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Commentary

Charles Scriver: Epitome of the physician scientist

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ABSTRACT

Charles Scriver is a towering figure in the medical genetics community. At 92 he can look back upon a remarkable career that established the field of biochemical genetics, a subsection of medical genetics that is translating the developments in basic genetics into the diagnoses and treatments of inherited biochemical diseases. This biographical sketch summarizes the key achievements of Dr. Scriver in research and medicine, integrating the different components of medical genetics into comprehensive provincial programs, teaching a generation of physicians and researchers, and developing worldwide collaborations.

Charles has been a mighty figure in so many ways. He began his career by bringing amino acid chromatography from London to North America, thereby greatly enlarging the scope of metabolic disorders. Subsequently, his editorship of the classic Metabolic and Molecular Bases of Inherited Disease brought metabolism into genetics and established the field of biochemical genetics. He discovered a number of new diseases and was the first to recognize shared mediated amino acid transporters in the kidney, a medical breakthrough that has become a basic concept of amino acid homeostasis. He led the formation of the Quebec Network of Genetic Medicine, incorporating screening, diagnosis, counseling, treatment and research of genetic diseases, which to this day serves as a model for collaborative and comprehensive medical genetic programs internationally. He initiated the development of sapropterin (Kuvan®), the first non-dietary treatment for phenylketonuria (PKU) and helped identify the mechanism of this cofactor's action on phenylalanine hydroxylase in variants of PKU. His laboratory also led the development of phenylalanine ammonia lyase (Palynziq®), an enzyme substitution therapy that now serves as an alternative to dietary treatment for PKU.

The ecosystem that Charles generated at the deBelle laboratory was collegial and highly fruitful. With the input and support of his remarkable wife Zipper, he found a way to integrate the concept of family into his work environment. Bustling with an endless series of evolving activities, he generated an inclusive setting which drew on the talents of brilliant clinical and research staff, as well as the input of patients and their families. In all these efforts, Charles managed to answer his own musings summarized in the following three questions: Who do we serve? How do we serve? Why do we serve?

Charles Scriver's life is one well lived. An extraordinary physician scientist whose accomplishments are cause for pause and wonder; generating volumes of contribution which will forever seem impossible for one individual to deliver.

Abbreviations: BH_4, tetrahydrobiopterin; HPA, hyperphenylalaninemia; LSDB, locus specific database; MBID, Metabolic Basis of Inherited Disease; MMBID, Metabolic and Molecular Bases of Inherited Disease; OMMBID, Online Metabolic and Molecular Bases of Inherited Disease; *PAH*, phenylalanine hydroxylase gene; PAH, phenylalanine hydroxylase enzyme; *PAHdb*, phenylalanine hydroxylase mutation database; PAL, phenylalanine ammonia lyase enzyme; PEG, polyethylene glycol; PKU, phenylketonuria; PoC, proof of concept.

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1. Introduction

At this exciting time with the emphasis on new therapies for metabolic disease – it is easy to forget or overlook the pioneering research so foundational to our field. However, we should not fail to recall this history, not only because history is important for its own sake but also because the history of metabolic disease – discoveries of the disorders, identifying and understanding the basic biochemical derangements, delineation of the clinical consequences, early diagnosis and development of therapies – has critically important lessons for us today.

Among the pioneers in the development of metabolic disorders, no one has been more important and influential than Dr. Charles Scriver. During his long career, Dr. Scriver, now 92, singlehandedly moved metabolic disorders into medical genetics, or more specifically, biochemical genetics. He accomplished this in many ways including assuming editorship of the classic "Stanbury" *Metabolic Basis of Inherited Disease* and, with his co-editors, enlarging it to include many additional genetic disorders, changing the scope of this compendium and correctly renaming it *The Metabolic and Molecular Bases of Inherited Disease*. This expansion included the metabolic features of many non-metabolic genetic disorders and, most importantly, established biochemical genetics within the interstices of modern medicine.

The impact of Charles Scriver's contributions cannot be overestimated. This biography is a testament to his enormous influence as a transformative figure to the field of biochemical genetics (Fig. 1).

2. Family and early life

The only child of Dr. Walter de Mouilpied Scriver and Dr. Jessie Marion Boyd Scriver, Charles Robert Scriver, CM, CC, GOQ, FRS, FRSC (Canadian pediatrician and biochemical geneticist), was born on November 7th, 1930, in Montreal, Canada, towards the beginning of the Great Depression.

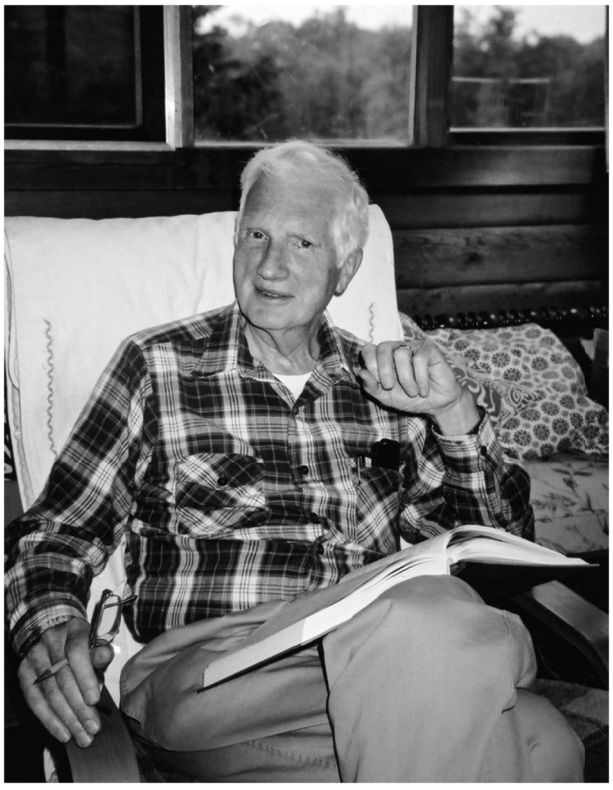

Fig. 1. Charles reading a manuscript at his family cottage in Vermont, USA; 2006 (Photo courtesy of Scriver family archives).

Fortunate to have a stable homelife with the support from his working parents and guidance from his nanny "Effy" Everendon, Charles was blessed with a strong foundation from which he was able to grow, protected from the ravages of the Great Depression and the terrible war in Europe. Indeed, the Depression came to a close when he was still in grade school and the Second World War ended only a few years before his eighteenth birthday; his timing could not have been better.

Unusual for the era, both his father and his mother worked full-time as physicians. His father, Dr. Walter de Mouilpied Scriver, a veteran, and survivor of the First World War, was an internist who became Physician-in-Chief at the Royal Victoria Hospital. Walter's research focused on care of patients with diabetes and diseases of the kidney. His own effort to create a supportive environment for young clinician-scientists is one of Walter's enduring legacies (Charles Scriver Memoir, October 15, 2019, personal communication).

