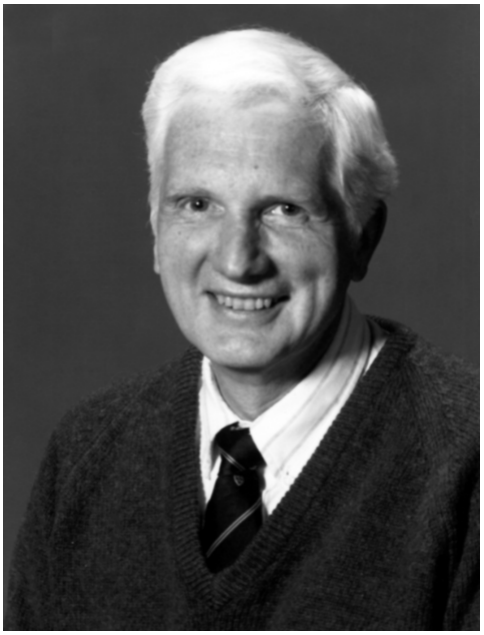
Charles Scriver



Personal Details

Name	Charles Scriver
Dates	Born 07/11/1930
Place of Birth	Canada (Montreal)
Main work places	Montreal
Principal field of work	Metabolic genetics
Short biography	See below

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
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Edited transcript available	See below

Personal Scientific Records

Significant Record set exists
Records catalogued
Permanent place of archive
Summary of archive

Biography

Charles R. Scriver was born Nov. 7th, 1930 in Montreal, Canada where he pursued his education at home, at Lower Canada College, and at McGill University (B.A. 1951; MDCM 1955). His career as a clinician scientist originated in encounters during his clinical training at McGill and Harvard (1955-1958); and also from exposure to research as a McLaughlin Travelling Fellow (1958-1960) in London, England with Charles Dent and Harry Harris. He was then appointed as a Markle Foundation Scholar (1961-66) at McGill where he established the deBelle Laboratory in Human Biochemical Genetics at the McGill University - Montreal Children's Hospital Research Institute, where he worked with a large array of talented colleagues and students until retirement in 2009. His work, which involved him in inborn errors of metabolism, genetic screening, community genetics, aspects of population genetics and bioinformatics among other fields, resulted in many publications and recognition both civic and scientific. His wife and he met in 1947. They have four children and seven grandchildren

INTERVIEW WITH DR CHARLES SCRIVER, 25TH OCTOBER, 2005

PSH. It's Tuesday 25th October 2005 and I'm speaking with Dr Charles Scriver at the ASHG meeting in Salt Lake City, Utah. To start right at the beginning, when and where were you actually born?

CS. I was born in Montreal on November 7, 1930.

PSH. And did you grow up all your early life in Montreal?

CS. I grew up and was educated and lived in Montreal until I graduated from medicine following graduating in arts, majoring in geography and literature. I graduated in medicine in 1955. I did two years of clinical training in Montreal and then took the obvious step and went somewhere else. Went to Harvard for one year and encountered some important chance events there and then I was encouraged to do something else if I wanted to be on the faculty of McGill and that led to how I got to be in London with Charles Dent and Harry Harris.

PSH. If I go back a little bit and ask was there any kind of medical or scientific influence from your family background?

CS. Absolutely. My father was a physician who also had a huge cultural interest and my mother was a physician. She graduated from a class of medicine in 1922 at McGill, the first class that tolerated the presence of women and because the selection process was so high on women the five women in the class ended up in the top 10% of a class of one hundred.

PSH. So apart from what you might call family background were there any things that specifically influenced you to go into medicine?

CS. I don't think so, other than the fact that both of them clearly loved what they did. They both had an interest in enquiry and what we would call clinical science today. My father had been a Rockefeller scholar and had an interest in kidney disease. But the time for him was wrong to pursue that. The emphasis was on pulmonary disease at McGill so there wasn't the door to go through. My mother actually published a famous paper at the end of the twenties where she looked at Sickle Cell phenomenon and my way of presenting it is, she looked down the microscope from a child who was in a sickle cell crisis and noticed that the cells were sickling as she looked down the microscope and she said, "I wonder why that is?" And by chance the Van Slyke apparatus had arrived at McGill and with a colleague they measured the oxygen tension in the sample and plotted oxygen tension versus sickling percent and that paper is still occasionally cited. There was an in Vivo experiment, the high technology that was involved was, she put a rubber band around her finger to change the oxygen tension and those were the samples and then she did one other thing which was to prove that babies would not only not die but they would thrive and grow by eating bananas. It is hard to believe that in the late twenties bananas weren't a food for infants. But the bad side of that story is that the United Fruit Company of America paid for the study and today that would probably be unacceptable.

