MY TORONTO YEARS WITH CHARLES H. BEST

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Intoductory Note: *Seldom do we find science and romance as closely intertwined: a girl and a boy attend the same school in Bratislava. It is quite a progressive school – it has student government. The girl (her name is Anna) is president of the school council. The boy (his name is Otakar) is leader of the loyal (?) opposition. They compete, mainly for the honour of being the top student. But neither can win; both are consistently and, I believe, equally, top students.*

Time marches on and they begin to date, mostly each other. A romance blossoms. They finish high school, jointly the best students in their class, and enroll at the medical faculty of the Comenius University in Bratislava. As we will read later on, both of them received a golden gift from the President of Czechoslovakia and that gift is also wrapped up in a pretty story: only one student from every graduating class (obviously the best of the bunch) was entitled to receive the golden gift from the President. But here were two best students. Which of them should get it? They approached the dean of the Law school who sagely advised them that there is a notion in the old Roman law that husband and wife are deemed one person. Since Anna and Otakar planned to marry anyway, they married prior to the graduation and voila – both received the golden presidential gift!

In 1994 professors Anna and Otakar Širek *were invited to Japan to deliver a lecture at a meeting of the Japan Diabetes Association in Tokyo. The lecture was delivered by Professor Otakar* Širek. *The following is the text of that lecture.*

Josef Cermak

Ladies and Gentlemen:

My wife and I are greatly honoured to be part of this distinguished gathering and would like to thank Dr. Isogai and his Organizing Committee for inviting us. Japanese hospitality is famous for its attention to detail, it is gracious and full of surprises that can put us Westerners easily to shame. Having been retired from active research, I have asked myself what do I have to offer in return for this great honour bestowed upon us today. I am certainly not in a position to give you a valid account of the state of the art. Friends told me that the story of my, and for that matter of our lives – by being a research team for more than thirty years with my wife – are unusual and, therefore, worthy of sharing with colleagues. Other friends, with tongue in cheek, have told me that the fact that I was born in 1921, the same year insulin was discovered, must have something to do with my becoming a Postdoctoral Fellow at the age of 29 in Dr. Best‘s Research Department in Toronto. This great man liked to be called simply Dr. Best.

As indicated in the title, the core of my talk today will concern my association with Dr. Best. However, I feel that my experience of the Toronto years will come forward more clearly, if I first touch on the events that preceded my joining Dr. Best‘s Department. I think it is equally appropriate to speak also of the years following Dr. Best‘s retirement, because they underline, albeit by contrast, Toronto‘s glory of the fifties and early sixties.

I consider myself fortunate that I was born in the First Czechoslovak Republic, mainly because of its excellent educational system that even the war years were unable to destroy. My basic education was the key to my meeting successfully the many challenges of the future. Imagine a young Medical Doctor coming with his wife from a war-torn country to peaceful Sweden, a country untouched by the turmoil that shook the rest of Europe. It took us no more than a few weeks to realize that major adjustments will have to be made by us. The fact that both of us graduated in medicine with First Class Honours and received a golden gift from the President of Czechoslovakia, was of very little help to us at that point. Professionally, in spite of solid foundations, much had to be learned by us to familiarize ourselves with the advancements in science and medicine made in the free World. I believe that a number of people in this room will be able to relate to the frustrations one endures when suddenly transplanted to a country where everything is very new and different.

The Carolinska Institute, as the Medical Faculty is called, was already at that time a famous centre with visitors from all over the World. Here we made our first scientific contacts with the United States and Canada. My wife and I were not working together as yet. She was interested in the surgical correction of congenital malformations of the heart, and I was working under the leadership of Professor Moellerstroem in a rather unique setting for the late forties: a well equipped biochemical laboratory that was attached to a fourteen-bed metabolic ward for diabetics. Here I was exposed for the first time to the concept that metabolites in blood and urine can fluctuate in a cyclic fashion. Studies of the rhythmical secretion of biological substances, including hormone secretion, were at that time in their infancy; nevertheless they kept me fascinated for all the years to come. In our own Toronto laboratories, we devoted much effort in the eighties to elucidate the relationship between the rhythmic secretion of Pituitary Growth Hormone and the rhythmicity of pancreatic islet secretion of insulin and glucagon. Some of you may recall my lecture on this subject given inTokyo a few years ago.