Charles' mother, Dr. Jessie Boyd Scriver – known to most in the tight-knit Montreal medical community as "Dr. Jessie" – is recognized as a pioneer in Canadian medicine; in 1917 she was admitted to the first class of medical students at McGill University (henceforth referred to as McGill) to accept women [39]. She and Mary Childs graduated as the top two in their class; for Jessie, it was the beginning of a distinguished career; her research on sickle cell anemia is still referenced today. Jessie was an active author well into her 90s. She was Montreal's first female pediatrician, first female head of Pediatrics at the Royal Victoria Hospital, and the first woman to serve as president of the Canadian Pediatric Society (Charles Scriver Memoir, October 15, 2019, personal communication).

Charles' parents modeled a fierce dedication to their work, so much so that Walter had a laboratory in the basement of their house that was set up for examining the urine and blood samples of his patients. Charles remembers that his parents always had a telephone at the dinner table that would typically ring multiple times during a meal with requests for consultations that often led to one or the other parent having to leave on a house call or to meet a patient at the hospital (Charles Scriver Memoir, 2019-10-15, personal communication; Paul Scriver's personal interviews with Charles Scriver 2021-08-16 and 2022-01-09).

Charles was, by his own reckoning, not an exceptional student through grade school and high school, but he remembers having some extraordinary teachers at Lower Canada College. As a result of a shortage of students enrolled in university during the war, some remarkably well-rounded teachers who normally taught at the post-secondary level were relegated to teaching a considerably younger crowd in high schools across Canada. It was by this curious turn of fate that Charles, at an impressionable age, was provided the opportunity to learn Latin and ancient Greek and was introduced to poetry by a highly motivated and expert classics teacher. The experience sparked a life-long interest in reading and later provided inspiration for his medical research in history, literature and poetry (Charles Scriver Memoir, 2019-10-15, personal communication; Paul Scriver's personal interviews with Charles Scriver 2021-08-16 and 2022-01-09).

In 1948, Charles enrolled at McGill as an undergraduate in geography with a parallel degree in comparative literature. Towards the end of completing his undergraduate education, he realized that as much as he was fascinated by geography, he did not feel he was "good enough with the math" to continue (Paul Scriver personal interview with Charles Scriver 2021-08-16); he did, nevertheless, compete the degree cum laude in 1950. Faced with the question about what to do with himself after graduating, he decided to make a single application to study medicine at McGill, "…besides," he said to his fiancée, "I might as well [apply] because I probably won't get in." To his surprise, he was admitted (Charles Scriver Memoir, 2019-10-15, personal communication).

Asked if it was the direct influence of his parents that convinced him to apply to medicine, Charles said that his parents were "very good at answering the question [about what a life in medicine would look like], but never at formulating it" …i.e., the influence to apply was

Fig. 2. L to R - Dr. Walter de Mouilpied Scriver, Dr. Jessie Marion Boyd Scriver and Dr. Charles Robert Scriver in 1955, on the day of Charles' graduated from Medical School – McGill University, Montreal, QC, Canada (Photo courtesy of Scriver family archives).

powerful, but *indirect*. Charles' later interest in the writings of Charles Darwin may have been an opportunity to muse on the question about whether it was nature or nurture that influenced his decision to pursue medicine, but it is likely fair to say that the family influence, overt or not, was strong (Charles Scriver Memoir, 2019-10-15, personal communication; Paul Scriver's personal interviews with Charles Scriver 2021-08-16 and 2022-01-09) (Fig. 2).

Throughout his studies, it was his long-time girlfriend and eventual fiancée and wife Esther Peirce (known to everyone as "Zipper") who not only encouraged and challenged him to excel in his endeavors but also completed, with distinction, her own degree from McGill University in Nursing. The daughter of another prominent Montreal physician, Dr. Carleton Peirce, Chief Radiologist at the Royal Victoria Hospital, Zipper was the powerful and positive influence that inspired Charles to succeed through the rigors of the medical program at McGill.

It was there that Charles found himself again with a fortunate educational opportunity, this time as part of a cohort that included some older students who were Canadian and American veterans of the Second World War. Some who were there on the Servicemen's Readjustment Act of 1944, the American G.I. Bill, many having seen some of the best and the worst of humanity during the war, were highly motivated in their pursuit of a medical degree. In these heady post-war years, Charles profited from the societal desire to move past the difficulties of the previous decades (Paul Scriver personal interview with Charles Scriver 2021-08-16), and he excelled in his studies, graduating with an M.D. from McGill University in 1955 cum laude (Fig. 3).

3. Training and discovery - from Montreal to Boston to London

In 1956, the year that Charles was working to complete his internship at the Royal Victoria Hospital, he and Zipper were married. Shortly following the wedding, with the help of his mentor Alan Ross, Charles was offered the opportunity to further his studies at the Children's Hospital in Boston. Zipper was offered a job as a nurse at the same institute and the two of them set off to the US together (Charles Scriver Memoir, 2019-10-15, personal communication).

In Boston, Charles' duties were as the Junior Assistant Resident in Pediatrics at the Children's Hospital, the primary pediatric hospital of the Harvard Medical School. Here he expanded his knowledge of clinical pediatrics and delved further into learning about inborn errors in metabolism.

During his residency, he was involved in the discoveries of a new disease and a very important concept of renal amino acid transport in two different patients. Both diseases happened to be Mendelian disorders of metabolism, and the learning experience would influence the direction of his career path from then forward.

Two of his Boston patients experienced hearing loss, renal anomalies, and cerebral dysfunction [24]. Since the combination of nephropathy and deafness was known to possibly be hereditary, the family was investigated, and the mother and two sisters were found to also have renal anomalies. The question was whether there could be a genetic mechanism that would explain these clinical abnormalities in a single family. Here at the beginning of his biochemical genetics career, this line of inquiry was an indication of how his future investigations would unfold. By challenging the preconceptions of what these patients' symptoms indicated and examining the evidence linking his observation to current research, Charles was able to integrate them into a deeper understanding of a likely cause for the abnormalities in his patients. This was to be a precursor to his lifelong quest to understand the core of human biology as expressed in disease and with that understanding to develop programs for patients that would ease their burden and better their lives [24].

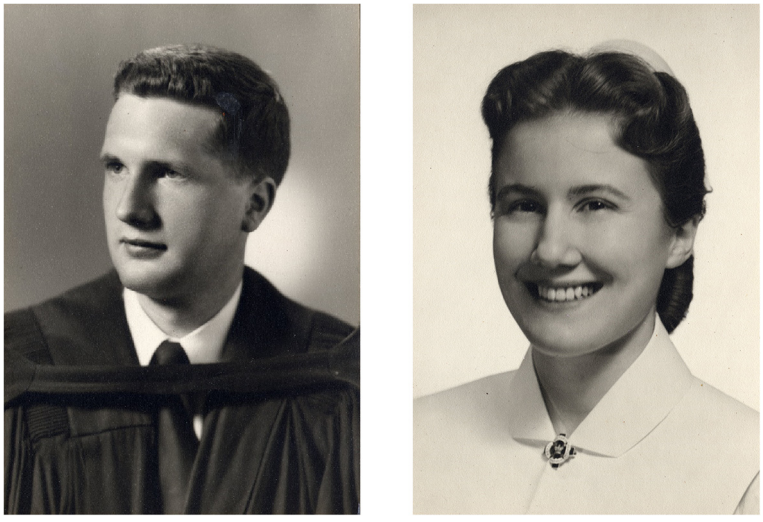

Fig. 3. A family dedicated to improving the health of others. On the left - Charles Scriver – graduating from Medical School (McGill University – Montreal, QC, Canada; 1955); on the right - Zipper Scriver – graduating from Nursing School (McGill University – Montreal, QC, Canada; 1956) (Photo courtesy of Scriver family archives).

