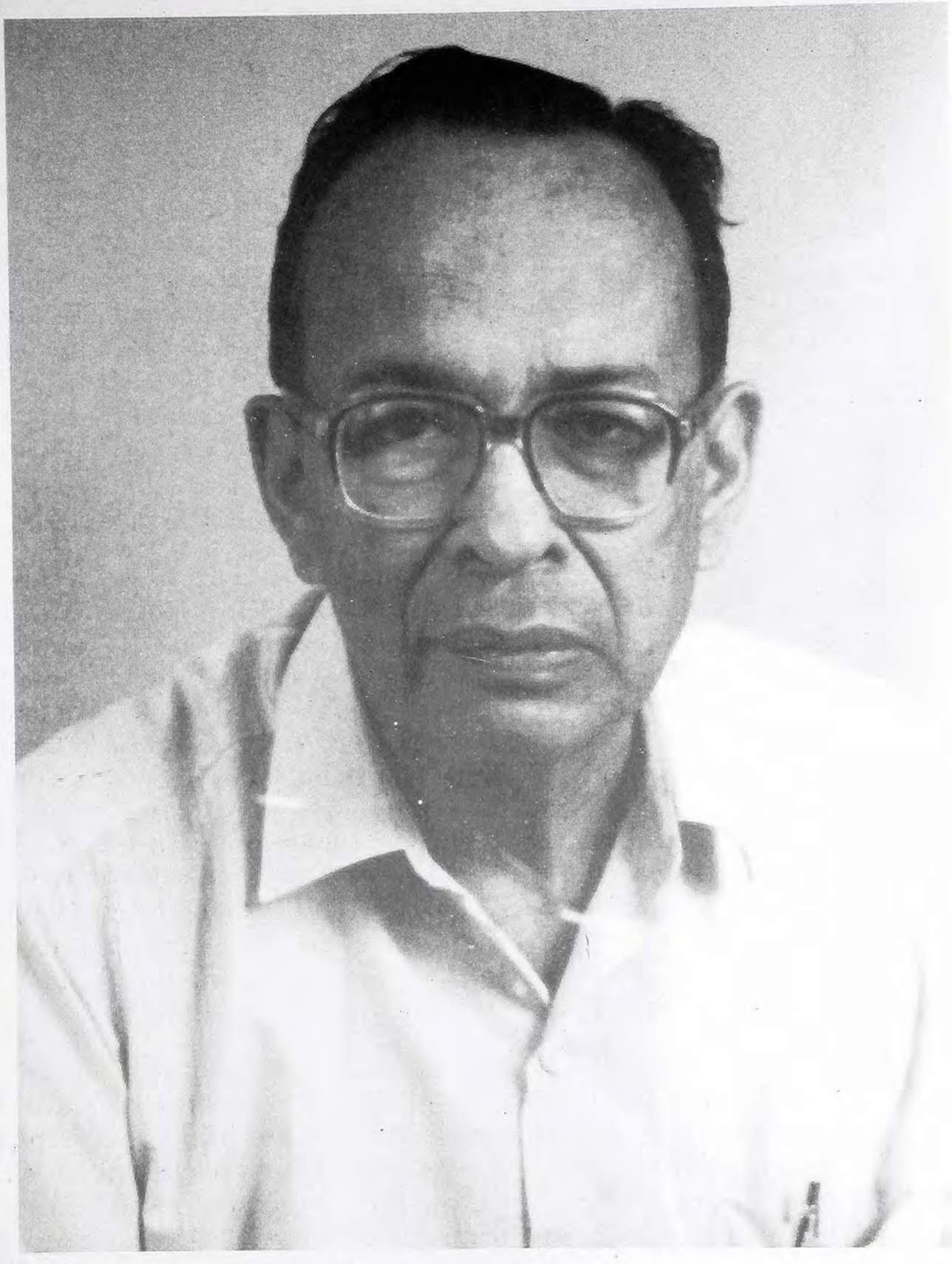

MANOJIT MOHAN DHAR

(1927-2003)

Elected Fellow 1973

The scientific community of Lucknow woke up to a rude shock and disbelief on the morning of May 26, 2003 to learn that they have lost one of the respected scientists Dr MM Dhar. He spent most of his active research career as a scientist at Central Drug Research Institute, Lucknow. He was responsible for formulating bioactivity-guided research on natural products at CDRI. To many of his students, friends and associates his death is a highly personal loss of a wise, loving and kind fatherly figure.