PSH. When you were doing your medical training and soon after you had qualified had you already thought of metabolic disease as an area?

CS. No.

PSH. . . . or did that happen when you got to London?

CS. No. What I got from my parents was the love of, not just information but the use of the information to create a body of knowledge, and they were always interested in what could you do with the facts that you've got. As I put it, their life was largely now dedicated to an enquiry that would be an inch deep but a mile wide, which was what clinical practice was, although they both specialised; my father in metabolic disease of the day and my mother in paediatrics. And my father was interested in the relationship between metabolism, as it was talked about in the fifties, and homeostasis was something that he was aware of, and so there was a climate of interest and support in this area but nothing specific.

When I went through medical school, I was not the greatest student in biochemistry, but I had taken some biology in the undergraduate years and I was exposed to an extraordinary man John Berrill, who was a member of the Royal Society and who talked about the mystery and wonder of biology and growth and development and I guess that had a subtle background effect. But what I found when I graduated and was actually an intern and then a resident was that what I really wanted to know was "why this person had this disease now". I was more interested in that than just putting a label on the disease and I was also interested in "how does this disease process come about", so there was something percolating that was a little different.

And because it was noticed by the Physician in Chief, who my father recruited and was now in charge, who was Ronald Christie and was brought over from England to McGill. He called me into his office one day and said "Charles, what do you want to do?". I said "I want to be like my parents and I'd like to have an academic appointment". And he said "So what are you going to bring to the Faculty of Medicine that isn't already there? What is your arbeit?" as he used to say and I said "I don't know", and this is a true story. So he said "You had better go to the library and find out what it is you want to do". This is chance at work. This is Darwinian. I walk into the library and right facing me is a journal that has a red, white, red, band on the cover. It gets my attention. I go and pick it up. It's the British Medical Bulletin with an issue devoted to chromatography. So there are a couple of Nobel prize winners discussing a lot of equations, a lot of physical chemistry. No I don't want to do that. Towards the back of the issue there is an article by Charles Dent, saying you can use these new technologies to investigate the chemical composition of your patients' bodily fluids and he showed cystinuria and a couple of other things. Well the aesthetics of two dimensional partition chromatography appealed to me and the idea that here was something that maybe I could actually do. So I went back to my next meeting with Ronald Christie and John Beck (who was the other person who influenced me) and I said I would like to do chromatography. So they looked at each other and they say shall we send him to the Rockefeller to work with Stan Moore or shall we send him to

London to work with Charles Dent. My question was, “If I go to the Rockefeller will I see patients?”
“No you won’t see patients at the Rockefeller with Stan Moore.”
“Then I think I would prefer to go to London to work with Dent.”

Later on I got to know Stan Moore. He taught me how to wash resin when he visited Dent in London because he was quite friendly with Dent. And Stan Moore was in his quiet way effective in helping me to pursue what I ended up doing. But I went to London and the interesting thing was that Dent wanted me to feel free to do a lot of work in the clinic, and I realised that if I was ever going to learn to do the laboratory side of things I had better do it now. So I said to Dent, “Sir, I would prefer not to spend a lot of time in the clinic. I would like to learn something about chromatography and what you can do with it.” I don’t think he was exactly happy about that, but he let me do that, meaning he was a good mentor. He let me follow my own lead. Roland Westall was his colleague and Westall was a biochemist who knew a lot about amino acid metabolism. So we had an in-lab lunch course in amino acid metabolism and then across the street at the University College was some marvellous biochemistry, in those days given by Baldwin and Shooter and so on, and so we were invited to go to these courses. Suddenly my knowledge went like that, expanded, and then I had a couple of ideas and I tried them out on Charles Dent.

One was for Hartnup and I noticed the chemical group of amino acids affected in the Hartnup amino acid phenotype, and I said maybe they would be all carried by a single transport system. Dent and at that time Malcolm Milne were thinking hard about Hartnup and their response was ‘push off!’ It’s an enzyme defect. It’s an inborn error of metabolism. I said, well I don’t know. So Dent did the right thing. He said, so you’ve got a hypothesis. Prove it or test it. And I thought well if it’s a disorder of amino acid reabsorption in the kidney maybe it’s also a disorder of amino acid transport in the intestine, because derivatively they’re descended from common origin. So I said to my colleagues I think I had better look at faeces to find out what the amino acid composition was. It wasn’t a very popular experiment but it was right. It produced the data which led to a paper that I eventually published in the New England Journal.