Around this time, his McGill advisors, senior physicians Dr. Ronald Christie and Dr. John Beck as well as Dr. Alan Ross asked him what sort of a specialty in pediatrics he might pursue after Harvard. Dr. Christie suggested he'd best have a "gimmick" if he wanted to succeed and make a name for himself in the field. In response, Charles found a moment at the end of his 36-hour resident's shift to go to the medical library where he chanced upon an article about chromatography, an article which inspired him to learn about the technique and how it could be used to diagnose inborn errors in metabolism. His advisors told him that he had two options if he wished to study this new technique being used in the field of biochemistry: he should either stay in Boston and go to MIT or head to the laboratory of Charles Dent at University College, London (Paul Scriver's personal interviews with Charles Scriver 2021-08-16 and 2022-01-09). Together, Charles and Zipper chose the latter, the more adventurous option, and so in 1958, with the support of a McLaughlin Travelling Fellowship for Charles, they headed to England on the Queen Elizabeth II steamer with their new baby girl (Do-Ellen) in tow (Charles Scriver Memoir, 2019-10-15, personal communication).

It was at Dent's lab in London when Charles discovered what he really wanted to do. Although he was 29 years old with two academic degrees, a young daughter, another baby on the way and 4 years committed to the study of clinical medicine, he determined that he wanted to become a clinician-*scientist*.

At the Dent Laboratory, Charles realized that the relatively new field of amino acid chromatography would allow him to pursue some interesting avenues of investigation. He was introduced to partition column chromatography, destined to be a powerful tool for the analysis of amino acids. Harry Harris (King's College, London), Charles Dent and Alex Bearn (on sabbatical in London from Cornell University Medical College, New York) were now his mentors in human biochemical genetics; they convinced him to pursue his interests [26]. Accordingly, Charles used the chromatographic techniques to investigate one of the patients he had cared for in Boston. By analyzing the blood and urine from the patient and family, he discovered that the patient and his sisters had a specifically increased amount of proline in their plasma and, surprisingly, that their urine contained marked increases of glycine and hydroxyproline [36] as well as proline. When he saw these additional amino acids in their urine that were not elevated in their blood, he immediately recognized that this might have important implications for renal transport of the amino acids, that the increased urinary excretion of hydroxyproline and glycine could indicate shared renal transport with proline [24].

Charles said that he could recall the place and the time of day when he experienced this "sudden insight" that an excess of proline could saturate a shared transporter in the renal tubule and at the same time displace its other substrates if all three used a shared mediated transport system. For the late 1950s, this was quite novel thinking in human biology. He tested the hypothesis by infusing himself with proline. Knowing that he himself didn't have the condition, he still found that the same triad of increased amino acids appeared in his urine.[1] He recalls that "…two other hardy post-docs in the lab thought this was fun and we repeated the experiment two further times" [26]. Thus, not yet having completed his pediatric training, he discovered both a new inborn error of metabolism, hyperprolinemia, and a renal transport system that illustrated a new concept of transport. He was able to present his findings a year later at the plenary session of the American Society for Clinical Investigation and to publish them both in *Nature* [36] and the *New England Journal of Medicine* [24]. His professional life was sealed.

While in London this insight into renal transport led Charles to ask whether renal transport might be an example of epithelial transport in general and whether epithelial transport of amino acids might be genetically determined. To examine this question, he investigated the intestinal transport of amino acids in Hartnup disease, a renal transport disorder of neutral amino acids that had been discovered in the Dent laboratory several years before [1]. The Hartnup family was well known to those in the laboratory, so he was able to meet the original patients and collect urine and feces from one of the affected siblings. Upon analysis, he found that the amino acid pattern in feces was virtually identical to that in urine and markedly different from a normal control. This demonstrated that the selective impairment of membrane transport for neutral amino acids in Hartnup disease was expressed in the intestine as well as the kidney, and that, indeed, epithelial amino acid transport was genetically determined. Furthermore, his mentors had considered the Hartnup phenotype to be an inborn error of amino acid metabolism, but this discovery showed that the findings were more compatible with an inborn error of membrane *transport* involving a subset of neutral amino acids. The fact that membrane-located carriers could recognize group-specific sets of substrates was a novel idea for the time [25].

Moving forward, Charles would pursue the field of clinical medicine as a clinician-scientist with an abiding interest in human biochemical genetics, to ask the question "Why does this person have this disease now?" and to follow, the axiom: "treat not the disease, treat the patient."

4. Montreal and the deBelle laboratory

The time in London was intense, productive, and fruitful, but after two years, Zipper and Charles returned to Montreal where their roots were deep and where they would spend the rest of their lives. Now with two young children, two-year old Do-Ellen and newborn Peter, they once again boarded a steamer headed back to Montreal to fulfill Charles' commitment to being the Chief Resident in Pediatrics at the Montreal Children's Hospital. To him, the prospect of the grueling work of another residency was not alluring. He felt that there were better clinicians than he, and he wanted to continue his research. Fortunately, his supporter and mentor who was also Chair of Pediatrics at McGill, Dr. Alan Ross, recognized his talents as a researcher and supported his wish to develop a laboratory at the Montreal Children's Hospital. Dr. Ross also nominated Charles for a McGill Markle Scholarship and so for five subsequent years he was "protected" and was able to further his research and develop what would become known as the deBelle Laboratory. Charles became, as it happened, Canada's first human biochemical geneticist and his appointment at McGill with its integrated opportunities allowed him to realize his vision of "community genetics" (Fig. 4).

Charles has always credited his home city, his colleagues, and the educational institution he was fortunate to attend with his "luck" in finding the thread that he followed throughout his career. He credits the McGill University Hospital network for supporting him, and since 1961 called the Montreal Children's Hospital his "place of business"; but it was also his home. For a time, it was his home away from his family as well. As many researchers know, meeting the demands of home and work-life make a difficult balancing act. Perhaps it is with another "lucky" stroke of genius then that Charles found a way to integrate both his family life and his work-life.

From its very beginning, the Charles Scriver Biochemical Genetics Unit and deBelle Laboratory at the Montreal Children's Hospital were buzzing with the activities of an ever-expanding team of gifted trainees and staff. Named for its founder and funder, this was no ordinary environment, and Charles, the director, was no ordinary leader. This facility was dedicated to clinical care and research involving the diagnosis and treatment of inborn errors of metabolic diseases.

Starting in 1960, technicians, fellow researchers, graduate students and staff were invited to share in the life of the growing Scriver family (now expanded to include Julie, born in 1960 and the youngest, Paul,

[1] In a personal communication of Paul Scriver with his mother, Zipper Scriver vividly recalled when Charles arrived at her bedside in the maternity ward in London while she was waiting to give birth to their second child. He excitedly told her that he had just injected himself with proline to 'see what might happen'.