FAMILY BACKGROUND, EARLY EDUCATION AND PERSONAL LIFE

Dr Manojit Mohan Dhar (MMD) was born in Calcutta on January13, 1927, the older of two sons of illustrious parents. His father, Satyendra Mohan Dhar (SMD) was a Lecturer in Mathematics at the University College, London (1917-19) before entering the Indian Civil Service. During an assignment as Development Commissioner, he produced 110 detailed plans for the post-war development of Bihar. These included the Sindri Fertiliser project and the Damodar Valley Scheme. After an early retirement, he became Tata's Agent (Chief Administrator) in Jamshedpur (1948-59). During this period, TELCO came into existence and TISCO doubled its steel production. MMD's mother, Ava was from a family of exceptional cultural talent and involvement in social activities. She herself was a very good pianist and her activities with the blind and the deaf and dumb earned her a ***Kaiser-e-Hind***. She relentlessly collected clothing and foodstuff for the Armed Forces that got her an OBE. The last seven years of her life were spent in building up and administering Raphael, the Cheshire establishment in Dehra Dun, which has a large leper colony and provides shelter for the incurably ill.

Dr. Dhar had an excellent childhood was evident from the way he fondly talked about it. Some recollections of his childhood that he always talked about include. When four years old, his father was DM of Palamau Distict and was provided with an elephant and horses for tours to parts of the District inaccessible by vehicle. The house in Daltonganj therefore housed an elephant, horses, tiger cubs, goat and a dog. The time spent with Ram Piyari, the elephant and Jimmy, the dog developed in him a love for animals. It was also found that he was not interested in toys, but a gramphone kept him happy. It was at early age that he started listening to and enjoying simple pieces of western classical music.

For his seventh birthday he asked for a bicycle. His father, SDM decided he would have to pass a math's test. This was duly conducted and consisted of multiplication

and divisions involving five or seven digits. SMD was pleased with the performance and a bicycle arrived, but more significantly it became apparent that mathematics was not going to pose any difficulties in the future. MMD had his first schooling from his mother. This was up to the age of seven, when his brother was born. For the next two years, he had private tutors before he was sent to the Doon school at the age of 9 (1936). He stayed in the school until 1944 (school certificate-1942, ISc-1944). As a young boy, he found studies enjoyable. The decision to move into science came during the last few years at school.

He took up photography as a spare time activity, in his first year of school so that by the age of ten, he was developing and printing photographs. He constructed an enlarger at the age of thirteen. This enabled him to produce his first lot of quality photographs. He also started having piano lessons in his first year at school. These he gave up after three years but continued to play the piano and composed music on his own. Familiarity with Rabindra Sangeet led him into Indian music. He learnt to perform well on the flute and mouth organ. During his last years at school his compositions for Indian orchestra won prizes in state competitions and he played other compositions on the piano during the school assembly. Music had remained a constant companion with him and he got a great deal of pleasure comparing performances by different artists on a particular piece of music

Sports were of considerable interest to him at school but he never represented the school in any game. The next two years at the Science College, Patna University for a BSc (Honors) degree provided little academic stimulus and if it were not for parental pressure, MMD would have happily joined a tea garden. The period at Patna provided an opportunity to play plenty of cricket and billiards. These two sports were of considerable value in getting him known to his colleagues while he was at Manchester some five years later.

MMD was sent to Fitzwilliam College, Cambridge in 1946. The University lectures were his first taste of enjoyable academic work irrespective of which subject he studied. Supervisions during the first year by Dr Peter Maitland provided a solid foundation to those by Dr AW Johnson who often provided raw data from his own research on Aphid pigments and MMD was asked to work things out. These were truly incisive lessons in structure elucidation.

Failure to get a first division in the Natural Science Tripos- II precluded the possibility of scholarship support for PhD programme at Cambridge. Fortunately, two terms of biochemistry at Cambridge was followed by the award of a British Empire Cancer Campaign Research Assistantship for research under Dr GR Barker at Manchester University. Dr Barker was a very kind and considerate supervisor and his problem of working on pyrimidines with anticancer activity gave him a chance to be involved in animal tests with Dr LD Parsons at the Chester Beatty Cancer Institute. The chemistry involved was the synthesis of pyrimidines and their glycosides.

Subsequently, experience was gained in using tracer technique. 4-Aminouracil was synthesised with ^{15}N and its fate studied in rats. The mechanism of action of the active pyrimidines was also studied enthese involved inhibition of enzymes such as ribonuclease and examination of the possible conversion of these pyrimidines to folic acid derivatives. In addition, the Barker group met once a week over coffee reviewed literature and argued freely on chemical problems. This was also the time when Professor ERH Jones was in full flow in Manchester enclose contact through frequent seminars provided considerable information and knowledge of triterpene and steroid chemistry. This was to be of great help in later studies on Natural Products at the CDRI.