That was test number one, that it could be fun having a hypothesis. It was experiment number two that really hooked me. We had a strange boy that I met in the emergency of the Children’s Medical Centre at Harvard at 1.30 in the morning and this little guy, Francis, really puzzled my senior who was Irwin Schafer and myself and we never sorted out all the explanations for his problem but we recognised he probably had Alport’s syndrome and maybe other stuff. So Schafer said you are over there doing that stuff with Dent. Why don’t I send you the urine and the blood and just find out what’s going on. So here is serendipity at work. Samples come. I do the analyses, I do partition chromatography on the urine and I do quantitative chromatography on both, and there’s a bloody big proline peak in the blood, but in the urine, three amino acids, proline, glycine and hydroxyproline. Roland Westall says “That’s very interesting. We’ve never seen anything like that before. Maybe you’ve discovered a new inborn error of metabolism”. Mary Efron, who was a third person on the paper that we published in Nature and in the New England

Journal, was back at Harvard by this time and she decided that she would work on the enzyme side of things to see whether there was a proline oxidase defect. And I had this idea that maybe proline was sitting on a transporter that was shared by the three amino acids so this was a combined aciduria with saturation and competition. And I phoned up Harry Harris and I said, you wrote those papers with Dent way back on cystinuria and that sort of work has been done for cystinuria; what do you think? He said "Oh I like the idea. Why don't you investigate it further". And I said, well I know what I could do. I could infuse myself with proline and produce hyperprolinaemia in me and see whether the three amino acids appear in the urine. He said that's an interesting way to do the experiment. Anyway I did it and there was the data. So there were a couple of other people in the lab who said 'Hey, we'd like to be part of that.' So I infused them and this is . . .

PSH. Did it have any harmful effects of any kind?

CS. No. And I guess we were lucky, but it was something you wouldn't be able to do today but everybody in Dent's lab was very interested in this and they were really excited. And the other thing I discovered was the joy of absolutely working completely off schedule. I was running the Moore-Stein columns as written up in the JBC. I calculated how many analyses I would have to make to get a solid paper and I figured that I couldn't do it by running the column at the regular speed. So I ran it at double the speed and everybody said now you know why they said 8 mls an hour. You have to come in at 2 in the morning, don't you? I talked to my wife. We were having a wonderful time living in London and I said, if I do this this way, I'll get data that I'll never get any other way, back home. And she said, that sounds like a good thing to do. We can go to the concert or whatever it is in the evening and then you take me home and you go back to the lab and do your ninhydrin analysis; (and that's a comment about your partner). I did that. I got the data I needed and I was invited by Christie and John Beck to put it into an abstract and submit it to the American Society for Clinical Investigation at the Spring meetings, and for some reason or another, by chance it was selected for plenary session presentation. Everybody laughed at the simplicity of my explanation about how the transporter might be shaped but nonetheless, Alex Bearn was in the audience and he said "I was really interested in your paper". And a couple of other people came up and I got introduced to Hal Christensen because there were about a dozen of us all working on transport and my idea was that Mendelian variation would pick off the various transport systems.

I spent twenty years working on transport systems and their phenotypic identification and gave it all up when I realised that if I really wanted to make a continuing contribution in that area I would have to do patch clamp and electrophysiology and I said no. So then I switched over to population work and distribution of genes in populations. But if I were to review what was important, it was the tolerance of the laboratory. Instead of saying this is what you do, it was a modest support by a Canadian fellowship, MacLaughlin travelling fellowship. It was the patient instruction and education; leading out rather than dragging out. Not training but education by Roland Westall and just the enthusiastic sympathy of Harry Harris who said 'That's a good idea. Why don't you go for it?" and when I would get depressed or stuck I would

phone him up and he would say let's go out and have a curry meal and talk about it.

PSH. What year was it that you actually went to London?

CS. '58. The summer of '58 and I stayed until June of '60. Two years.

PSH. At that time was Harry Harris with Dent or was he over at the Galton?

CS. He was at Kings then. He actually hadn't gone to the Galton. That came later. .