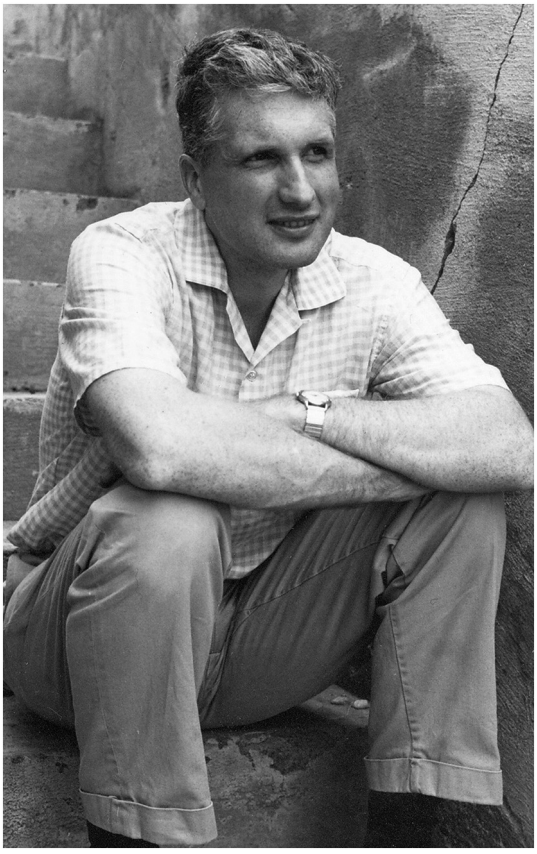

Fig. 4. Charles, Apple Tree Point, St. Albans, Vermont, USA; 1960, (Photo courtesy of Scriver family archives).

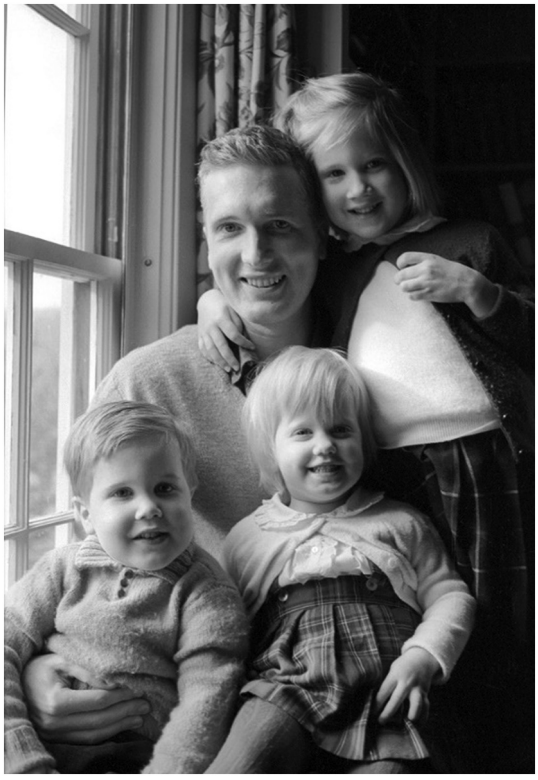

Fig. 5. Charles with the children in their home living room, Montreal, QC, Canada. L to R: Peter, Charles, Julie and Do-Ellen. Circa 1962, before Paul was born. (Photo courtesy of Scriver family archives).

born in 1963). Significant holidays were often the scene of parties hosted at the Scriver family home in Montreal West. The Scriver children share many memories of beautiful affairs hosted by Zipper that began with graduate students playing with toddlers on the living room floor, and later – as the food and drink turned into dessert and coffee, and younger children were hustled off to bed – 'devolving' into discussions between colleagues on the couch and draped around the living room floor about inborn errors in metabolism. This convivial, inclusive atmosphere was part of the culture of the young deBelle Laboratory. As the young families of the lab staff grew, weekend picnics on Mount Royal (at the heart of Montreal) would be a mix of playing children, cheese, wine, and discussions about research into the new field of genetics (Fig. 5, 6 and 7).

In 1965, the new lab found a toehold above the boiler room, and below the cafeteria in the strapped-for-space Montreal Children's Hospital. With an awkward, L-shaped floor plan, the lab had very little space and only a few windows – each with a view of the hospital's red-brick heating and incinerator chimney. Now a young father with a family of four and a burgeoning career as a clinician-scientist, Charles would often find that he needed to check in on an experiment at the lab on a Saturday morning. His attempt to balance home and work-life often meant that these Saturday morning visits were shared by one or other of his young and curious children. Possibly, this was a way of remaining connected to his family, but it also gave Zipper some respite and as a collateral effect, it did engage his children in the excitement of his work. From the perspective of the Scriver children, the lab was a place of wonder, full of mysterious instruments, tolerant adults and lab rats; it was also the home for innovative ideas in the development of new methods to screen, counsel and treat a variety of Mendelian disorders (Fig. 8).

This description of the connections between the research, family and specifically the lives of the children around the lab mentioned here, is not so much for the purpose of nostalgia, but as an example of the spirit of inclusion and rootedness that has been a feature of the work of the deBelle team and of Charles' career at large. The lives of children and how their health impacts the communities they come from was a driving force in the series of initiatives originating from the deBelle team with Charles in the lead. It is perhaps why he and his collaborators created the newborn screening program for early diagnosis and treatment of genetic diseases. Working with extraordinary colleagues like Dr. F. Clarke Fraser, Carol Clow and Terry Reade, and later with Drs Myriam Charbonneau, Claude Laberge, Jean Dussault, Bernard Lemieux and

Fig. 6. deBelle laboratory Christmas party, Scriver home, Montreal, QC, Canada; 1968 (Photo courtesy of Scriver family archives).

Fig. 7. Family gathering, with all the children as adults at the Scriver home, Montreal, QC, Canada; early 2000s. Front row Left to Right – daughters - Julie and Do-Ellen, and daughter-in-law Nicola. Back row Left to Right - Charles, Zipper, son - Paul, granddaughters - Julia and Claire, son - Peter (Photo courtesy of Scriver family archives).

Serge Melançon to establish the Quebec Network of Genetic Medicine [3,34]. His work encompassed multiple aspects of medical genetics - screening, diagnosis, counseling, and treatment - all integrated and derived from research; a complete understanding of genetics as it applied to the human.

4.1. Solving the riddle of vitamin D-deficiency rickets in Canada

An early example of community medicine, in 1970, Charles and the deBelle laboratory teamed up with Arnold Steinberg – a member of the board of governors of the Montreal Children's Hospital, and the CFO of the Steinberg grocery chain. The connection to Steinberg came out of an interest Charles and the deBelle team had in phosphate transport, which, in turn, led to an investigation of infantile rickets. The coordinated effort between Steinberg Groceries and the Montreal Children's Hospital would soon eradicate rickets in the province of Quebec.

