

My Mentor- Late Professor Saul Roseman

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My mentor Professor Saul Roseman was born in Brooklyn, New York on March 9, 1921 and passed away on July 2, 2011 in Baltimore, Maryland. Since 1970 (the year I left his laboratory) I never missed each year to send him my birthday greetings. On March 9th in 2011 when I called him, complained not having the 90th birthday symposium as we had on his 80th birthday in 2001 and wished him to make a century. I heard from the other side "...a wishful thinking Professor...my heart condition is not good at all...". That is the way we used to address each other since I graduated from his laboratory in 1966 because after my thesis oral, when he came out of the examination room to greet me, he found I was smoking a bent pipe like him. Of course that was inspired by my good friend Ben Snyder, who was an undergraduate researcher in his laboratory at that time. When Gracia from the journal office asked me to write a Minireview only a month ago I thought it would be appropriate to start where I started my research career in Glycobiology until now I really could not decide where to start: when I opened Google I found at least six or seven obituaries written by some of his close associates (e.g. Harry (Dr. Schachter), Bill (Dr. George W. Jourdan), Bob (Dr. Robert Simoni), Ron (Dr. Ronald Schnaar), and Amy Lunday. All of the basic information about my mentor has been documented and I request readers to consult those articles if they are interested to know his background. I will try to give those at the end of my article in a condensed paragraph. This article is primarily focused on my interaction with him as his graduate student and his colleague.

The name "Roseman" shone in the sky of "Carbohydrate Galaxie" for at least 55 years. Out of more than 200 people who were trained in his laboratory perhaps I was the only one who stayed in his laboratory almost 9 years (February 1962 to August 1970). I came to the University of Michigan from the University of Calcutta, India, in September 1961 (arrived after the last day of registration) to do graduate studies in Biochemistry. I remember after my 45 days of boat trip (from Bombay to New York) and one day overnight trip by Greyhound bus (New York to Ann Arbor) as soon as I entered in the corridor of the Biological Chemistry department in Ann Arbor I discovered him (Professor Roseman) with his apron on in front of a chalk board; he immediately asked me to write the structure of Starch and Glycogen. Perhaps from that very day he was convinced I had a future in carbohydrate chemistry and biochemistry. Although I came as a new graduate student in September 1961, I walked into his already famous laboratory in February 1962, after my rotations in the other laboratories. At that time he was already a vigorous full professor. On the very first day he reminded me I should not be argumentative like many other bright Eastern students, and I should have a plan to work in his laboratory for at least 12 years. He knew that in ancient time in India, students used to go to their Guru's house for 12 years of residency to study Sanskrit grammar, religion, or medicine. During that period they also helped their Guru feeding cows and doing agricultural work. He also told me that when he was a graduate student under Professor Karl Link (trained in Germany) at the University of Wisconsin (1946-51), among many extra duties he cleaned his windows also. Of course my training in

Bar-tendering was given by my mentor when he threw parties in his basement for some invited speakers. That is the most useful training; I am continuously benefiting even these days.

He always believed in serendipity in scientific discoveries since his discovery of correct structure of sialic acid. Many years later in 1991 when I wrote the article "Serendipity of Ganglioside Biosynthesis" in his 70th birthday commemorative volume of Glycobiology Journal (Vol 1, 469-475;1991) he congratulated me and told, "Professor you still have 4 more years of training due with me...according to the old Hindu tradition". In it's reply when I told him that the word "serendipity" came from the term "Serendeeep, or Sarnadeep (in Bengali it means "golden island" of Ceylon) discovered by the king "Bijoy Singha" of Bengal, India (from why were I came from), when all of a sudden he discovered the glittering island of Ceylon from the ship during sunset in the middle of the endless ocean. As we all know that the name "Roseman" became famous overnight in the field of carbohydrate chemistry and biochemistry when he published a one page paper in the JACS (Journal of American Chemical in 1958 [1]. The story I heard many times from him convinced me that every discovery depends on the four M's- "man or woman", "mind", "money", and "moment". Of course he always defined that moment as "serendipity". In 1956-57 when his first postdoctoral fellow, Don (Dr. Comb) was working on the characterization of the products obtained from Sialic acid by catalytic cleavage by Nanaldolase, he always obtained the molar ratio of pyruvic acid to hexosoamine, 1:0.75. He was using N-acetylglucosamine standard curve to estimate the hexosamine. In one serendipitous moment Roseman suggested to Don to use the values from the N-aceylmannosamine standard curve and the ratio became 1:1. That very discovery gave birth of the pathway for biosynthesis of sialic acid-9-phosphate from the aldol condensation of pyruvic acid and N-acetylmannosamine-6-phosphate. Years before 1957 Professor Gattchalk already published papers for the structure of sialic acid where he proposed an aldol condensation from two precursors: pyruvic acid and N-acetylglucosamine. At that time it was a closed chapter on the structure of sialic acid. This discovery was followed by the discovery (in 1960-61) of biosynthesis of CMP-sialic acid from CTP and sialic acid by the catalysis of widely distributed CMP-NeuAc synthetase [2]. Later on it was discovered by Ed (Dr. Edward Kean) that this enzyme was present in the eukaryotic nuclei nuclei [3].