PSH. So was there a lot of interaction generally between Dent's lab and Harry Harris or was it just yourself particularly?

CS. I don't know how much interaction was going on. All I knew about was myself.

PSH. There was an amazing constellation of talent in London at that time and so if we think of Charles Dent to start with, I only knew him in his later years. As a person to work with he must have been a pretty amazing guy?

CS. He was very quick in mind and he was trained as a chemist and his original work was in dye chemistry, and by one route or another he ended up being a medical student as the war unfolded and found that he could bring his own personal experience and a very alert awareness to the importance of partition chromatography, which of course had contributed to the understanding of wool composition which was what Martin was doing, for which I think he got his Nobel prize and Dent was in that smaller group of people who quickly perceived the relevance of this and then applied it to body fluids.

PSH. And Harry Harris, what was he actually working on principally at the time you were there? Had he gone on to his haptoglobin and enzyme work or was that later.

CS. No he was working on haptoglobin, I may have it wrong. He might have been working on transferrin. We liked each other, so he invited me to go out on a field trial. He was going to go to a family to collect samples because he had found somebody in that family with an interesting finding and so that's when I got my first exposure to field work. Then after I went back to Montreal, I had to do a clinical year. I had to complete my qualifications as a paediatrician, so I was Chief Resident and my next story about mentorship is about the Chief of Paediatrics at McGill. That time he was Alan Ross, who recruited the most amazing department in Canada at the time, partly because he was the only chair, I think I'm honest in saying this, he was the only chairman who didn't require his faculty to have the Royal College imprimature and he said 'I want you to be on my faculty because of what you do, not because of the label you have'. And that was a brave thing to do and so he recruited a bunch of us who were mavericks by Canadian standards. He noticed that when I was finishing my training that I was unhappy, because I was frustrated between having to do the clinical side and I wanted to write the

paper about the hyperprolinaemia and I wanted to be down at Harvard with those two, Efron and Schafer, etc and so they'd phone up my wife and say "Charles looks unhappy. I think he'd better take a week off and go down to Boston and work on that paper and we'll cover." There were people who were much more clinically competent than I. So that sort of insight and support I think was very important. We got papers out and I was able to, with the help of Harry Harris, write a paper for Nature on selective transport systems. So I had a paper in the New England Journal and I had a paper in Nature and these sort of things were helpful.

The other thing that Alan Ross did for me was, he put my name up to be interviewed for a Markle scholarship. Now Markle scholarships in North America, there were 25 appointed a year and the candidates came from the United States and Canada and every medical school. There was a big pool, many were called, fewer were chosen. And I went to this absolutely intimidating, exhausting interview. My wife said that when I came back from the Markle 3-day interview process all I did was go to bed and fall asleep. Fortunately I must have done something right. Anyway they picked me to be a Markle scholar. And that was important, because in those days in Canadian schools you were either attending the clinic or you were not ,and if you were not doing that then you were somewhere in the basic science department and don't tell me that you are in a clinical department

So the Markle scholarship allowed me to be an emerging fledgling biochemical geneticist and Alan Ross made it possible for me to have a laboratory, and my job was to make the laboratory work. And about two years into this, we were beginning to find patients and the residents in the hospital were noticing that there was some exciting stuff going on in this new area. But my peers were getting jealous because Scriver never appeared for clinic. And Alan Ross came to me and said "You know there are rumblings in the department that you don't do your turn in the outpatient department or the ER and so forth. And I said well I'm still reasonably competent but there's no one else in the department who can do what I'm doing. I work every night. I'm in the lab running the columns, doing analyses etc and if one of them will do my job and keep that going, I'll go and help them out with theirs. So this beloved man, my chief, went back and he came back a couple of days later and he said "No contest, no problem, just keep doing what you are doing." And so the financial support of a Markle and a chief like that is another thing, but it explains, besides luck, how things unfolded the way they did. And we got interested in little tests which allowed one to do screening tests as in the newborn on blood and we developed our own little assay. It was OK but the Guthrie approach was even better. And then I got involved with colleagues; Carol Clow worked with me to make it possible to do this sort of work and then I realised, and this is an important side of things, I realised that if the patients we were finding through testing and so forth, and it was really big burgeoning clinical discoveries, if I devoted all my time to the clinical follow-up of that, I wouldn't be a biochemical geneticist the way I wanted to be. And I had colleagues in the lab, particularly Carol Clow, who were very good at listening to the patients and out of that came the idea of the Allied Health Personnel which became the genetic counsellor, and we established the first programme in Canada based on our laboratory experience. And so here we were sort of in the foundation of that type of community, new people in the community.