The Stockholm years were another good preparation for the future. They were productive, both scientifically and also in terms of personal development. Stockholm had an exciting cultural life and I remember fondly many beautiful performances at he Royal Opera House and the Concert Hall. Our attendance at the Nobel Prize festivities in 1947 must not go unmentioned. We saw the Coris as a husband and wife team to receive their award, and Domack received his Prize belatedly for the discovery of the bactericidal effects of sulphonamides.

Gradually, my first English publications appeared in peer reviewed American journals and our international contacts intensified. Although my wife was still occupied primarily

with surgery, the investigative approach in the clinical sciences was not much different from that in the basic sciences and that drew us together in our interests. At that time Czechoslovakia fell under Communist rule and closed its doors on us. In these tragic times we were occupied by correspondence with Dr. Best, then Director of the Banting and Best Department of Medical Research and Head of the Department of of Physiology in the Faculty of Medicine of the University of Toronto. The subject was an invitation for me to work in his Department as a Postdoctoral Fellow. We had to work out many details and this helped us to take our minds off the unfortunate situation in Czechoslovakia. The major factors that made Toronto for us attractive, were the high scientific standards and the international character of the Department. The Banting and Best Department of Medical Research was autonomous within the Faculty of Medicine and was endowed as a research facility by a special grant from the Province of Ontario. Physiology was a regular teaching Department with the mandate to provide classes for medical students as well as all other students in the Health Science, like Dentists, Nurses, Pharmacists and others.

In 1950, the time we came to Toronto, Dr. Best was 51 years old and was on top of his career. He was not only a dedicated scientist, but also an efficient organizer who had little patience for bureaucratic excesses. The Physiology Department was faced with a heavy teaching load, but he saw to it that nobody was overburdened. The division into research staff and teaching staff was fictional. I still remember Dr. Best‘s dictum: *„You are paid for teaching and promoted for good research.“* Although an oversimplification in many ways, it worked well for Dr. Best in the fifties.

The other innovation in Dr. Best‘s little kingdom were cross-appointments with clinical departments, which at that time was rather uncommon. The core staff, combined with cross-appointees and foreign visitors, provided a healthy mix of people with a variety of interests – it certainly made seminar debates really lively. Moreover, all big names in carbohydrate metabolism visited Toronto quite frequently. I remember vividly the visit of Dr. Elliot P. Joslin. In the fiftees my stature was portly and Dr. Best was not exactly slim either. When Dr. Joslin said good-by to us before returning to Boston, he commented politely on all the nice things he saw, but to my embarrassement he poited at Dr. Best and myself, saying: *„You and you are too fat.“* Since we all knew about Joslin‘s religious belief in weight reduction, it was taken as a witty remark and we had much fun from it for a long time.

While transplantation from Central Europe to Scandinavia required major professional adjustments to be made on our part, the transition from Stockholm to Toronto was a continuation of my research activities without major interruptions. Hyperlipidemic diabetic patients showed an increase in urinary choline excretion and my Swedish work fitted nicely into the category of Dr. Best‘s pet projects. I suppose Dr. Best‘s interest in choline dated back to his years of association with Sir Henry Dale, the „Acetylcholine Dale“ of England. Choline as a diatery factor and hepatic lipotropic agent was for a long time a major research interest in the Banting and Best Department, and a number of prominent scientists, like Solandt, Lucas and Rideaut were members of the team.