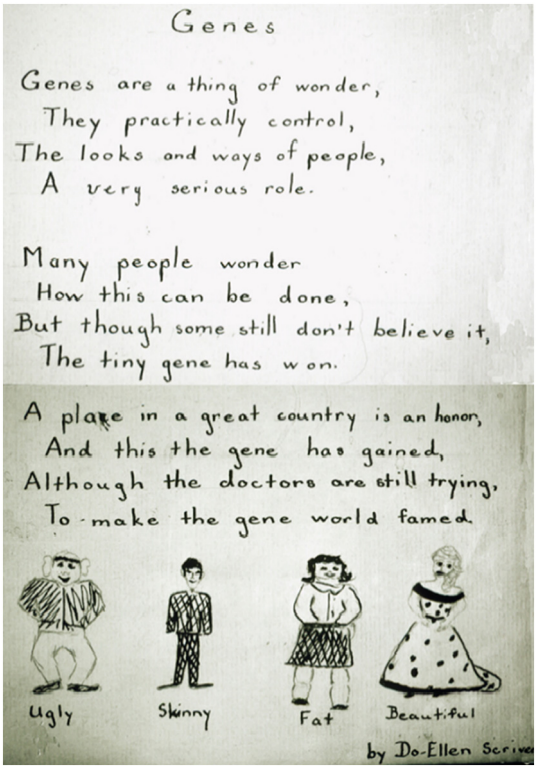

Fig. 8. Poem and artwork by a teenage Do-Ellen Scriver.

At the time, Quebec was experiencing an annual quasi-epidemic related to vitamin D deficiency, especially prevalent in poorer urban populations. By means of a project in epidemiology, Charles solved the riddle of why vitamin D deficiency existed in the province. He observed that the problem occurred almost exclusively in poorer infants whose sole source of nutrition was bottled dairy milk; the milk at the time was not fortified with vitamin D. Meanwhile rickets associated with vitamin D deficiency was absent in infants from more affluent families where formula fortified with vitamin D was used to feed their babies. He also noted that when the poorer infants began receiving nutrition that contained vitamin D, their hyperaminoaciduria and rickets disappeared.

Charles worked with Arnold Steinberg to leverage the power of Steinberg's large grocery chain and demand that their milk suppliers simply add Vitamin D to their product. With the support of the Montreal Children's Hospital, he then campaigned for the addition of Vitamin D to all milk, a bold act that effectively eliminated childhood Vitamin D deficient rickets from the Quebec population [43].

The decline in vitamin D-deficiency rickets spotlighted the new cases of childhood rickets that were inherited. Another form of rickets discovered by Charles and his colleagues revealed that these patients all had various inborn errors of calcium or phosphate metabolism. In this case, his attention was drawn to this deficit because hyperaminoaciduria was known to occur in some but not all affected infants and he asked the question: why not all affected infants? Their study led to the discovery that the deficiency progressed through three stages and that it was reactive hyperparathyroidism appearing in the second or intermediate stage which accounted for the hyperaminoaciduria as well as phosphaturia [9]. His laboratory then found that hypophosphatemic rickets associated with renal hyperglycinuria and glycosuria could be dramatically improved with dietary phosphate supplementation [31]. Again, his original interest in renal transport bore fruit by establishing a link to hypophosphatemia.

4.2. The extraordinary Scriver collaborations

Charles' research involved the discovery and elucidation of several “new” inborn errors of metabolism. This work required him to both

shepherd and to be guided by the exceptional minds of his ever-growing community at McGill and beyond. One amazing example was the collaborative relationship he shared with his long-time colleague and friend, the late Orval Mamer: the professor heading McGill's on-campus Mass Spectrometry Unit in the Department of Medicine. Charles' work was always state-of-the-art, and it was thanks to the ingenious abilities of clinical and scientific partners like Orval who made it possible. Throughout the years, Orval's lab developed a multitude of assays that teased out metabolites otherwise unidentified or detectable by commonly used methods. Together, and over four decades, they published dozens of pivotal articles.

Supported by Orval's innovations, Charles organically immersed himself in human biochemical genetics and in the investigation of several new inborn errors of amino acid metabolism. Charles' earlier study of vitamin B6 deficiency later led to an interest in the possibility that the clinical findings could be due to impairment of vitamin binding to relevant apoenzymes producing vitamin dependency [32]. Coenzyme binding to apoenzymes quickly became a major interest of his.

Vitamin cofactor responsiveness appeared to have great significance in the treatment of metabolic disease. He and his colleagues investigated a subset of vitamin (cofactor)-responsive hereditary disorders of amino acid metabolism that involve mutations affecting binding kinetics of the coenzyme or a chaperone-like effect in the response to pharmacological doses of the agent [26].

They were also involved in the development of new methods to screen, counsel and treat a variety of Mendelian disorders, such as phenylketonuria (PKU), Tay-Sachs disease and Thalassemia in individuals, families, and communities. Charles and his team developed high school screening programs run by genetic counselors, administrative technicians and coordinators. These programs were ground-breaking at the time, with little technical help available to resolve the problems as they arose [26].

A multitude of centers around the world benefited from these activities, given that many of Charles' mentees went on to launch and run their own programs around the globe. With hindsight, it was truly the beginning of "community genetics" (which moved biochemical genetics along). It is therefore not surprising that their involvement in such "translational knowledge" would shift his main focus onto therapies and genetic disease, engaging Charles in a meta-analysis of the modes, progress, and efficacy of treatments.

On a national level, Charles contributed and influenced the Canadian medical research efforts and growth tremendously. One of his notable achievements was the generation of the McGill Group in Medical Genetics, which he established and guided with Dr. Clarke Fraser. Formed in 1972 and supported by the Medical Research Council and successor Canadian Institutes for Health Research until September 2009, it was the longest active biomedical research group in the history of Canada [2]. While a focus on "medical genetics" loosely defined the Group for the duration of its tenure, its 14 members were specialists in various areas of biomedicine, including teratology, cytogenetics, biochemistry, population genetics, endocrinology, and molecular biology — fields of study that converged and diverged at different times from the 1960s to 2009. During its 37-year history, Group members published over 1400 articles that helped define and develop a still-inchoate field of research. Most articles were collaborative works co-authored by Group members and associated researchers. The Group's success and longevity was augmented by proficient and strategic grant writing, which provided the members steady and expansive support for basic and clinical research [2].

Between 1989 and 2007, Charles was also part of a novel and innovative government-industry funded and academic-industry collaborative program headed by the Network of Centres of Excellence - Canadian Genetic Diseases Network. Here, Charles was able to realize his vision of multidisciplinary academic-industrial partnerships which would eventually translate into a cutting-edge FDA approved therapy for PKU which both started and was developed in his own laboratory. The success of this strategy has inspired and serves as model for the development of similar global programs to this day.

4.3. Communication and teaching

On a separate level, Charles immersed himself (and many of his mentees) into teaching both his immediate team as well as the biochemical genetics community at large. Always patient, he never had a harsh word for anyone who was interested in his communications, and often peppered his lectures with classic literature and current events to keep the attention of his audience. Chanced upon in hospitals throughout the country, his favorite co-lecturer and colleague Mr. George Kritikos (also a Thalassemia patient), to this day continues to be thanked by Charles' students for the famous and highly animated lectures that incorporated the patient. It was Charles' initiative to bring in patients to teach the students about the true day-to-day experiences of their lives.