PSH. What year have we got to now Charles?

CS. Sixties, mid sixties.

PSH. Mid sixties.

CS. We did this pilot study for newborn screening and completed it in 1967, and then we were blessed with a new Minister of Health who thought genetics should be part of healthcare and we, with my Francophone colleagues at the other three universities created the Quebec Network of Genetic Medicine which again allowed a lot of things to be done, new tests, field pilot studies, development of the programme and so on.

PSH. Had you much contact with Clarke Fraser over this time? Was he back at McGill?

CS. Absolutely. He had created the Clinical Genetics Service in 1952 and it had grown and his big emphasis was on cleft lip, cleft palate, from the mouse research to the developing the multi-disciplinary team in the children's hospital to treat patients with cleft lip, cleft palate. When I came back from London, Alan Ross told me that the council of wise men said 'Oh Scriver and Fraser will never work together. This is a bad idea to put them together in a new programme in genetics'. Well that was totally false. Clarke and I got along fine. We had a wonderful time, so he created the first hospital based clinical genetics programme in Canada and I created the first biochemical genetics lab and clinical programme in Canada and we were excited as hell with what we were doing and by 1972 it was apparent that we really were achieving something, and even putting the information and the knowledge back into society, with the developmental programmes that we recognised were among the early evidence that you could actually prevent the genetic disease with early diagnosis and treatment. So we decided to put together a proposal to create a Medical Research Council Group in Medical Genetics and we went into competition and there were five other applications to do medical genetics. There were many other applications to create groups in cardiac and neurology and so on and we won, and the rest is history.

PSH. So by that stage had you got very extensively involved in PKU?

CS. Yes, it's a neat question. I did go and meet the intimidating Lionel Penrose when I didn't know any genetics. By the way I had to learn all my genetics al fresco. There were no courses in genetics.

PSH. I was going to ask about that. Did you kind of take time out to go across to the Galton and learn things there, or did you pick up your genetics elsewhere?

CS. No. I picked up my genetics by osmosis. By reading, Clarke pointing out, you know you might like to read this paper. Biochemical genetics was an easy way to start for me, because here were these pathways. Here was this idea that a mutation in the gene could change an enzyme and I was well aware of what Harry Harris was doing with polymorphisms and that work, and

neutral versus selective evolution, and so I got exposed through that work and those papers. Having known Harry I'd pay attention to those papers when they came out and it's interesting to see the papers that I felt I wanted to photocopy and put into my own personal library. In those days you remember photocopying was quite a tedious process with wet-face and everything. So no, it was self education and with help from Clarke.

PSH. And Penrose then, because Penrose always had a strong interest . . .

CS. In PKU.

PSH. In PKU, so did you kind of link with him while you were in London specifically on PKU?

CS. No, absolutely not. My introduction to PKU was through developing our version of a newborn screening test. Screening 40,000 families. Picking up PKU patients and saying 'Oh my God, now I've got one of these patients. Now I have to do something about it.' And because I had to do something about it I learnt a lot about changing the environment. How difficult that is. I got interested in improving the quality of the diet. I had to learn more about the enzyme and more about the biochemical reactions than I knew at that time. I was aware, because of a biochemical genetic focus, that the phenylalanine hydroxylation reaction required tetrahydrobiopterin and I very quickly picked up on the fact that there was work coming out of Europe, your country and Australia. That there were patients with "classic" PKU who weren't doing well and turned out to have disorders of tetrahydrobiopterin. So the next thing we did in Quebec was, we said we had first layer screening for hyperphenylalaninaemia. Then we need the second layer diagnosis to rule out tetrahydrobiopterin disorders. We were the first place in the world to do that. It was possible to do that because biochemical genetics mode of thinking and the fact that we were finding hyperphenylalaninaemia patients required to think about that possibility and do something about it right away.