During his stay at Manchester he met Alberta Kathleen Robinson (Berty) with whom he got married in December 1950. Dr Dhar's married life can be aptly described in his words". The association with Berty has proved to be exceptional and nobody could have looked after him and supported him as well as she has done and nobody could have been a better mother to their four lovely daughters". MMD was awarded a PhD in December 1952 and in January 1953, he returned to India with his small family. An unacceptable offer from the Tata Cancer Research Institute and failure to be appointed as Lecturer at the Indian Institute of Sciences, Bangalore, brought him on a visit to the CDRI to meet Dr Nitya Nand whom he had got to know in Cambridge. From the very start he knew CDRI is where he wanted to work.

PROFESSIONAL CAREER

MMD joined the CDRI on May 4, 1953 and started working on plant constituents. The first of these was *Rivea cuneata*, a plant with antidiabetic activity on which Dr Rajaram Rao was working in the Pharmacology Division. It soon became evident that emphasis had to be directed towards isolation of the active constituents and not other crystallizable entities. Twelve years later activity-directed studies on plants became the norm of the CDRI programme on screening of biologically active Indian plants. This had been made possible through a collaborative programme with NIH. Plants were to be collected, identified and a 50% EtOH extract sent for anticancer screening. The setting up of a large battery of tests for a wide range of biological activities made the general screening of the plant extracts, the basic function of the project for investigating Indian plants for biological activity.

In spite of the realization that only active plant constituents should be studied, efforts during those first years followed the usual pattern of examination of any product isolated. Even so, metabolism studies on reserpine were undertaken with Dr JD Kohli and SK Srivastava, metabolites identified and data generated for tissue distribution and excretion. Also of considerable significance was the establishment of a reliable procedure for isolating Digitalis glycosides with Dr NM Khanna. This process was the CDRI's first patent and first process to be handed over to industry.

MMD always had an interest in instruments - starting with manual UV and IR spectrophotometers, which he personally installed and looked after until an Instruments Section was set up in CDRI. It was the availability of these, with NMR and Mass spectrometers, GLC, HPLC and Electron Microscope at CDRI that led DST to have one of its RSIC at CDRI. MMD supervised its functioning since its inception until 1979.

An award of a Rockefeller Foundation Fellowship enabled MMD to spend one year (1960-61) at Harvard University with Professor EJ Corey. This visit had a profound effect on MMD's future activities. The programme on plants became totally activity oriented. He took over administration of botany and regulated the plant collection. Nucleotides and peptides had been his major activities in Harvard. On his return, he started work on synthesis of peptide sequences with enzymatic activity, and chemical synthesis of nucleotide bond that would enable synthesis of a complementary strand after aligning triplets. The peptide studies led to the synthesis of a nonapeptide with glycosidase activity and of other peptides of biological interest. The nucleotide work came to a halt as no method was evolved to form the internucleotide bond under mild conditions. Nevertheless, a useful synthesis of the internucleotide bond was developed involving anhydronucleosides. In 1958-59, MMD had started collaboration with Dr OP Babbar of the Virology Department. They found that adenosince-5-phosphate reduced the activity of Ranikhet disease virus. On his return from USA, collaborative activity was continued with vigour. Purification of infective nucleic acids from Ranikhet and Vacccinia viruses was isolated and considerable work undertaken on purification of interferons. This led to the examination of possibilities of the clinical uses of interferons.

During 1967-70, MMD had additional charge of the Antibiotics Division. At that time, he was already supervising groups working on plant constituent with Drs DS Bhakuni and JS Tandon, on peptides with, Dr KL Nagpal and the Botany division with Drs. B Gupta and BN Mehrotra. His association with the Antibiotics Division resulted in studies on the generation of echinomycin analogs synthesised *in vivo* with analogues of the heterocyclic moiety. This in turn led to the proposal that antibiotics are secondary metabolites formed due to detoxification of a toxic fragment.

It was at this time that MMD was helping a friend breed a lemongrass plant that could produce an essential oil distillate of CP Citral. Though successful in achieving this objective, the plant was a fragile one and sadly, all were lost in the floods that year. During 1979-84, MMD was Science Counselor in the High Commission of India in London. During this period, he had opportunities of visiting multinationals such as ICI, Pfizer, and Wellcome Laboratories and of getting to know what was required for producing a new drug. These ideas were to form the basis of the changes he brought about in the CDRI when appointed the Director.