Charles also sat on multiple editorial boards and was acknowledged repeatedly by receiving numerous accolades for the quality of his written communication. Among the many of his writings was an early monograph *Amino Acid Metabolism and its Disorders,* which he coauthored with his careerlong friend and colleague, the recently deceased pioneering geneticist, Leon Rosenberg [35]. Published in 1973, this book has served as an educational text for geneticists in training for five decades. Later, in assuming editorship of the paramount reference for biochemical genetics "*The Metabolic Basis of Inherited Disease*" (MBID), in the 1980s, he greatly enlarged its scope into the "*The Metabolic and Molecular Bases of Inherited Disease*" (MMBID), which, ahead of its time in 2001, went virtual as "*The Online Metabolic and Molecular Bases of Inherited Disease*" (OMMBID) [28]. The volumes included a comprehensive basic and clinical examination of virtually all known genetic diseases in which there are metabolic implications. Scriver's idea was to examine the range of human biological diversity as expressed in disease states, a concept learned from Drs. Harry Harris, Charles Dent and Alex Bearn during his time in London, and later from Dr. Barton Childs in the United States. In this, he has been eminently successful, using Mendel, Darwin and especially Archibald Garrod as his guides. Charles saw inborn errors of metabolism and transport as "extreme examples of a pervasive human biochemical individuality" and what this implied for treatment and prevention [34]. From the very beginning of his career, he never wavered from the idea that human biology required a full understanding of its pathological deviations, and that the understanding of these deviations needed to be integrated into treatment regimens designed to allow the patients to lead as normal a life as possible.

Archibald Garrod, who famously developed the concept of the inborn error of metabolism (1909) appeared to have had an especially great influence on Charles. In fact, Charles, along with Barton Childs, would later edit a reissue of Garrod's second book *The Inborn Factors in Disease* [29]. In this book, originally published in 1931, Garrod advanced the thesis that inherited traits expressed as chemical individuality answered the question "Why does this patient have this disease now?" [29]. The preface by Scriver and Childs brilliantly explored this question; the question that also consumed Charles' entire professional life. In effect, this was and remains the Scriverian philosophy of medical genetics.

4.4. On to phenylketonuria

Towards the latter years of his career, Charles' research attention shifted almost entirely to phenylketonuria. It was not a new endeavor; Charles' interest in PKU dated back to the beginning of his career. Over the years, his work, along with that of his international colleagues, had established PKU as the epitome of biochemical genetics [30]. This "old" and relatively common inborn error of metabolism had become a prototype to study the development and effective use of various

methods of genetic screening in newborn populations as well as a model to test new therapeutic approaches for "orphan" diseases.

Since his Fellowship with Charles Dent at the end of the 1950s, Charles, having acquired skills in chromatography for inborn errors of metabolism detection, had been applying them to better investigate his patients. He often spoke of this original work and encouraged the use of related techniques, in the lab's PKU research.

Charles made it a point to learn about all innovations in the field. In his ceaseless effort to remain cutting edge, this business-minded academic leader furnished his team with all that was necessary to keep their work both competitive and transformative. As a result, the PKU story in his ecosystem started early, and undoubtedly far earlier than his first disease-related publication indicates.

In 1968, with less than a decade of medical practice behind him, Charles published his first PKU paper with colleagues Katz and Clow; a letter in the Canadian Medical Association Journal describing studies in Eastern Canada that clearly established the effectiveness of the dietary intervention, started before the age of 2 months [33]. This was a definitive answer to the belief among some influential investigators that the diet was not only ineffective in preventing the developmental and intellectual deficits in PKU but might even be harmful. The following year, Scriver and Clow again collaborated in the development of a thin-layer chromatographic analysis that expanded newborn screening to metabolic disorders beyond PKU. Scriver and Clow led the way in Canada in both PKU and newborn screening.

The relationship between Charles and Carol Clow was both unusual and exceptionally productive. They knew of one another through family connections during their high school years but did not keep in touch until they were reintroduced much later under challenging circumstances. Carol was working at the Montreal Children's Hospital in the early 1960s and was known to Charles' mother, "Dr. Jessie". Dr. Jessie had learned of the tragedy around the death of Carol's child, a victim of sudden infant death syndrome, what was then known simply as *crib death.* She told Charles: "Mrs. Clow will teach you about the dying child". At that point, Charles, under his mother's advice to find Carol a meaningful distraction, employed her to run a large pilot study for genetic screening in Quebec. Carol did an exceptional job with the program. Her unique and gentle follow-up approach with patients and their families, naturally drawing empathy from her own experiences, became teaching moments for the clinical team at the Montreal Children's Hospital Biochemical Genetics Unit; it generated the prototype for a province-wide genetic counseling program, the first in Canada. Scriver did his part through education, promoting the program and applying for grants. In his words, the success of the program was rooted in the fact that he built support from the bottom up. He began with his local community, with individuals who knew him, rather than with lobbying and legislation on a provincial scale [7]. Thus, the Scriver – Clow duo, through their initial Phenylketonuria program, became the architects of genetic screening and counseling in Canada [5,6]. Their contributions were large and tremendously impactful, and so with a strong recommendation from Charles, Carol, without even a high school diploma, became a faculty member, and associate professor, at McGill University.

The late 60s and 70s afforded multiple pivotal contributions, including a *Nature* paper discussing the heterogeneity in Genetic Control of Phenylalanine Metabolism [20]. This was based on the pioneering work of David Rosenblatt who looked at phenylalanine-to-tyrosine ratios distinguishing PKU subgroups. Scriver and Clow then communicated the two decades of experience gathered from their genetic screening and counseling network in their classic two part review article for the *New England Journal of Medicine*, describing the central role of PKU in biochemical genetics as well as the related unsolved problems [30].

By this time, the lab had moved to the 7th floor of the A wing. Far more spacious grounds for his growing research team, Charles' space seemed to be mysteriously shrinking. The irony was not lost on his guests. One of us (HLL), during a visit to deliver Grand Rounds at the Montreal Children's Hospital, commented that "the size of the office appeared to be inversely proportional to the person's contributions".[2]

In these quarters, Charles could often be found tucked away in this tiny office; the somewhat hard to get to room with his favorite view of the distant Vermont Green Mountains where the six member Scriver family had built their own cottage. Stacks of manuscripts piled nearing shoulder height, on a never-ending series of topics, always surrounded him.

The 1980s brought new excitement to the field when the *Phenylalanine Hydroxylase (PAH)* gene was cloned by Savio Woo's team at Baylor [14]. The *PAH* gene encodes the PAH enzyme (EC 1.14.16.1), which hydroxylates phenylalanine to tyrosine, the rate-limiting step in phenylalanine catabolism impacted in most PKU cases. Thanks to this discovery, a new era of research was underway, and Charles, with a fortified team, was about to embark on another three decades of contribution [26]. Charles, in an historical account, describes his involvement during these years as follows:

1. Newborn screening
2. An online locus-specific mutation database
3. Locus heterogeneity and malignant PKU
4. Proteomics – the *in vitro* expression analysis of missense alleles
5. The generation of a National Food Distribution Center
6. Allele-specific tetrahydrobiopterin (BH_4) therapy – a chaperone-like effect
7. Enzyme substitution therapy in PKU

Based on his initial Geography degree, Charles came to genetics with a more global perspective on stratification of populations. He had a keen interest in studying population genetics and the geographic diversity of alleles at particular loci in human populations. This, along with the pivotal work of Carol Clow, had led to the organization of the Quebec Network of Genetic Medicine.