My own interests along these lines were limited and after a few months I embarked on an ivestigation concerning the role of insulin in the protein anabolic effects of certain other hormones, particualrly testosterone and Pituitary Growth Hormone. It was believed by some members in the Department that insulin was the true protein anabolic hormone, the hormone that caused nitrogen retention and was responsible for growth; the protein anabolic effects produced by other hormones were allegedly mediated through the agency of insulin. This notion proved to be only partially correct. In our hands, insulin had only a „permissive“ effect, meaning that insulin was essential and had to be present in adequate amounts, but other hormones, such as testosterone and Growth Hormone exerted protein anabolic actions on their own. The findings concerning the relationship between testosterone and insulin and their effects on nitrogen retention in dogs was my first major paper from Toronto and was published with Dr. Best as senior author in ENDOCRINOLOGY, in the spring of 1953. It was received with considerable interest, judging from the reaction of endocrinologists at the International Physiological Congress held in Montreal in the summer of the same year. Thus, my work went well and Dr. Best let me know that for us to return to Sweden would be counterproductive.

Dr. Best was a remarkable man in more than one way. He was absolutely fair in matters of credit for work by his co-workers. In his lectures he never failed to mention the name of the individual that was responsible for the actual work. Many times I heard him say: *„Dr. Sirek in my Department did so and so…“* Dr. Best had empathy, he was one of the few people I met, who in spite of being in a leading and high-ranking position did not lose the human touch. In dealing with his staff he took keen interest in the lives of young people who needed guidance not only in scientific matters but many times also in personal affairs. Kindness did not mean that he failed to be task-oriented. He was a man who worked hard himself and he expected the same from his staff. There was no question that Dr. Best was a benevolent dictator, but in the fiftees this created little resentment. I am still very grateful to him for giving me rather firm advice on a couple of occasions. It was Dr. Best who insisted that we stay in Canada, remain in the basic sciences and both my wife and I proceed through the academic ranks as teachers and researchers. We have never regretted his advice. The second occasion when he offered firm advice was the time when sporadic collaboration with my wife was to be turned into permanent teamwork. My research work was centred around in vivo experimentation and, therefore, required animals, more specifically dogs in which hormonal deficiencies were produced by surgery. Pancreatectomies and hypophysectomies if done according to protocols set out by Animal Care Committees, needed expertise in surgical techniques and meticulous postoperative care. The skills of my wife were particularly suited for fulfilling these requirements. There was general agreement among colleages that my surgical skills were non-existent and Dr. Best shared their opinion. Thus, he advised firmly, or better to say decided on our behalf that the Sireks ought to be working together and share a laboratory. My wife moved from the Hospital for Sick Children to the Charles H. Best Institute, the building that was housing the Banting and Best Department of Medical Research – and we became a team. This was a revolutionary move, because the rule in existence was that man and wife must not hold positions in the same Faculty or Department, let alone share

the same laboratory. It was quite characteristic for Dr. Best to break bureaucratic rules when they made no sense. Scientifically, these were most exciting times when crucial observations were made. The specificity of insulin measurements in serum were in the foreground of interest. Bioassay or immunoassay – that was the question. When pancreatectomized and hypophysectomized dogs, so called Houssay Dogs, deprived of endogenous insulin for several weeks, still showed considerable insulin-like activity in serum as measured by the epididymal fat pad method, the question of specificity was firmly settled by us in favour of immunoassays. The decisive presentation was made by my wife at the Atlantic City Meeting of he American Diabetes Association in 1963. It was the first paper on the programme, which traditionally was the one with the highest rating.

The Sirek team survived for more than thirty years. It was certainly one of Dr. Best‘s prudent executive decisions. Teamwork was the key element in our ability to remain professionally active while raising a family with four children. We bought a house around the corner from Dr. Best‘s house and ten minutes from the University, sharing duties both at work and at home. Colleagues who knew that the original pronunciation of our name was „Shirek“ frequently referred to us jokingly as „Herek“ and „Sherek“.