So that was how I got to be interested in PKU, then I discovered Penrose's 1946 paper, his inaugural address as Galton Professor, and then I got interested in, having given up transport biology and turning to something I thought I would never do, which was population related work, where you and I went to those meetings. I thought, well Quebec is an interesting area. It has a very defined history for its populations, and by that time I was working with a wonderful man, Gerard Bouchard, who was a sociologist, a demographer and a historian and he was interested in what I was doing and he gave us as it were the entrees into how to think about Quebec populations. So I began to look at the distribution of mutations in the Quebec population and developed that simple little phrase 'the history of the population can be the history of the allele.' And that captured people's interest, and so then I thought, well you have to keep a record of all of this, and so we developed a locus specific mutation database, and then that went larger and larger, and I got into informatics having no skills in it at all but working, the secret has always been to work with people who were better than I was at the thing, but were interested in what I was thinking was interesting. So we were always a team and I think that's another message. Before it was fashionable to talk about networks of people working together, which is how we begin to talk now and

the Barabasi approach about what is a social network and how does it produce a product, I think our MRC group and the way we were working at McGill in Quebec was a good example of that. Someday somebody might do a historical examination of that to find out how that network happened.

PSH. It would be valuable. It really would.

CS. Claude Laberge came back from his work with McKusick and was interested in Tyrosinaemia and he discovered that I and Carol had been developing a screening test for amino acid disorders and he said, so Tyrosinaemia is important in the end of the province that I live in and work in. So we got together and he had a genius for understanding how government worked. His father had been in government so he and I, Carol, Serge Melançon, and other people thought that this was the opportunity to create the Quebec network, and that was an infrastructure that allowed so many of the things that I am talking about to be done. They were feasible in Quebec, whereas elsewhere there was either no interest in it or perhaps if there had been interest, not as interesting in the results because of the different population structure.

PSH. At what point Charles, did you get involved with what was then 'Metabolic Basis of Inherited Disease?'

CS. Again I think that was pure chance. Another thing that happened was I was lucky enough to be at a meeting, rather like this. It was actually in Colorado and Barton Childs was part of this small group of people. He took a shine to me and if I have another mentor after Harry Harris and Dent, Harris and Alan Ross I would say it was Barton. And Barton did what he has done all his life. He asked difficult questions. Why don't you think about doing it, getting those numbers and so forth, and he stimulated me to continue doing what I thought was interesting to do, but not too many people in my immediate environment other than people who were in the lab thought that this was great stuff. But fortunately our reviews for the MRC group were supportive. We were renewed and renewed. I must have been publishing enough stuff to catch the notice of Stanbury and his colleagues, because John Stanbury phoned up one day and said, we would like to talk to you and he said, we've looked at people we would like to consider taking over this book because we've had enough. It may have been Joe Goldstein that helped move me in that direction because Joe and I had met somewhere and I think it may have been Howard Hughes, because one of the people in the Howard Hughes outfit at that time was keen about the stuff I was doing and so I was invited to join the advisory board for Howard Hughes projects. And I think that Joe Goldstein, who I think had been associated with the fifth edition of Stanbury, might have shared that name. Anyway, they asked me whether I would like to do it, and I had no idea what I was getting into and I said, I would like to work with certain people, so David Valle and Art Beaudet and Bill Sly and I met in a room with George Cahill (the name I was looking for at Howard Hughes). Anyway Stanbury, Wyngaarden and Fredrickson walked into the room and they looked like giants, you know. We'd felt like pigmies in this room in a New York hotel where the transition took place.

PSH. What year was that you took it on?

CS. It must have been in the eighties, because the next edition came out in 1985 and we produced that edition, and that was two volumes and then the seventh edition was three volumes, and now we are on line.

PSH. Did you get the feeling this was taking over your life at any point?

CS. Not with those guys. Not with the people we were working with. Bill and I were reminiscing about it today. I think the other people may have found that more of a challenge. I found that it was an acceptable challenge. I took the book into the on-line area, which on the first go-around was not user friendly and as successful as we had hoped it would be. It is being launched tomorrow, the new Mark II version which I think will be a lot better, and it will have a Google search engine on it and things like that, so I think it's been moving in the right direction and I find that now I'm quasi-retired, officially retired from McGill, that I have more time than my colleagues to think about things. So I have spent a lot of time in the last two or three years bullying the publisher to think about this and think about that and Art Beaudet would feed a very hostile opinion to the publisher saying if you don't have paper view you might as well give up. Things like that. It's been a team effort

PSH. One very different publishing venture which I know you've always enjoyed being involved with is the Society for Inborn Errors Monographs. When did you start getting involved with that? Was it at the very beginning?

CS. This is the Oxford Monographs you are talking about?