In brief at the CDRI, he decided on the need for departments with specific responsibilities aimed at new drug development that these were Clinical and

Experimental Medicine, Toxicology and Pharmacokinetics. In addition, all products taken up for development had to be made in the Process Development Division by standardized procedures that could be scaled up by industry later. A major responsibility of the Pharmaceutics Division was to be quality control – it was up to them to guarantee the quality of all material going in for toxicology and clinical trials. Four separate departments were also set up around outstanding scientists to promote quality research. Emphasis was placed on accountability and time targeting of all projects became a must. After handing over charge as the Director on May 31, 1988, he planned to work on bioactive peptides of marine origin. Difficulty in obtaining such materials led to his returning to peptides and in particular Enkephalin analogues as immunomodulators.

SCIENTIFIC CONTRIBUTIONS

Research Activities of Babul at CDRI (1953-79): The studies carried out may be broadly classified as natural products chemistry and biochemistry and have involved alkaloids, terpenoids, steroids, quinones, antibiotics, steroidal and other peptides, synthetic enzymes, interferon inducers (ds RNA) and nucleotide synthesis.

The more important contributions include the structure elucidation of the hypotensive proapomorphine alkaloids of *Croton sparsiflorus*, the anti-cancer bisbenzylisoquinoline bases of *Coculus pendulus*, the anticancer naphthaquinones of *Arnebia nobilis*, terpenoids from *Randia dumetorium*. *Sagitaria sagittifolia* and *Hedychium specatum*, anticancer glycoside from *Ipomea peari*, isolation for the first time of the infective nucleic acids of Ranikhet desease virus and Vaccinia virus, preservation of RDV-RNA with lipids and demonstration of the single-stranded character of Vaccinia virus DNA, development of new method for synthesizing the inter-nucleotide bonds employing purine and pyrimidine cyclonucleosides, conception of the existence and significance of steroidal polypeptides and their synthesis, synthesis of peptides with predicted glycosidase and other biological activities, microbiological and cell-free synthesis of antibiotics and analogues, a hypothesis on the manner and reason for the formation of antibiotics and a mechanism for the distinction of foreign proteins for the latter has now been obtained as also for the identification of interferons as repressor proteins.

Apart from the possibility of producing drugs, the studies on constituents of Indian plants are of particular value in giving indications of new types of structures having biological activities. This information can then form the basis for synthetic programmes aimed at obtaining drugs. For instance the structure of the *Arnebia nobilis* naphthaquinone, Arnebin, had been the basis for a programme for synthesizing anticancer agents. For his work on *Arnebin*, Babul was awarded the country's highest scientific award ***"Sir Shanti Swarup Bhatnagar Award"*** and in 1973 AV Mody Research Foundation Award for Pharmaceutics. The same year, he was also elected a Fellow of

the Indian National Science Academy. The work on *Arnebia nobilis* initiated by Babul was being pursued at CDRI until the year 2000. This work has brought collaboration with US based academia/industry. His second seminal contribution to natural product chemistry is isolation, chemistry and pharmacology of Coleonol. Although the structure of Coleonol was subsequently corrected (Coleonol/Forskolin) by other research group, his contribution to the realm of bioactive natural products has been significant. Since that time there have been more than one thousand research papers on various aspects of Coleonol/Forskolin. The utility of Coleonol/Forskolin as a research tool is because its ability to specifically activate adenyl cyclase in intact cells and tissues. Regardless of its clinical use Coleonol/Forskolin has taken the center stage of new wave of research activity on adenyl cyclase. A mini-symposium on Coleonol/Forskolin at the International Cyclic Nucleotide meeting and a session at the Gordon conference on cyclic nucleotide were held.

Perhaps the most significant contribution is the synthesis of peptide sequences with conformational control and predictable enzymatic or biological activities. Of a more applied nature is his involvement in the development of fermentation cum chemical process for the production of L-ephedrine and a synthetic procedure for the preparation of ampicillin, which have been handed over to industry. Consultant in establishing a functioning pilot scale fermentation unit in the laboratory of a pharmaceutical concern for the production of new antibiotics. His scientific contributions have resulted more than 200 research papers in peer reviewed journals and several patents for technology/drug development. He has supervised the work of 22 colleagues for PhD degrees, eleven in the area of phytochemistry, seven in peptides and four in nucleotides and medicinal chemistry.

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