The Network soon became involved in population genetics, with special interest in this unique and isolated French-speaking Quebec cohort that was bound to be different from the surrounding Ontario and Vermont communities and beyond. On newborn screening, Charles wrote: "screening in worldwide populations provided opportunities to sample *PAH* mutations identified through patients with hyperphenylalaninemia. Evidence of *allelic stratification in human populations* emerged with the paradigm that 'the history of the population is the history of the allele'. We studied this paradigm in detail and became population-geneticists - of a sort" [26].

The locus-specific mutation database for *Phenylalanine Hydroxylase* was purposefully interwoven into the efforts cited above. The curators for the database were many but began with the web engineering expertise and creativity of Liem Hoang, and continued with the work of David Cote [37], Manyphong Phommarinh, and later to be completed by Jacques Mao. On the matter of databases, Charles wrote: "We formed an international consortium and created an *online locus-specific phenylalanine hydroxylase mutation PAHdb database* (housed at the McGill University Montreal Children's Hospital Research Institute), which soon became a prototype for locus specific databases (LSDBs); it is linked to the newly created Human Variome Project. *PAHdb* has also taken us into another world and we became involved in *bioinformatics* and databases" [26]. In a conversation shared with the historian Nathanial Comfort [27], Charles referenced how this project not only informed scientists and clinicians working around the globe but also became a training opportunity at McGill. Peter Nowacki, one of Charles' later students, expressed an interest in computer science and databases. Charles took this request to the university. Peter was the first student at McGill

[2] As Charles' career-long friend and collaborator, Harvey Levy, in all his modesty, had failed to recognize that he himself was suffering the same fate across the border at the Harvard Boston Children's Hospital. *(CNS)*

who received a joint Master's degree in computer science and biology. Together with international colleagues, Charles and Peter helped combine bioinformatics and population genetics [27].

Most phenotypes don't have the same genotype. In reference to the Locus heterogeneity and malignant PKU, Charles wrote: "It was known that the phenylalanine hydroxylase reaction required the catalytic cofactor tetrahydrobiopterin (BH_4). The scene was set for the discovery of patients reflecting *locus heterogeneity* (malignant PKU) rather than allelic heterogeneity (PKU). The locus heterogeneity reflects genes and enzymes involved in synthesis and recycling of BH_4. If one could monitor the newborn for evidence of disorders in synthesis or recycling of cofactor, one could identify the affected patient early. This is important because the correct treatment requires replacement of cofactor by pharmacological means; the low phenylalanine diet is not sufficient. Our screening program in Quebec was the first in the world to address this issue systematically" [26].

With the database growing, and the mechanisms of action/inaction studies swiftly expanding the understanding of genotype-phenotype correlations, Charles became interested in expression analysis of the *PAH* variants. On introducing the world of Proteomics into the deBelle laboratory, Charles wrote: "Our LSDB showed that 63% of *PAH* alleles are missense alleles. By means of *in vitro expression analysis*, we were among the first to show that missense alleles cause *misfolding of nascent protein* with subsequent aggregation and loss to the proteasome [41]. The paradigm of misfolding proteins due to allelic variation has become a general one in genetics. We had penetrated a little way into the proteomic world" [26]. This work conducted by Waters generated a series of publications on mutation analyses and misfolding of proteins, including the pivotal paper addressing genotype to phenotype and structure to function [42]. The knowledge gained had a further practical impact, as it helped identify potential BH_4-responsive patients for the upcoming KUVAN® treatment under development by BioMarin at the time.

Charles' forever mantra "who do we serve" was most apparent in his efforts to bring the very best, and ease of care to his patients. As their strongest advocate, Charles had every intention to find the most advanced treatment, and to make it both available and affordable. On the subject of dietary therapy, Charles wrote: "Whereas *treatment of PKU* was a highly significant development in the field of human, medical and biochemical genetics, treatment was neither easy nor pleasant for the patient. We helped to improve the organoleptic properties of the low phenylalanine diet. We also learned that delivery of diet products to patients could be a real problem. In response, we created the National Food Distribution Center as a purchasing and distribution resource for Canada, approved by the Federal and provincial governments. We became food merchants of sorts." [4,26].

During the final years of Charles' tenure at McGill, his focus shifted entirely to alternative treatment modalities for PKU. There were two innovative options that showed the best promise: (a) Chaperone therapy with BH_4 (the misfolding proteins project by Waters had sparked his curiosity regarding the potential use of the cofactor (BH_4) which regulated the enzyme phenylalanine hydroxylase, for the treatment of milder forms of hyperphenylalaninemia), and (b) Enzyme substitution therapy (thanks to the transforming development of cloning technology, the treatment of all forms of hyperphenylalaninemia would finally be possible using a foreign enzyme called phenylalanine ammonia lyase). Charles had been waiting for years to set this second project in motion.

The chaperone-like effect of BH_4 on specific mutations was already making headlines following a Japanese publication [13] on tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. It was also apparent from the studies by Waters that large doses of BH_4 would likely help more than the formerly identified small subpopulation of patients with malignant PKU [42]. Charles wrote: "Whereas a few rare patients will have inborn errors of BH_4 metabolism, others far more numerous respond to pharmacological doses of the 6R-BH_4 isomer, even though they do not have a primary disorder of cofactor homeostasis. In a collaborative study with colleagues at the Scripps Institute, benefits from cofactor was shown to reflect *a chaperone-like effect* in some patients; the response is allele-specific [8]. Here was an early demonstration of patient – and allele-specific therapy in a genetic disease. This work created a new demand for BH_4 being met by a corporate response (BioMarin, CA)" [26].

In a personal message, the Chief Medical Officer at BioMarin at that time, Dr. Emil Kakkis, recently reflected on how this story played out for his company as they took this chaperone therapy from idea to bedside. He said:

> *"The best story was around BH_4. You (Charles) told me about it in a taxi and how it was really starting to have great effects on a number of patients, and how people were getting excited about it. But the fear was that no one would finish it, no one would develop it; you asked us to look at it and take it. We did do it. I looked at it; I saw the value that you were talking about and was able to convince BioMarin at the time to work on it, figure out how to make a stable version of it, and then make it in large scale. We got it done, we got it approved. What an amazing story."*

As BioMarin generated a world supply of the chaperone, sapropterin dihydrochloride (KUVAN®), the contribution by the deBelle lab, in collaboration with Raymond Stevens' Lab at the Scripps Institute expanded. The duo, Christineh Sarkissian (Montreal) and Alejandra Gámez (San Diego), who were already working together on the enzyme substitution therapy project, conducted phenotype-genotype response analyses on the data generated by the sapropterin dihydrochloride clinical trials [21].

With KUVAN®'s approval, Charles' final research focus was on enzyme substitution therapy for the treatment of PKU. The journey in the deBelle lab had started more than a decade prior and was one that was likely the longest and certainly involved the most diverse teams of scientists working together. This therapy promised to treat all forms of hyperphenylalaninemia.