PSH. No I'm thinking Inborn Errors of Metabolism Society and its annual meeting.

CS. Oh yes yes yes. Well, because of what I was doing and because I had been in England and people knew me, I mean they were a very small community at the beginning. I don't know. There was George Komrower or who it was who was in the SSIEM but I began to get invitations to go to the meetings, and so I think it was probably in the sixties that I started to go and I sort of became a fixture at the meeting. I was the foreigner who came, and I liked those people and you probably remember the name Gerry Milner. He was the patron of the SSIEM and he took a shine to me and we talked about these monographs and how important they were. They were theme issues and they represented opinion at the time and the information at the time that could make a difference. So SSIEM produced these monographs as you called them, and every now and then I would have an article in them. I wasn't the editor or anything like that. They had theme specific editors. But I remember going to Belfast at the beginning of the troubles and encountering civil violence, and at the same time a very intense meeting about homocystinuria and cystinosis and sulphur amino acid related disorders. And there was a guy in our lab who was an interesting example of creative mind and person, who never claimed to be a scientist but always came up with interesting things to do in either culture or science. And Hy Goldman thought wouldn't it be interesting if we used DDT to deplete the cystine pool in cystinosis. So we did cultures and we did that, and that was the paper I presented at SSIEM that year and people thought my, that's interesting. And

we said we are not sure Dithiothreitol is the stuff you want to give to patients but actually we did that, and showed that you could deplete the cystine pool in vivo and published that paper at Paediatric Research. And then I guess that catalysed other people to do it in a different way and use cysteamine but I think the principle was there, that you could do something about that disease, and now cystinosis is a totally different disease because of this but I like to think the seminal paper was given in Belfast while the bombs were exploding.

We got back from the SSIEM dinner and this was the first time in our life that my wife and I brought the children. We had four children and we went to Belfast and when we came back that night our children were leaning out of the window with their eyes like this and saying "There was a very big bang", and an Anglican Church or Protestant church had been blown up across the road.

PSH. I have been asking everyone I have talked with, Charles, a couple of questions and one of them you have partly answered. I have been asking people, who were the key folk who had the most influence on their careers. I suppose you have partly answered that, but if you had to choose one person would you be able to single out anybody?

CS. No, because they all played different roles. That's why I stressed Alan Ross. So many people I have seen, careers start out with such promise and it languishes. It's destroyed because they don't have a sympathetic chief or somebody who will protect them. There comes a time when you are wet behind the ears. You don't know really what you are getting into and you need somebody to protect you and that's what Alan Ross did. He never claimed to be anything except a nice man who happened to know something about paediatrics, but those of us who were in his department in the sixties look back on him with great love, because that's what he did for all of us who wanted to be different.

PSH. The other thing I have been asking everybody is looking back on the different pieces and areas of work you have done, is there one that stands out as being something you identify most with? If you had to just keep one of these pieces of work, is there one you would feel is, not necessarily the most important, but the one you feel fondest of?

CS. Somebody was trying to review McGill University's contribution to medical science knowledge, and this woman had really spent 6 months doing intensive work and she got my name off various places and then she phoned me up. She said I'm having a hard time with you. There doesn't seem to be any particular mountain peak, you didn't get the DNA structure. You didn't do this. But you keep turning up in all these searches, and that's the answer to your question. I was interested in transport and I got a lot of people interested in transport. Hal Christensen and I became good friends. I'm really delighted to see the Hartnup gene turning up. I'm delighted to see the gene for a transporter for proline, glycine and hydroxyproline, turning up forty years later. My contribution was to say it's there. It will eventually be found. I'm delighted that I was in at the beginning of genetic screening and I suppose people think that may be one of the things that will put a label on me. I'm very happy to have been involved in the community of Montreal, communities of Montreal where we were able to take the knowledge and the technologies that we had

to develop community based bottom up screening programmes for Tay Sachs disease and Thalassaemia. And have those people call me an honorary Greek, an honorary Jew, because of how they felt about what we had done. It's not high profile but what comes back to you is that what you have done has made a difference for an individual or a family in the community, and I'm delighted that I got invited to the CIBA conference on population genetics and that what we were doing with the PAH locus mattered. And I am delighted to know that you and I and those other guys spent that time at that 1994 meeting getting the nomenclature of mutations settled so that journals could talk to each other, scientists could talk to each other because there was now a common taxonomy in language for mutation. That's not big stuff. It's not the sort of stuff that's going to turn up on a search, but when I told the lady who was searching she said "Oh that's really interesting". And I understand the importance of those things. They are humble but they make a difference.