I believe that my wife and I are the last surviving individuals who were in close professsional contact with Dr. Best to the end of his career and as a matter of fact, right to the end of his life. The Congress of the International Diabetes Federation in 1964 was held in Toronto. The event was to give recognition to the Toronto era, and to honour Dr. Best especially. It was unfortunate that severe attacks of depression leading to a complete nervous breakdown prevented him from enjoying the celebration. Of course, there were signs and symptoms of mental problems before, but in the year preceding the Congress, Dr. Best was no longer capable of functioning effectively either as leader of his Department or as the Chairman of the Organizing Committee for the Congress. There were periods when his indifference or lack of judgement, particularly in scientific matters, was to the detriment of all of us concerned.

In retrospect, I think that Dr. Best‘s feelings were permanently hurt back in the years of the discovery of insulin. We know that the Nobel Prize in 1923 went to J.J.R. Macleod and to F.G. Banting. It was Banting‘s decision to share his portion of the Prize with C.H Best and Macleod‘s decision to share his portion with J.B. Collip. I believe Dr. Best felt that the Nobel Prize Committee was not quite fair to him and I know that Dr. Houssay and other Nobel Prize laureates tried in later years to rectify the apparent lack of adequate appreciation of his efforts. In spite of the fact that all other conceivable honours were bestowed upon Dr. Best in his lifetime, the lack of appreciation of his contribution to the discovery of insulin by the Nobel Committee remained a thorny issue in his heart. I worked with him frequently on lectures on the history of diabetes and the discovery of insulin; I don‘t recall him ever making negative comments on the personalities involved. He implied that all four of them, i.e. Banting, Macleod, Collip and he himself had done their fair share, working to the best of their abilities; Best believed that the discrepancies which were so well publicized for many years, were rooted in the incompatible

personalities of the four individuals. It is interesting to note that Professor Michael Bliss, in his profoundly researched book on the discovery of insulun, written some 4 years after Dr. Best‘s death, independently reached the same conclusion.

For instance, it is not quite true that Macleod in the critical summerof 1921 took off for Scotland, leaving behind two utterly inexperienced individuals to mess around, and that only good luck led to an important discovery. There is evidence available, uncovered by Professor Bliss, that Macleod prior to his departure left precise instructions, defining the logical sequence of experiments to Banting. There is further evidence that Macleod‘s contributions were substantial, because he was not only familiar with the scientific literature, but had personal contacts with those investigators who were doing research with pancreatic extracts, and was aware of their hopes and failures. Banting had the idea and some surgical skills, but Macleod knew the international scene, had the insight and experience. Macleod‘s somewhat tarnished reputation had recently been restored by naming our main auditorium of the Medical Sciences Building in his honour. It is the same Building in which the Department of Physiology is located. Collip with his training in organic chemistry was an important member of the team, useful in the purification of insulin. This is not to say that Best, as an incumbent medical student, was the least qualified member of the team. Best at that time was a graduate from a four year elite course in Physiology and Biochemistry offered by the Faculty of Arts and Science of the University of Toronto. As a result, Best was familiar with the state of the art of laboratory procedures and the new methods for glucose determination in blood. A careful study of the pertinent literature reveals that the lack of a specific method for measuring blood glucose concentrations was the most serious handicap in the successful isolation of the blood sugar lowering principle from the pancreas. Hypoglycemic episodes brought about by pancreatic extracts went unrecognized and were interpreted as toxic effects. As a result, many an investigator in spite of being on the right track abandoned further research. Thus, each of the four team members back in 1921 had skills that were complementary to one another and the dedication to a common goal led to the successful discovery of insulin. Eventually, Macleod returned to Scotland, Collip accepted an appointment at the University of Alberta; Banting and Best remained in Toronto. Banting became Director of the newly created Department of Medical Research and Best became Head of Physiology. Following Banting‘s tragic death in an army plane in 1941, Best became head of both Departments. A few years later my own Toronto saga had its beginning.