I had the good luck to start research (in February 1962) at the dawn of Glycobiology in the Roseman-Lab when it was possible to ask many quantitative and technical questions for glycosyltransferases to

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a group of very young, energetic postdoctoral fellows: Sudhamoyda (Dr. Sudhamoy Ghosh), Bill (Dr. George W. Jourdian), Don (Dr. Don Carlson), Bernie (Dr. Bernard Kaufman), Ed (Dr. Edward Kean), Eddy (Dr. Edward McGuire), Werner and Freddie (Drs. Kundig) in his laboratory. Only one very hard working graduate student (Jack Distler) who was there for an indefinite period but was visible only in the night time. Jack made it clear in my mind that for a new graduate student only time and space (2ft x 32 inches bench space) would be available in that crowded Rackham Arthritis Research Unit (RARU) after 9 pm until 8 am. The highest priority for use of "High Voltage Electrophoresis", "Packard Scintillation Counter" (that was the first scintillation counter invented by Packard company for beta emitter radioactive compound) or even a "Cold Centrifuge" belonged to the senior researchers (postdoctoral fellows). As a result of that I practically used to live in the laboratory most of the nights and had the opportunity to be touched by "serendipity" the spirit for discovery of "Ganglioside Biosynthesis Pathway".

I would like to devote the next few lines to that history (1962-70) at the Roseman laboratory. During 1961-62 both Bill and Don characterized the first sialyltransferase from rat mammary gland [4] for synthesis of sialyllactose from CMP-[14C] sialic acid and lactose. When I arrived in that laboratory, the synthesis and isolation of substrate quantities of many of those radioactive sugar nucleotides were established by the joint effort of Saul Roseman and HaraGobind Khorana [5]. Of course the silent worker behind that was Jack Distler. However, I fell into that slot of glycosyltransferase work a year later.

As soon as I moved into the laboratory in 1962, Bernie (Dr. B. Kaufman), gave me a can of frozen goat colostrum (first milk) for isolation of sialic-bound protein and lipids. After one year of hard work I characterized a small glycopeptide from goat colostrum which contained sialic acid and N-acetylglucosamine. Both Don and Bill were thinking to use the desialylated goat colostrum glycopeptide as the acceptor for their newly discovered rat mammary tissue sialyltransferase. In fact that was the first glycosyltransferase [3] reported in the field of Glycobiology from Roseman laboratory.

In the meantime (February 1962-Fall 1963) I was trained by Sudhamoyda (Dr. Ghosh) in the isolation of Mannoseamine kinase which catalyzes the synthesis of Mannoseamine-6-phosphate from N-acetylmannoseamine and ATP) and Nanaldolase from pig submaxillary glands. However, in one afternoon in the summer of 1963 I walked in the chemistry library of the University of Michigan. By the touch of serendipity I opened the pages of the current issue of "Chemie Berichte" two papers [6] from the laboratory of nobel laureate Richard Kuhn: i) Structure of a sialic-bound glycopeptide from cow-colostrum and ii) structures [5] of bovine brain sialic-bound gangliosides GI (GM1), GII(GD1a) and GIII(GD1b). The nomenclatures in parentheses are commonly used and were given by Professor Lars Svennerholm at much later dates. Of course seeing the structure of a glycopeptide published, very similar to my one year of hard work, brought tears in my eyes. However, seeing the exact structures of brain ganglioside containing sialic acids gave me an optimistic dream in finding enzymes for its biosynthesis for the first time. In Roseman lab (between June 1963 to October 1965) the spirit "Serendipity" touched me several times which made it possible to write in January 1966 my thesis, "Studies on the Biosynthesis of Gangliosides" in embryonic chicken brains [7].

