In memoriam – T. R. Govindachari (1915–2001)

There has been a worldwide resurgence in natural products for therapeutic purposes. India provides plentiful opportunities in this area with its abundant flora growing in vastly different climates and indigenous systems of medicine like Ayurveda developed during several centuries and making extensive use of medicinal plants. One of the important prerequisites for realizing the full potential of our floral wealth is a thorough investigation of constituents of these plants by using modern scientific methods. T. R. Govindachari (TRG), who passed away on 28 December 2001, was one of the pioneers who devoted his entire career to the chemical investigation of Indian medicinal plants as a single-minded pursuit, undeterred by changing fashions in his chosen profession. I have been associated with him ever since I joined his first batch of Ph D students in Presidency College, Chennai in 1950. I have written about him on a few occasions, the latest one being in the form of a tribute in *ARKOVIC* (ed. Subba Rao, G. S. R., vol. 2001, part viii) brought out to honour him on completing 85 years of age. This extensive article details TRG's career and scientific contributions with copious references and structural formulae. With considerable nostalgia and a heavy heart, I wish to offer some further insights into his personality and achievements.

Born in Chennai on 30 July 1915 to Raghavachari and Rajalakshmi, TRG had his collegiate education in Loyola and then in Presidency College, wherefrom he obtained his Ph D degree under the guidance of B. B. Dey in the area of isoquinolines which form the core of a large number of naturally-occurring alkaloids. In 1946, he went as a Government of Madras scholar to work for 3 years as a postdoctoral fellow with Roger Adams at the University of Illinois, Urbana. The renowned Professor who was at the peak of his career was investigating the structures of the Senecio alkaloids. TRG was assigned the daunting task and was able to solve the problem in a short time through his meticulous and insightful investigations, which I believe involved elaborate column chromatography, manual collection of enormous number of fractions and careful examination of every fraction. Adams was mighty pleased with 'Govinda' and perhaps this endearing association confirmed TRG's resolution to devote his career to natural products.

The thread was pursued after his return to Chennai in 1949 and appointment as Additional Professor of Chemistry in his alma mater in January 1950. He became Chief Professor in 1952 and Principal in 1961. I joined

him in July 1950 to work for a Ph D degree along with N. S. Narasimhan (retired Professor of Chemistry, Poona University), N. Arumugam (retired Professor of Chemistry, Madurai Kamaraj University), B. S. Thyagarajan (retired Professor of Chemistry, Texas University, San Antonio) and M. V. Lakshmikantham (University of Alabama). In the next few years, newer students enrolled under him, some of them being K. W. Gopinath, S. Rajappa, N. Viswanathan and P. C. Parthasarathy. With the able administrative support of the late B. R. Pai, TRG was soon able to build a very active research group and carry out path-breaking work in natural products chemistry, particularly on a large number of Indian medicinal plants. Quite a few of these such as *Tylophora asthmatica*, *Wedelia calendulaceae*, *Carica papaya*, *Enicostemma littorale* and *Alstonia scholaris* yielded very interesting structural prototypes, e.g. tylophorine, wedelolactone, tiliacorine, echitamine, kopsine. I must mention here that compared to other Indian university laboratories, TRG's were more spacious. In terms of funding, in addition to the allocation for the chemistry department, he was able to get more from the less active (read inactive) departments and was in a position to have a good stock of research chemicals and glass equipment (a set of *Quickfit* became a prized and envied possession). Nevertheless, instrumentation was primitive and most of the structural elucidations were done by hard work through classical degradations such as the one named after Hofmann. Such work may not be appreciated much by students of organic chemistry of this era, when Fourier Transform ^{1}H and ^{13}C NMR, HRMS and single crystal X-ray structure determination can accomplish in a few hours or days, what it took years in those times. But it must be said in justification of the earlier practice (mandated more by necessity than by choice) that it imparted very good training to the aspiring students in theoretical concepts, logical analysis and experimental skills in manipulating small quantities. I must also add here that while TRG valued tradition, he was quick to adopt emerging techniques to aid structural investigations of natural and synthetic products. A perusal of his later papers will demonstrate how extensively he has used ^{1}H and ^{13}C NMR as well as optical rotatory dispersion, circular dichroism and exciton chirality. He also collaborated with X-ray crystallographers like S. Ramaseshan, (late) Gopinath Kartha and a few others. The appointment of S. Swaminathan to a chair in the University Chemistry Department ushered in an era of intense interactions between the two groups and created a stimulating scientific scenario in Chennai.