Dr. Best left the scientific scene in 1963 and passed away in 1978. An era came to an end. The dictum that what Boston with Joslin was for clinical diabetes, Toronto with Best was for the experimental side of it – this was no longer valid. It is certainly true that the departure of Dr. Best contributed significantly to the loss of fame for Toronto, but it would be unfair to leave things with such a dramatic single statement. After all, the same people who were working in Toronto while Dr. Best was alive, continued to do so after his death and many competed successfully at the international level. A major factor in the loss of Toronto‘s uniqueness was the fact that new centres of excellent basic research in metabolism became established all over the world and many of them were known for

offering unique expertise. New improved means of communication united diabetologists into a global village, international meetings were mushrooming and the number of topics included in such meetings grew larger and larger.

In 1967, three years after the Toronto Congress, I initiated with the help of a number of dedicated colleagues The Canadian Workshop on Diabetes. Through the generosity of Hoechst Canada (Hekista) and later the Connaught Research Laboratories, which were closely associated with the University of Toronto, it became possible to invite some 40 diabetologists from Universities across Canada to a comfortable convention centre in the country and discuss for a couple of days topics of mutual interest. Over a span of 11 years, altogether nine Workshops were held, and I have reasons to believe that these Workshops helped to keep alive the spirit of Canadian diabetes research at a time when Toronto lost Dr. Best‘s leadership. The Canadian Workshops on Diabetes, with the magnanimous financial support of Hoechst Canada, established the Charles H. Best Prize, consisting of a monetary award, a gold medal with Dr. Best‘s likeness struck on the face of it, and a citation. The organizers had high hopes that this noble endeavour would stimulate Dr. Best and help to revive some of his old vigour. When I was chosen as the recipient of the Prize in 1975, Dr. Best happily signed the citation, but his interest in the Award and the Workshop remained marginal.

It is the sign of our times that interdisciplinary research is what is expected to be fostered by institutions of higher learning. There is no question that it has produced good results – the discovery of insulin is in itself a good example of that. Some Universities went so far as to abandon the departmental structure in favour of Research Interest Groups. However, in a setting like the University of Toronto, the abolishment of departments was and is unthinkable. Indeed, there is no need to dismantle everything in the name of innovation, particularly when it continues to serve satisfactorily. I believe firmly that teaching of the well-defined subjects such as physiology,pharmacalogy, biochemistry and above all the clinical disciplines requires the existence of formalized entities, i.e. departments with a core staff that is responsible for preservation of the discipline itself. This does not preclude collaborative efforts amongst departments to mount jointly courses that fulfil the variable needs of our students at the undergraduate and postgraduate level.

Research is something else. Interdisciplinary teamwork is not easy to foster in a big university where physical remoteness of individual members of a team can create problems, from sharing special equipment to administration of grants. A partial solution is the creation of Institutes and Research Centres. Apart from practical advantages, such arragement is psychologically supportive of the investigator, in that it helps to combat the feeling of isolation. In Toronto, such an umbrella organization in which individual members remained physically separated in their departments of primary appointments, but became united in their interests, was formed in the early eighties under the name Banting and Best Diabetes Centre. It is part of the Faculty of Medicine and its chief mandate is to foster collaboration among investigators. Also, the Centre is responsible for invitations of distinguished speakers, it sponsors postgraduate fellowships and lately the Centre supports a laboratory for routine determination of hormones in blood, mainly

insulin and glucagon, on a fee for service basis. The Toronto Diabetes Centre has as its only physical assets offices for the Director and a secretary, all other physical facilities belong to individual departments.

I look back on my Toronto years with great satisfaction. I feel privileged that life has given me the opportunity to develop my intellectual and professional abilities in harmony with my wife, my most faithful ally. I am immensely grateful to Dr. Best for providing an environment for peaceful and productive work and it has given me much pleasure to speak to you about these magnificent Toronto years of ours. I look back with great happiness and satisfaction on the years when in succession altogether six postdoctoral fellows and several other visiting scientists from Japan graced our laboratory in the best of Toronto‘s international tradition. In my opening sentences I said that Japanese hospitality is gracious and ful of pleasant surprises. It was certainly a pleasant surprise for me to learn that Dr. Hotta, a former fellow of ours and a friend of long standing, would be chairing this session. What a pleasure – and how thoughtful!

Thank you very much.