

Recollections

How I Became a Biochemist

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I was born in India during one of the most turbulent times in the subcontinent's history. My childhood memories include vivid images of the Second World War (1939–45), Mahatma

Gandhi's non-violent movement to free India from British rule, and the horrific aftermath of the partition of Pakistan from India in 1947. The entire region was engulfed in communal violence: almost a million dead and some 10 million in flight, one of the largest mass migrations in human history. Born into a family of well-known lawyers and writers, I was privileged to attend a private Catholic school for my kindergarten and primary school years, where major emphasis was on strict discipline and the 3Rs. When the place where I was born became East Pakistan (today's Bangladesh), my family migrated to India as refugees, leaving behind everything that we possessed.

My family was determined to rebuild all that we had lost, but it was a struggle in the beginning. I received special attention from the family because I was so little and my mother had died when I was only one year old. Mathematics, English and Music became my favorite subjects as I grew up. As a child, I enjoyed doing complicated arithmetic 'in my head'. My love for English literature stems from my father's influence. He helped me read several Shakespearean tragedies and selected poems of Wordsworth and Coleridge before the age of 12. I was fond of songs and poems written by the Nobel Prize winning Indian poet, Rabindranath Tagore. I did not think much about science in those days!

Despite lacking resources after migrating to India, my father and two brothers always thought that I should be given the best possible education. With the money they could provide, plus an Indian Government Scholarship, I was admitted to one of the most exclusive residential universities in India at that time, Banares University, in the ancient holy city of Varanasi. After much debate, I chose an undergraduate program in pharmaceutical chemistry, with the idea that I would get a job in an applied field. My love for mathematics was still strong but there were no job prospects.

The closest I came to biochemistry in those days was when I took a summer studentship in the Central Drug Research Institute in Lucknow. There I met a brilliant young scientist, Babul Dhar, a graduate of Cambridge University, who would have a lasting influence on my career. He spent hours

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discussing medicinal chemistry and drug design with me. Together we read critically the important papers of the time, such as Bob Woodward's cortisone synthesis involving a microbiological step and Dorothy Hodgkin's vitamin B₁₂ structure. Babul's many interests matched mine. He was a pianist and talked to me about the Goldberg variations with the same ease as he would discuss a complex organic reaction. I had dinner at his house almost every other weekend. His wife Bertie, a delightful lady from Yorkshire, was equally nice to me. As time passed, Babul became a real role model for me. He was the one who kept encouraging me to go abroad to do my graduate studies.

I wanted to go to Cambridge University, but I did not have the money nor did I find any scholarship. (In later years I did go to Cambridge as a Nuffield Foundation Fellow to work in Hal Dixon's lab and was thrilled to use the same electrophoresis tanks that Fred Sanger had used in his pioneering work on the insulin sequence.) I started writing to universities in the United States and received financial assistance from the University of Southern California, Los Angeles in 1959 to do my graduate studies in chemistry. To minimize the costs, I traveled by an American President Lines ship across the Pacific. Although my strong points were physical chemistry and mathematics, I did not find anyone in the Chemistry Department with a biochemical interest. By Christmas of 1959, I met Paul Saltman, a young, charismatic and most outgoing Assistant Professor of Biochemistry, and I decided to do my PhD studies in his lab in the Biochemistry Department. Paul had received a new grant from the Atomic Energy Commission to work on iron transport and he thought that I had the perfect background. It was in Paul's lab that I started to become a biochemist—with a new twist: 'inorganic biochemist', a term which was yet to be invented. In those days, metals were left either to inorganic chemists or to nutritionists and there was not much communication between them. Many thought that metals in metalloenzymes were mere contaminants. Iron chemistry itself is complex, but my work on the interaction of iron with biological ligands turned out to be even more challenging. Paul was a great supporter, which kept my spirits up. It was during this time that I had the good fortune to meet Bo Malmström, a visiting professor at USC who would make a great impact on my future career as a biochemist. I took a course from him on metal-activated enzyme kinetics. Later he served on my PhD thesis supervisory committee. During those years Bo really guided me in the studies of metal-protein interactions, at that time an area hardly explored. Unfortunately, he left for Göteborg, to take up the position of a Chair of Biochemistry in the Chalmers Institute of Technology before I finished my PhD. Prior to leaving, he offered me a postdoctoral fellowship if I wanted to come to his lab in Göteborg. Bo was a musician who played the recorder, and specialized in Baroque music. I would often accompany him and his wife to Los Angeles Philharmonic for concerts. We communicated regularly even after he became so

busy with his chairmanship of the Chemistry Committee for the Nobel Prize.

I graduated with a PhD in Biochemistry in 1964. Paul sent me to Chicago to present my thesis work at the FASEB meeting, just before my defense. There I met a delightful man, Andrew Sass-Kortsak, a clinician-scientist at the Hospital for Sick Children in Toronto, Canada. Andrew was at the meeting to recruit young scientists for the Hospital's Research Institute. He invited me for dinner and told me over dinner how much he liked my talk and invited me to come to Toronto to give a seminar. I came to Toronto to give my seminar and on the same day I was offered a position of Staff Scientist to work in the Genetic Metabolic Research Program. It was a real dilemma for me, since I had several postdoctoral fellowship offers lined up, including one from Bo in Sweden. I was also very hesitant since I was a fresh PhD and had no postdoctoral experience. But the offer from Toronto was too tempting, with start-up funds and my own lab. Despite opposition from many colleagues, I finally decided to join the Research Institute of the Hospital for Sick Children at the age of 28. Soon thereafter, I was cross-appointed to the Department of Biochemistry at the University of Toronto as an Assistant Professor.

Although I never had a formal postdoctoral training, several factors made up for it. Andrew's vast experience in clinical medicine opened new horizons for me. I found a perfect niche where I could apply my basic biochemistry knowledge to solve medical problems. I started going to the Grand Rounds with Andrew and would also go to the wards to visit Wilson disease patients. During one of my discussions with Andrew, I said that copper cannot circulate in blood in ionic form—it must be bound to some ligands. He threw a challenge and asked me to find the copper-transporting ligands in human blood. This led to my discovery of copper-histidine in human blood. Little did I know at that time that this finding would lead to a treatment for a fatal genetic disease known as Menkes disease, which causes copper deficiency, resulting in neurodegeneration and death before the age of three. Also around that time, I was joined by a brilliant geneticist, Diane Cox, a recent graduate from McGill University. The strong bond formed between Andrew, Diane and myself in those early years became an asset to my future research. Later, Diane would clone the Wilson disease gene and my lab would express and characterize the copper-binding domain of the Wilson disease protein.

Andrew and Diane were not the only ones—I also had close interactions with John Edsall, Ted Peters, Jr., Frank Gurd and Esther Breslow during those years when I was working with human albumin. It was then that I developed the idea of designing a simple glygly-L-his peptide molecule to mimic the native copper transport site of human albumin. I never imagined that this would form the basis for such diverse endeavors: for Linus Pauling to kill Ehrlich ascites tumour cells with it by generating free radicals in the presence of

copper and ascorbic acid, Peter Dervan to cleave DNA specifically by attaching this peptide to a DNA-binding protein, and Julie Forman-Kay and Lewis Kay to use this motif for structure characterization of proteins by NMR.

When I look back, I feel satisfied that I made a good decision 40 years ago to come to Toronto's Hospital for Sick

Children and the University of Toronto where I grew up as a biochemist. At the same time the whole field of inorganic biochemistry came of age. My career was enriched by so many lives—every one of them has a place in my science.