In the course of his 12-year stay at Presidency College as Professor, TRG had about 100 publications in national and international peer-reviewed journals and established a sound reputation for himself and the department which had been known in research circles from the days of the terpene chemist, Simonsen. The international scientific community took note of TRG's performance by

inviting him to give a plenary lecture in the first ever meeting of the Natural Products section of IUPAC. This also brought him to the attention of A. Wettstein, International Director of Research of the Swiss Pharmaceutical Company, CIBA. CIBA was planning to start a basic research centre in Mumbai and was looking for an eminent scientist in the right age group to head it. CIBA accepted Wettstein's recommendation that TRG would be the right choice. TRG had by that time become the Principal of Presidency College. While he was administering it very ably, he was beginning to feel heavily circumscribed in his scientific activities and hence chose to accept the new assignment which offered plenty of challenges in the area of new drug development. This was a major objective of the proposed centre, wherein natural products could play a significant role. I may record here that this move from academia to industry, an unknown phenomenon in India at that time although not uncommon in the West, caused much consternation in the Indian scientific circles, particularly to T. R. Seshadri, the doyen of natural products chemistry at that time. Subsequent events, however, proved that this move only strengthened TRG's involvement with the field rather than attenuated it.

CIBA Research Centre which had TRG as the first Director started functioning from January 1963, but was formally inaugurated by Jawaharlal Nehru in March that year. Set in a sylvan campus of 80 acres of undulating land, in Goregaon East of suburban Mumbai, the centre was the realization of the dream of Kapelli, CIBA's chairman at that time. Modern laboratories, remarkable instrumentation facilities, availability of abundant funds, picturesque surroundings and a pleasing ambience added to the unobtrusive but inspiring leadership of TRG attracted the best young scientists of the country to the centre, which over the next several years came to be known internationally for its basic work. While guiding all these activities, TRG pursued his interest in Indian medicinal plants along with B. S. Joshi, N. Viswanathan and P. C. Parthasarathy, with occasional participation from me, while my major concern was synthetic medicinal chemistry in which I had the association of S. Rajappa and a few other scientists. There was one more former student and colleague of TRG from Presidency days, S. Selvavinayakam, who played a pivotal role in organizing and maintaining the analytical, spectroscopic and biological instrumentation of the centre in working condition all the time and earned a just reputation in the years to come. TRG's students were recruited by Wettstein in an open competition and owed their positions to intrinsic merit and not to any favouritism. The analytical-instrumentation facilities of CIBA were generously extended by TRG to very many research institutions in the country and probably hundreds of students would have acknowledged in their theses, the support provided to them.

By the time TRG retired in 1975, the natural products group had more than 200 publications; TRG himself had participated in about 100. The synthetic chemistry and biology group had also a very creditable publication record. But more relevant to the prime objective of the centre was the fact that it had examined more than 10,000 new synthetic molecules, plant extracts and isolated pure compounds. Among a large number of active new chemical entities discovered and developed at the centre, twenty reached the clinic and were taken through its various phases. Of these, five succeeded finally in receiving marketing approval from the Drug Controller of India. I have written about this on other occasions, but I wish to emphasize it again, since there have been repeated (hopefully not deliberate) attempts to belittle the role that CIBA Research Centre had played in new drug development. Unfortunately, CDRI which had also performed equally creditably in this area, also suffered alongside. TRG was greatly pained by these wanton and unjustified insinuations and on one occasion, we wrote an article in *The Hindu*, setting the record straight. Even today it surprises me to no end when one or another Indian pharma company claims that it is taking a compound for the *first* time to phase I clinical trials. One's achievement does not become more valuable by downgrading or ignoring an earlier accomplishment.

Coming back to TRG's work on natural products in CIBA, he continued and bettered his earlier record in examining a very large number of plants and isolating a wide variety of compounds with unusual structures. Ishwarone, a heptacyclic sesquiterpeneketone and ancistrocladine, a polyketide naphthylisoquinoline are just two examples of this output. In-house availability of biological screening facilities added much significance to these efforts.

During the post-retirement, third phase of his career, TRG organized a research centre for Amrutanjan, a Chennai-based pharmaceutical company (1977–1981) and later, an agrochemical research laboratory for the SPIC Science Foundation. Both the laboratories were well-equipped and attracted good chemists with whom TRG pursued his interest in natural products chemistry, but with the emphasis now shifted to plants with biocidal activity. His work on *Azadirachta indica* (neem) leading to the preparation of beautiful crystals of azadirachtin A and the isolation of several new congeners, illustrates vividly his endless energy and infectious enthusiasm. He remained active till late 2000, beyond the age of 85, until he became bed-ridden. By that time he had increased his publication record to over 330.

In earlier articles I have recorded the awards, honours and fellowships he had received in recognition of his contributions to natural products chemistry. I would only like to mention that he was one among the first batch of recipients of CSIR's Bhatnagar Prize. He was awarded the prize for Chemistry in 1963, when he was 48. The citation was for his work till 1960, when he was 45. His performance through the years had been outstanding and had to be recognized.