One Saturday afternoon, in the beginning of the fall of 1963 Dr. Roseman brought to my attention the paper of Garrigan and Chargaff (1963) [8] in which they published data about the increase of lipid-

bound sialic acid in embryonic chicken brains. When I gave that paper [7] to the Journal club in the Roseman group, our newly arrived bright postdoctoral fellow, Eddy (Dr. Edward McGuire), pointed out that I should carefully consider the sharp rise in sialic acid content between the 9th and the 11th day of embryonic development. That afternoon, I ran to the nearby Public Health building and entered their virology laboratory. I asked for a few fertilized chicken eggs and the lady in charge gave me a dozen.

I grew up in India in an atmosphere of biology (my father late Professor Sunil Chandra Basu, was a professor of biology at the University of Calcutta) but my interest was in chemistry; I came to this country after finishing chemistry honors. My mentor Dr. Roseman also came from the chemistry background. Both of us did not know even how long it takes a chicken to hatch and what should be the incubation temperature. However, we both were interested to know the chemistry and biochemistry behind the attachment of sialic acid to brain gangliosides.

I came to know from the late Dr. Norman Radin (his laboratory was across the street at the Mental Health Research Institute in Ann Arbor) that it is not 37 degree centigrade, but 38.1 degree centigrade. We did not have any egg incubator in our laboratory of RARU at the Kresge building. Being poor in knowledge of embryology, I bravely injected 14C-Sialic acid (1 microCuri/egg) straight into the yolk, sealed with paraffin and incubated in the warm room (set at 37 degrees centigrade). After 9-11 days I took the embryos (those which were not dead) out of those shells, dissected the brains, extracted gangliosides, followed by the Folch wash [9]. In my excitement I found 14C incorporation was 500-1000 cpm/gmw of brain. I repeated that experiment for next two months, but I was not very happy with the results for its variation in the duplicates or triplicate experiments.

In October 1963, one night I was brave enough to homogenize a few 9-day-old embryonic chicken brains in tissue culture medium-199 and incubate with CMP-14C-NeuAc (a gift from late Dr. Don Carlson who also taught me how to make it) in two different flasks. One contained 1 mg of lactosylceramide and the other one was blank control. After overnight incubation of those two flasks, I extracted with chloroform-methanol (2:1) and Folch wash followed by overnight dialysis. I ended up with 500 cpm of 14C incorporated into the total lipids of the flask which contained lactosylceramide. I ran to Dr. Roseman and suggested that perhaps 9-day old embryonic brain contained the sialyltransferase which catalyzes the transfer of sialic acid from CMP-14C-sialic to lactosylceramide. He puffed his pipe, smiled, and told me, "Well, it is encouraging; go ahead and repeat it." Next time I became little careful and homogenized in phosphate buffer at pH 7.0, but after 3 days of toil I ended up with 0-cpm. It was time for me to pray or to receive the touch of serendipity. After careful scrutiny of my ingredients in the first experiment, I discovered that in the first time I homogenized the embryonic chicken brains in tissue culture medium-199 (I borrowed from the technician of late Dr. Bill Castor in the Lab), it contained Tween-80, a detergent.

During the summer of 1963 when I isolated 250 mg of lactosylceramide from 80 Kg of fresh bovine spleen tissue I noticed that the material was water insoluble. Even Dr. Roseman with his lighted pipe was helping me with the drying of minced bovine spleen with gallons of acetone. Fortunately, no fire occurred in the laboratory on the top of the acetone vat. He even helped me to run a big Silicic acid column chromatography. However, my quantitative organic analysis knowledge told me perhaps that Tween-80 in the medium-199 helped