PSH. Well she's right. They are interesting.

CS. When you put them all together it makes for an interesting career. I think the amusing thing is, this is amusing. The thing I am probably most famous for and they always get it wrong when they cite it, is, when I came back from England I set up chromatography in our lab and Carol Clow and I would read these two dimensional chromatograms every day, and we noticed a generalised hyperaminoaciduria in the first year. We thought, I don't know what that is. We would go and see the patient and never make any clue. It wasn't Fanconi syndrome. Then the second year when it was apparent that it was beginning in the winter months and when we got up to the ward it was a child who was maybe with seizures because of hypocalcaemia but the rickets sign turned up on the X-ray and so forth, and then the third year when we had done our mini epidemiology study of who these hyperaminoaciduric infants were, because they were always infants. We found that 95% of them had French names but French named patients were not the majority of the patients in the hospital at that time. So there was an epidemiological question, a cultural thing here. And it turned out that these infants were all being fed bottled dairy milk, and the other infants who didn't have rickets were likely to be anglophone and their culture, they were using formulas which by Federal Law had to have vitamin D in it and I found out that bottled dairy milk in Quebec did not have vitamin D in it, whereas in Vermont to the south, Ontario to the west, New Brunswick to the east had provincial or state regulations that requires vitamin D, 400 units per quart. So I said, we are looking at vitamin D deficiency and it produces by some mechanism hyperaminoaciduria but that's the signal. And the interesting thing is we paid attention to the signal. We said 'this is unusual' and then we tracked it down and we ended up with a cultural explanation for this epidemic. So this is all going on in the sixties and I tried to get vitamin D into the milk and nothing happens. I write to the Deputy Minister of Health. Get nothing back and a commission called the [Castonguay-Nepvue] Commission begins to be held in the province in about 1967 and I'm working at the hospital and the head of the hospital and the Physician in Chief, Alan Ross, goes and they grab me as I'm going out the door more or less and say come with us to the Commission, we have to present the viewpoint from our hospital. And partly halfway through the Montreal Children's Hospital presentation, Alan Ross turns around to me and says "Tell the Commission about your work on newborn screening and

those interesting findings about vitamin D and the fact that you can't get the vitamin D into the milk." So I tell the story and lament the fact that my letters have never been heard. Castonguay comes down at the end of the hearing and comes up to me and he says "That was very interesting. Have you thought about what a Government has to work with if we describe a variety of things like money, votes and so forth?" He said "Is your rickets story a money issue or a voting issue?" And I said it's money. 500 cases a year of a preventable disease. He said "Have you done the arithmetic about how much money your letter could save?" He said "Go home and do it and I predict you'll hear within 3 days from the Deputy Minister." He was absolutely right. We got the regulation changed that was keeping vitamin D out of the milk, because in Quebec they knew that they were supposedly going to put 800 units in according to the old regulation, whereas the Federal Standard was 400 and there were something about marketing and dark bottle. We got the regulation changed on economics and then we couldn't get vitamin D into the Montreal half of the Quebec population because the head of the Milk Marketing Association did not want his pure milk contaminated with vitamin D. So I was stymied again and on the Board of Directors of the hospital was a wonderful man by the name of Arnold Steinberg who was part of a family that was Steinberg's Groceries which was like your big Sainsbury's in England. And I went to Arnold and I said 'this is my problem' and Arnold said give me a couple of weeks. I'm going to be overseas doing stuff. I'll be back but I think the problem will be settled." Came back, rang me up and said problem settled and I said "How did you do it?" He said I phoned up my major supplier of bottled dairy milk and I said "No 'D' no contract". I learned a lot about the world.

PSH. Charles thank you very much. We've talked about a good few things. Is there anything you feel is really major element that I should have asked about?

CS. Well I should continue with the vitamin D story, because I noticed immediately, within a year that rickets had not disappeared but every new case of rickets that appeared after adding vitamin D had a hereditary disorder of calcium or phosphorous homeostasis. So I have been teaching and talking ever since that if you change the environment for the better you have to be increasing the heritability of the persisting disease in the population and perhaps that's one of the messages that has came out of all that work.

PSH. Very many thanks. I am going to turn the machine off now.

End of recording.