From the beginning of his career, TRG was as fascinated with the medicinal properties of the plants he was working with as he was with their chemistry. A few examples are therefore worth citing. *Tylophora asthmatica*, as the name implies, is reported to have antiasthmatic activity which was demonstrated in clinical trials by Shivpuri. Tylophorine, one of the alkaloids studied by TRG's group, was shown to have this property, but was a vesicant. This lead awaits further investigation. Incidentally, the phenanthraindozidine ring system of tylophorine was established by classical degradation. Around the same time, a similar alkaloid, cryptopleurine isolated in Austra-

lia, was shown to be a phenathraqunolizidine by X-ray studies.

Wedelia calendulaceae (manjal karisilanganni in Tamil) is a plant traditionally used in Tamil Nadu for the treatment of jaundice and had been endorsed also by reputed allopathic doctors. Attracted by this usage, TRG did a systematic investigation of the plant which resulted in the isolation of wedelolactone having a novel furocoumarin structure with a pterocarpan template. This was sent to Abbott Laboratories, USA to test for antihepatitic activity. Unfortunately the screening was carried out in the carbon tetrachloride model of acute liver injury and the compound was declared inactive. Decades later, the well-known German phytochemist, H. Wagner found it to be one of the most active liver peroxidase inhibitors, a clear indication of its hepatoprotective properties, which he also confirmed in an *in vivo* model. Another related plant, *Eclipta alba* also contains wedelolactone which can be surely developed *per se* as a drug or used as a lead for further synthetic exercises towards optimization. While speaking about wedelolactone, I cannot help talking about a related furocoumarin, coumestrol, which had been isolated from alfaalfa a year earlier by scientists of US Department of Agriculture. The structure elucidation was achieved in consultation with us, applying the methods we had adopted for wedelolactone which was published. However since their paper on the isolation of coumestrol had appeared earlier, the furocoumarin ring system to which many additions were made in subsequent years from plant sources, came to be known as coumestane, much to our annoyance. To add insult to injury, the Merck Index chose to list coumestrol as an entry, while wedelolactone was to be perceived as one of several coumestanes! Instances like these are not uncommon; and cries of frustration, despair and anger are bound to be heard again and again. Is chemistry like terrorism, colour-sensitive?

Enormous efforts were deployed at the CIBA Research Centre for systematic biological investigation of Indian medicinal plants. Many claims of activity could not be verified, including the well-known one for the antidiabetic property of bitter-gourd juice. *Mucuna pruriens*, with antiparkinson activity, was an exception. The plant is known to be a good source for L-DOPA, a widely used drug for treating the disease. In limited clinical trials, it was established that the observed activity was greater than what was expected from its L-DOPA content. During a search for potential agonists some alkaloids were isolated, but this lead has not been pursued. A reputed Indian company is now marketing the plant powder as a drug.

In yet another case, that of *Alstonia vanenata*, an initial extract showed hypotensive activity. Excitement mounted when further fractionation led to enhancement (contrary to common experience). Ultimately a crystalline alkaloid having potent activity was isolated, but elation turned to depression when it was found to be reserpine! But there was immense jubilation when extraction of the heartwood of *Nothapodytes nimmoniana* (*Mappea foetida*), a common tree growing in some parts of India, gave a bountiful yield of camptothecin which was then a hot lead for anticancer activity. The world's supply of the alkaloid was a few milligrams at that time and clinical trials had to await the maturing of a plantation, while CIBA had close to 500 g in a plastic bottle left casually on a workbench! This rich source of camptothecin was simultaneously and independently discovered by CDRI. While the alkaloid itself did not become a drug, semisynthetic ones became useful and hence the discovery came to be subsequently exploited on a commercial scale.

TRG was a builder of institutions and not empires. The various centres which he had established and nurtured stand testimony to his involvement in Indian scientific efforts. Yet another institution which he helped to start and foster is the National Organic Symposium Trust (NOST), which he founded along with four other senior eminent organic chemists, Nityanand, Sukh Dev, S. C. Bhattacharyya and S. Swaminathan. The mission of NOST has been to conduct periodic symposia, bringing together for a few days on the pattern of the Gordon Conference, serious researchers at all levels. The nineth such conference was organized in mid-December 2001. TRG had attended all the eight earlier events, seating himself in the first row and listening intently to all the presentations. He would also participate with great zest in the accompanying excursions, unmindful of heat or height. He would be greatly missed in future events. In developing institutions, TRG had the uncanny knack of spotting talent and stimulating and sustaining it with his readiness to delegate responsibilities. Of course he was human and did err in his judgement on a few occasions when his associates let him down in matters of science. This caused him much anguish, but his generosity and kindness overcame his just anger and his innate native gentleness drove away any desire for vindictiveness.

