide chains fold themselves into a single helix, and Watson, Crick and Wilkins showed that DNA is put together as a double helix, it was left to Ramachandran and Kartha to go one step more and identify collagen molecule as a coiled coil of three helices wound on one another, braided in the manner of the pigtail of a long-haired maiden from Madras. If the alpha helix were the California helix and if the double helix were the British helix, the collagen helix came to be known as the Madras



helix. (In a thoughtful tribute to GNR, and as an example of CSIR-University kinship, the auditorium at CLRI has been named the Triple Helix Auditorium by Dr. G. Thyagarajan, the then Director of CLRI).

It was the idea of irrational or nonintegral number of amino acids per turn that led Pauling and Corey to solve the alpha helical structure of proteins, and it was the base - pair regularity that led Watson and Crick to solve the double helical structure of DNA. In structural terms, collagen was a tougher molecule to analyse, and required new insights and approaches. It was the insight that every third monomer in collagen is glycine that helped Ramachandran in his formulating the triple helical structure of collagen. Time has shown that the original prototype structure of the Madras triple helix needed very little modification even with the highest resolution diagrams available today.

The Ramachandran diagram

Many people would have felt a sense of fulfilment after such a major discovery but not Ramachandran. What factors go to govern the myriad shapes that protein and polypeptide chains adopt was a question that enticed him. He wanted to find out the general rules and principles behind the folding of peptide chains into various shapes.It was the grammar of what shapes a protein chain can take, and what it can not, than he set out to unravel! To this end, he asked his students, notably V. Sasisekharan and C. Ramakrishnan, to analyze all X-ray diffraction pictures published until then on amino acids, peptides and proteins and to analyse them mathematically, so as to find out what sets of bond angles and shapes that they most often take. Using what is referred to as a hard sphere model, Ramachandran, Ramakrishnan and Sasisekharan were soon able to write out the entire conformational space that a polypeptide chain can occupy. It was possible to do so in much the same manner that cartographers do when they write out maps, based essentially on two coordinates. These two coordinates in proteins are referred to as dihedral angles, named after the Greek letters phi and psi. This analysis has come to be known in protein science as the celebrated Ramachandran map or the Ramachandran diagram. It is indeed a tribute to Ramachandran and that each and every one of the protein structures that has been so far been solved (and there are at least ten thousand of them) strictly obeys the principles and the allowances of the Ramachandran map. Ramachandran was thus able to give a conformational grammar to protein structure. This was his second achievement. Sasisekharan extended the conformational map to DNA chains, and V. S. R. Rao did so for sugar chains. The folding rules of these three biopolymer chains had thus been established by the GNR school.

His mentor C. V. Raman immortalized himself in physics journals and textbooks through the Raman effect, and GNR has immortalized himself in biophysics and biochemistry textbooks with the Ramachandran diagram. Indeed when one looks at contemporary scientists of India, no one else has had such recognition in professional literature and textbooks as Raman and Ramachandran. Many people in the profession have felt that these two achievements, namely the elucidation of the structure of collagen and providing a grammatical basis for the three dimensional shapes that a biopolymer chains can adopt, would suffice for award of the Nobel Prize. They both have stood the test of time, have helped us advance our knowledge not only in structure but also in the function of protein chains, and have opened up newer ways of designing molecules. It is indeed a pity that Ramachandran was not awarded the Prize, and never will be, now that he is no more. Nobel Prizes in biology have been given for lesser achievements, and it will remain a sour point, at least in my mind, that Ramachandran was not. It may justifiably be said that in this case that it is the prize who missed the master.

3-D from 2-D through convolutions

The third original idea came to Professor Ramachandran in the late 1960s. This had to do with the following problem. When we take pictures from X-ray machines, radiographs or electron micrographs, they come out in two dimensions as sheets. We need however, to get the three- dimensional image since the object under study is three dimensional. How do we then get the total three- dimensional picture? Is it possible to reconstruct in three dimensions the radiographs or electron micrographs? Around that time it was possible to try and do so by using the method of Fourier transforms, but the thought occurred to Ramachandran that such three-dimensional reconstruction can be made easier by the application of the method called convolutions. This method, that he worked out with A. V. Lakshminarayanan while at the University of Chicago, led to two very interesting papers and laid the foundations of one aspect of what is today known as tomography - a method used in medicine as CT scan, PET scan and imaging. (I am told that GNR actually tried at that time to raise some grant money from agencies, in order to bulid a tomograph, with no success. What a contrast to today, when easy money of this order is given away to lesser mortals who put up mega-projects with catchy buzzwords!)

The 18- year period that Ramachandran spent at the University of Madras was a golden era. Together with Dr. Alladi, who was a Reader, he brought forth a department that produced gems as students, each of whom has gone on to excel in his own right, excellence breeding excellence. It is worth reflecting on what made this magic possible. First is surely the man behind it and the passion that he had for academic brilliance (despite a slowly debilitating illness that started affecting him already). Second is the ability to choose students and colleagues, and the freedom to recruit them. Third is understanding and appreciation by the administrators, and their willingness to enable this to happen. It was here that Vice Chancellors with vision such as A. L. Mudaliar and neighbours with ready help such as Nayudamma become vital. How I wish we find modes to make their tribe increase!

Mudaliar left the University and the anchor of support to GNR weakened. Rule books were thrown at him, and he left the University in a huff. It is here that we must rend our appreciation to two other men of vision and foresight namely Drs. Satish Dhawan and S. Ramaseshan, who invited GNR to return to Bangalore and start the Molecular Biophysics Unit (MBU) at the I.I.Sc. Sasisekharan, Ramakrishnan and VSR Rao went along with him to the MBU, added more people and helped the MBU become a globally respected centre in biophysics.

Despite his progressively weakening illness (later identified as Parkinson's), GNR continued to be active, this time in area of mathematical logic. Having handed MBU over to able hands, he switched to this field and published a series of papers on what he called as Syad and Nyaya logic, *reminiscent of* and akin to what today is called fuzzy logic. But, alas, his illness weakened him and he suffered for over a decade before he passed away.

Man of many talents

A brilliant mind has multiple interests and talents. This was true of GNR. He was a founder member of the Indian Academy of Yoga. He translated the *Bhagavad Gita* in free verse in English. He was a connoisseur of Carnatic music, and looked deep into the grammar of Ragas. His wife Mrs. Rajam was accomplished in music, as are his daughter Viji (Professor of Computer Science at Austin, Texas) and daughter- in- law Bharati. His sons Ramesh (Professor of Astrophysics at Harvard) and Hari (Institute of Plasma Physics, Ahmedabad) too are interested in music and literature. Besides these, GNR leaves behind his brothers G. N. Mani (also trained in physics and retired from an engineering firm) and G. N. Srinivasan (chemist, retired from cement industry) and their families. GNR's *wife, soul mate* and helpmeet, Mrs. Rajam passed away two years ago, a great blow that GNR did not recover well from. May they rest in Peace!

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