The passage of phenylalanine ammonia lyase (PAL; EC 4.3.1.24) from plant enzyme to enzyme substitution therapy for PKU had begun long before the deBelle laboratory took it on. Between the 1950s and 60s, plant physiologists had learned that the enzyme deaminated phenylalanine to trans-cinnamic acid and ammonia [16,17]. This led to the subsequent consideration of PAL as a treatment for PKU. It was attempted as enteral therapy but showed only minimal efficacy [12].

Therapy for PKU required economically viable quantities of enzyme which could only be obtained when cloning technology became available [11,19]. In addition, PKU and hyperphenylalaninemic (HPA) orthologous animal models were necessary for preclinical proof of concept (PoC) studies [18,38]. It was therefore the molecular biology era, which made the undertaking of this drug development venture a possibility, and also Charles' prepared mind that was able to engage the required team to complete the journey.

In 1994, Christineh Sarkissian joined the deBelle laboratory as a graduate student, marking a critical event in the development of PAL as a treatment for PKU. Note that this was also the year before Charles officially retired from his clinical duties. From 1994 to 2000, Sarkissian studied at McGill as part of the Network of Centres of Excellence - Canadian Genetic Diseases Network collaborative program with IBEX Technologies (Montreal, QC, Canada). IBEX, at the time, was being led by MIT graduate Dr. Robert Heft. Together with scientists at IBEX Technologies, an economically feasible supply of the PAL enzyme was generated, and PoC for both enterally and parenterally administered recombinant PAL formulations in the PKU mouse were established [15,23]. Charles wrote: "We have been investigating *enzyme substitution therapy* in PKU, using recombinant phenylalanine ammonia lyase (PAL) from yeast [23]. We obtained proof-of-principle (pharmacological and physiological) with PAL substitution in an orthologous mouse model of PKU. This again led to collaboration with the corporate world" [26].

Fig. 9. Zipper and Charles in Adelaide, Australia (circa 2014). (Photo courtesy of son Dr. Peter Scriver).

In 2001, BioMarin Pharmaceutical Inc., Novato, California, USA, under the leadership of Dr. Emil Kakkis, acquired the PAL project from IBEX. Sarkissian began to work on generating further PoC with this young Californian company interested in developing a parenteral PAL formulation. Seeking ways to mask immunity, Dr. Raymond Stevens and his postdocs Alejandra Gámez and Lin Wang at The Scripps Research Institute in La Jolla, California joined the program. Their team applied further genetic and chemical modification, attaching polyethylene glycol (PEG) molecules to PAL, to improve the protein's characteristics.

The search for an appropriate formulation ended in 2007 [10,22,40]. The preclinical part of the program involving the McGill and Scripps Research Institute teams was over and the final PEGylated PAL product was on route into the clinic under BioMarin's sponsorship. It was approved by the FDA in 2018 under the brand name "Palynziq®."

The academic-industrial partnership engaged throughout this process was key to the successful pursuit of this project. Everyone brought something very important to the table and together this truly unusual setting for academic training and industrial collaboration resulted in an historic outcome. It wasn't a matter of chance, but fortune lay in the fact that someone as insightful and influential as Charles was present to maintain the momentum as well as to generate the type of collegial sharing that was required to keep all cohorts fighting equally as hard and together to complete the project. Of course, Robert Heft, Raymond Stevens and Emil Kakkis, exceptional leaders in their own right, also saw the value of retaining collaborations. Each element was key to the successful outcome, and this multidisciplinary, academic-industrial approach was what drove its final victory, quickly becoming a standard model for more recent drug development efforts (Fig. 9).

5. In closing

From the very beginning of his professional career, Charles Scriver envisioned a much broader view of genetics than simply isolated laboratory research. A pioneering geneticist, Charles intended the products of his research to be relevant not only to those with rare genetic disease but also to populations, which he termed "community genetics". A Renaissance man whose vision stood the test of time, he never veered from this course. In his unwavering focus, he taught so many of us so much and essentially revolutionized what is meant by human biochemical genetics today. As such, those of us who tried to follow in his footsteps and those entering into the field of biochemical genetics now, who may not know of his work, owe Charles Scriver an enormous debt of gratitude.

Known to his immediate team as someone who eliminated barriers and changed the rules, Charles waited for no one, dodged all obstacles, and reached out to all higher authorities required to generate the best of care for his patients. In these efforts he always answered his own musings summarized in the following three questions: Who do we serve? How do we serve? and Why do we serve?

Meanwhile, though he understood his mission perfectly, he never failed to acknowledge the fact that he couldn't maneuver the system without the help of his colleagues, the very backbone that catapulted his career and contributions. On the topic, Charles wrote: "'We' is the appropriate word because it refers to the extraordinary patients, colleagues, graduate students, and post-doctoral fellows who have populated the place of business these many years; the ones whose names are visible in the papers and remembered in my mind … If I could send a message, it would be to highlight: the influence and importance of mentors; the joy emanating from creative compatible colleagues; the need to be protected with time to think; the need for good space and stable funding" [26]. Accordingly, perhaps the most important qualities that Charles embodied were his organic ability to effectively lead enthusiastic and otherwise vastly different personalities, and his eternal gratitude for being able to do so.

Charles knew that his service was to more than his patients. He was managing a team and they needed as much care and respect to be able to perform optimally. The ecosystem that he generated at the deBelle laboratory was collegial, with all members learning very quickly to adopt his attitude. With the leader setting the tone, everyone treated each other like family, the group being respectful and kind to one another; Charles would have tolerated no less. To this day, so many of his former team members remember their time with him as Camelot. His international colleagues couldn't agree more (personal communication). As such, Charles' leadership modeled the ideal manner to inspire and extract the very best of innovation and contribution from his colleagues; a method that has now spread to his next generation and is continuing to make waves.

During his years of service, Charles was decorated with 7 honorary doctoral degrees from international institutions and 40 prestigious awards globally. He also generated over 700 publications and was part of numerous editorial boards (from advisor to chief) for journals and books.[3] He was appointed a member of the Order of Canada and later advanced to the highest level of the Order, a Companion of the Order of Canada, the Canadian equivalents of knighthood.[4] He was inducted into the Canadian Medical Hall of Fame. He had countless academic appointments and society memberships, and perhaps the most important recognition of all, endowments and gifts of scholarship from McGill University, for the up-and-coming Canadian clinician-scientists, honoring the generations of contribution by the Scriver family.

Nathanial Comfort, in his scientific biography on Charles Scriver wrote: "Biography based on face-to-face interviews will, for a given author, have a different character than one based entirely on documents" [7]. The above represents a brief summary of a similar sort where the experiences shared were based on extended and privileged face-to-face interactions between the authors and their mentor. The present group of authors are comprised of: (CNS) Charles' very last graduate student, mentee, and later colleague; (PPS) his younger son; (LP) his career-long administrative right hand; and (HLL) his cherished Harvard University friend and collaborator. Between the four of us, at least one of us experienced/journeyed through the events described above, the events that generated the volumes of contribution which will forever seem impossible for one individual to deliver.

[3] Note that these numbers are estimates, because over a decade following his full retirement they continue to grow.

[4] https://en.wikipedia.org/wiki/Category:Companions_of_the_Order_of_Canada#:~:text=Companions%20of%20the%20Order%20of%20Canada%2C%20the%20highest%20level%20of,Companions%20at%20any%20given%20time.

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