TRG was spartan in his habits and frugal in his speech and writings. He avoided superlatives and embellishments, although as an avid lover of literature, he would enjoy the Bard's description of the moustache as 'the knightly growth that fringed his lips'. His paper with N. S. Narasimhan and S. Rajadurai on the Synthesis of Ethyl Carpyrinate (*J. Chem. Soc*., 1957, 560) would beat the Britishers in understatement. He was modest about his achievements, saying with characteristic humility, 'we have done whatever we could, to the best of our ability under the given circumstances'. The first person plural rather than the singular signified his acknowledgement of the contributions of the group. In spite of his apparent mildness, TRG had strong views which would occasionally come out in mild satire. Two examples would be illustrative. He would characterize a colleague who would not commit himself on any issue as one saying the time is eightish rather than eight twenty. Commenting on the culture in some industrial circles particularly of the West, TRG would advise me 'Nagarajan, the way you hold your glass in the hand is as important or perhaps more so than what you hold in your head'.

TRG was a great lover of literature and the fine arts. He was also religious, but not in a conventional, parochial way, his faith being informed by the poetry of the saints, the sculptures of the Sthapathis and the great temples, mighty edifices of Indian culture. In all his scientific and extracurricular activities, he was supported and encouraged by his wife, Rajamani (who predeceased him) and later, by his offsprings, T. G. Rajagopalan, T. G. Sundararajan and Anuradha Jagannathan. The affectionate care they and their families bestowed on

TRG during his recent illness was exemplary and heart-warming.

I visited the family a few days ago to express my condolences. Rajagopalan was kind enough to show me one of TRG's bequests, his orchid collections, Dendrobiums, Vandas and a few other species. Some were on the ground, while about a thousand were in the climate-controlled terrace. He told me that he would try to preserve this inheritance for which he had trained himself. Natural products chemistry is another bequest of TRG which needs to be preserved and pursued. N. S. Narasimhan at Poona University practised it very ably for several years. I have retained a significant interest in the area, but circumstances took me into synthetic medicinal chemistry. Now the country looks to young, gifted organic chemists to carry on the work of TRG.

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Satish Dhawan

Satish Dhawan, former Director of the Indian Institute of Science (IISc) and Chairman of the Space Commission, and President of the Indian Academy of Sciences during 1977–1979, passed away on the night of 3 January. Although he had been growing physically infirm during the previous half-year, he had remained his usual cheerful self till the very end, and died peacefully within twenty minutes of complaining about difficulty in breathing. With his death the country lost one of its most distinguished sons, and the scientific community a truly unimpeachable representative. He had at various times in his career been teacher, research scientist, engineer, technologist, manager, leader and adviser – sometimes many of these at the same time. And to everything he did he brought dedication, breadth of vision, meticulousness and humanity, which, combined with his remarkable scientific and technological abilities, transformed every organization he worked for or led, and made it achieve what it had often not thought itself capable of.

Satish Dhawan was born on 25 September 1920 in Srinagar, and was educated in this country and the United States. He graduated from the University of Punjab (Lahore) with an unusual combination of degrees: a BA in Mathematics and Physics, an MA in English Literature, and a BE in Mechanical Engineering. In 1947 he obtained an MS in Aeronautical Engineering from the University of Minnesota, and moved to the California Institute of Technology (Caltech), where he was awarded the Aeronautical Engineer's Degree in 1949 and a PhD in Aeronautics and Mathematics in 1951 with the eminent aerospace scientist and fluid dynamicist Hans W. Liepmann (Honorary Fellow of the Indian Academy of Sciences) as adviser. This educational breadth, covering science, engineering and the humanities, and his distinguished family background, appear to have given Dhawan an ability to view the world from many different angles, and may explain in part his unique qualities as a leader.

Dhawan had spent a year on the shop floors of Hindustan Aircraft (now Hindustan Aeronautics, HAL) before leaving for the US on a government scholarship. As a student at Caltech he made an extraordinary impression, and left a glow of fond memories behind him when he left to return home in 1951 – for here was an Indian who was not only ingenious at hooking up new and intriguing experiments but could also play with hypergeometric functions, quote Shakespeare for every occasion, and regale his friends with stories about the camel answering to the name of Greta Garbo in the Khyber Pass (Dhawan grew up as a young man in what is now Pakistan). The charm of his personality overwhelmed everybody that came to know him, especially as it was accompanied by a very Indian sense of grace and modesty.

At the time that Dhawan began his career in aerodynamic research, supersonic flows and shock waves were still rather exotic phenomena; his earliest papers dealt with these subjects, and one of them, which had detailed observations of how a shock wave bounces off a solid surface (such as that of a wing, for example) became widely known for its revealing and defining observations. For his PhD thesis he

Dhawan laughing away with young scientists at the First Asian Congress of Fluid Mechanics, Bangalore, 1980.