me in solubilizing some lactosylceramide. The idea of solubilization of Golgi membrane bound glycosyltransferases [9] came in the horizon of GLT (glycosyltransferase) from our laboratory at Notre Dame almost a decade later [10,11]. At that time the realization of Tween-80 inspired me to collect a number of detergents in a kit (which I still have) and systematically study the incorporation of ¹⁴C-Sialic acid from CMP-¹⁴C-Sialic acid to lactosylceramide. The outcome of that investigation resulted in the discovery of optimum activity of most of the GSL-sialyltransferases with Triton CF-54: Tween-80 (2:1) under optimum concentrations. The use of cacodylate buffer was a right decision because much later we realized that heavy metals even in traces could inhibit the active sites of those GSL-GLTs containing active -SH groups. This particular serendipitous discovery opened up the gold-mine of GSL-GLTs (Glycosphingolipid- Glycosyltransferases) in the buffy coat from embryonic chicken brains [10-18]. Later, in 1974, we discovered that all of these GSL-GLTs are concentrated in Golgi bodies of different tissues [9]. Within next three months before I finished my thesis writing, always having amusing comments by Dr. Roseman, we already characterized four enzymes (SAT-1, GalNAcT-1, GalT-3 and SAT-4) of the ganglioside biosynthetic pathway [6,18], these were included in the thesis in 1966 [6]. Of course, it evolved from Dr. Roseman's deep insight in the subject, our combined dream, and also with the touch of serendipity to both of us at the same time. I still remember in October 1965 when he moved from Michigan to Baltimore in the Biology Department of the Johns Hopkins University, he left me in Ann Arbor with a forced vacation to recover my health. The picture given in this article was taken at that time in Ann Arbor in his little office (Figure 1). Even in the middle of the nights in Ann Arbor, he used to visit laboratory (on his way back from parties or concerts at the Hill auditorium) to encourage me during my work in the night time and was very particular about my safety in the laboratory also. In one of those trips he saved my life with the CO₂-gun when late Dr. Werner Kundig's ether distillation, set up under the hood, caught fire, and I was trapped in the corner where my little bench was.

During May 1965, while most of my classmates were finishing their thesis work, I fell in love with the embryonic-chicken-brain system. I remember with pleasure, Dr. Roseman said to me at that time, "Look, Basu, I think you have stumbled onto a gold mine. Why don't you dig hard for few more enzymes before you start writing your thesis



Figure 1: Professor Saul Roseman in his office at the University of Michigan in 1965.

[6]. Within next three months I characterized both GalT-3 [15] and GalNAcT-1 [16] and was working very hard in the laboratory. My health deteriorated. In August of 1965, while Dr. Roseman was preparing to move his laboratory from Ann Arbor (University of Michigan) to Baltimore (Department of Biology, Johns Hopkins University) he told me "Basu, take a break and do not sit down to write your thesis until you are completely well." In old Sanskrit literature there are lines, "a real human being could be strong like a thunder to the evil but could be soft like wind for the flowers". I found my mentor was the exact example of those Sanskrit words.

In January 1966 after I finished my oral examination of the thesis [6], he was surprised at my decision to continue my postdoctoral work with him instead of going to the famous laboratory of Professor HaraGobind Khorana. There was no confusion in my mind that the other two enzymes for synthesis of lactosylceramide from ceramide were present in the ECB-Buffy Coat (the goldmine of glycosyltransferases (GLTs) as Dr. Roseman collectively called it in 1965 which contained Golgi bodies as we proved in 1974 [9]. In February 1966 I joined his laboratory at the Johns Hopkins University. Within a year Manju (came from Moy Ghosh's laboratory in Bose Institute in Calcutta; my life time partner joined me in the laboratory of Dr. Roseman and together we explored the synthesis of glucosylceramide (glucocerebroside) [13,14], lactosylceramide [17,18], and galactocerebroside (115) biosynthetic steps and reported by 1968-73. This established the six chosen steps for biosynthesis of normal GD1a ganglioside starting from ceramide [17,18]; these days it is called Basu-Roseman Pathway [18].

When Father Theodore Hesburgh (at that time President of the University of Notre Dame) invited me in 1970 to the University of Notre Dame to start my independent laboratory, at first Dr. Roseman was hesitant to say it was all right to cut my umbilical cord. Finally he threw the biggest lab-party ever in his basement in Baltimore (in August 1970) which I will remember forever with pleasure. He even forced me to get my companion Nikon-FTn camera to record the event and I will treasure those pictures the rest of my life.

From many laboratories we hear that the relation between the head of a laboratory and veteran workers become sour as one stays longer in the laboratory. In my case our relationship was based on love and humor. When I decided to come to Notre Dame in 1970 with the junior faculty job, at that very moment a nun (Sister Stankevich) decided to move as a postdoctoral fellow from the biochemistry division of the University of Notre Dame to the laboratory of Dr. Roseman at the Johns Hopkins University. When he gave me the news proudly, I smiled and immediately told him, "What an irony of life. A devil is going to heaven and an angel is coming to hell!" Dr. Roseman enjoyed my humor and went to door steps of every senior Professors of Hopkins biology department and told those lines with his added line of humor. "Look who I raised with nine years of hardship...".

From the very first day I joined his laboratory and after eight and half years when I left, there was no lack of humorous exchanges between us. That humorous relationship we maintained until March 9, 2011, the last time I called, on his birthday.

Following is the bird's eye view of his scientific training (as I promised to write at the end). He received his Bachelor of Science in Chemistry from the City College of New York (CCNY) in 1941 and after a two years break (1944-46) to go to Europe for World War-II he came back to Wisconsin and obtained his PhD degree in 1948 from the Biochemistry Department of University of Wisconsin. He was

trained as an Organic Chemist and Biochemist in the laboratory of Professor Karl Link during his graduate studies. He worked with the late Professor Albert Dorfman (a pediatrician and a great researcher) at the University of Chicago for his postdoctoral training for five years (1948-53). His training on the structure and biosynthesis of Hyaluronic acid and Chondroitin sulfate inspired him to devote his whole life to the fundamental discoveries in the field of Glycoproteins and Glycolipids [19]. In 1962 the serendipitous discovery of a hexosamine kinase, which needed PEP instead of ATP by Moy Ghosh in his laboratory opened up the novel Phosphotransferase system [19,20] in bacterial sugar transport, a brand new area of research quite popular even today in the field of carbohydrate Chemistry and Biochemistry. In 1972 Dr. Roseman was elected as a Fellow at the US National Academy of Sciences and Arts. He was named the Ralph S. O'Connor Professor of Biology in 1975. He served as chairman of the department from 1969-1973 and from 1988-1990. I think we do not know the exact number of papers he published in his lifetime, perhaps over 230 full papers. The journal of Biological Chemistry honored him in 2006 for a lifetime contribution in the field of Glycobiology and Biochemistry. Of course for his boundless contribution in the field of Glycobiology [20] we all expected the big Prize to arrive any day before he passed away. However, if the Nobel Committee ever changes their rule to award a Nobel Prize posthumously, I am sure the name of my mentor would surface first.

In his thesis work he studied the physiological role of "Warfarin" (Coumadin), which is the anticoagulant drug still widely used after surgery all over the world. In my view my mentor late Professor Saul Roseman is a pioneer in the field of Bioanalysis and Biomedicine, and Glycobiology [21]. As an editor of this journal I am happy to write his obituary in the appropriate journal.

Dr. Basu started his ganglioside biosynthesis work in embryonic chicken brains in the laboratory of the late Professor Saul Roseman at the University of Michigan as his graduate student (1962-65). He continued his postdoctoral work under Dr. Roseman at the Johns Hopkins University where he completed the: "Basu-Roseman Pathway" work (from ceramide to disialosylganglioside GD1a; six new glycosyltransferases catalyze six steps).

He is on the faculty of the University of Notre Dame, Notre Dame since 1970. At present he is an emeritus professor in the Department of Chemistry and biochemistry and president of CDDRF (Cancer Drug Delivery Research Foundation). His graduate students, postdoctoral fellows, visiting scientists, and undergraduate researchers (a total of 170 in last four decades) have discovered 10 more new glycosyltransferases and established pathways for blood groups O, A, B, SA-LeX, Ii, and Globoside Glycolipids. Regulation of these genes after apoptotic induction by L-PPMP, D-PDMP, Betulinic acid, Tamoxifen, cis-platin in breast cancer carcinoma cells (SKBR-3, MDA-468, and MCF-7) was studied in the laboratory of Dr. Basu during the last decade [17,18]. Delivery of these apoptotic agents (potential anti-cancer drugs) in minimum quantities in the most effective way to treat the cancer patients would be the primary goal in the laboratory of CDDRF under the leadership of Dr. Basu at present.

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