

CHARLES SCRIVER INTERVIEW

First Session - August 22, 2006

1. Family Background and Education

NC: It is August 22nd, 2006, and this is Nathaniel Comfort. I'm in Montreal, Quebec, Canada, at the Montreal Children's Hospital, and we're doing the oral history interview with Charles Scriver. Would you first just state your full name?

CS: Charles Robert Scriver.

NC: It's great to be here, Dr. Scriver. I'm really looking forward to talking with you. What I'd like to do is just begin at the very beginning and have you tell me a little bit about your childhood and background and your parents and what it was like growing up.

CS: It's a very unglamorous history compared to how people move around the world today. I was born in Montreal, I was educated in Montreal, I've worked in Montreal, I'm going to die in Montreal.

NC: When were you born?

CS: I was born November 7th, 1930. I had parents who were both physicians and both on the faculty at McGill University. I was an only child. My mother was thirty-seven when I was born. It was a rather particular influence that, with my mother, who was a working mother in the 1930s, even though she was professional and from a place that didn't have to work, it was her moral obligation to use the opportunities she had been given to study medicine at McGill University. She was in the first class to tolerate women. She became a role model for women students after that. I don't think I was aware of it at the time, when I was a child, but later on I became very aware of it. She ended up being Pediatrician in Chief of the Pediatric Service of the Royal Victoria Hospital, which was one of McGill's teaching hospitals. **Endnote 1**

My father ended up being Physician-in-Chief of the Royal Victoria Hospital and was the person who specifically influenced me to pursue what I loved doing rather than what other people thought I should do. They were both interested in the place of science in medicine, so they had an influence on me. They also helped me understand what a clinician scientist does. Neither of them had quite the opportunities that I had to do things, but they were very definitely quiet influences in the background.

I grew up in a three-generation family. My grandparents lived with us, and you heard about my parents, and I was an only child. I had the opportunity to go to a good school. I have kept virtually no connections with the people I graduated from. They went off into business and other things, and they all thought the things that I was interested in were strange and not very interesting. (chuckles) I definitely would be called perhaps a nerd-like person today, and my self-esteem took great leaps and bounds when I found that I could do some athletics that no one else could do. I had the javelin throw record for years in Quebec at the high school level, and I developed a new corner shot in

basketball, which was kind of late in my development, but led to, as I say, some self-esteem.

I was smart in school. I loved school. I loved learning things, and teachers who introduced out-of-the-book things were a wonderful influence. So it was through the fact that our home was full of books and there were teachers at school who introduced me to Greek literature. I took Latin, and we had such an inspirational teacher in my last year in school that he actually excited us enough that we could read Virgil in the original Latin.

NC: This was in high school.

CS: This was in high school, yeah. But I discovered there that I was interested in the scientific side of the education, but I was not ever going to be very good at mathematics. And today, mathematics has become an important part of biology. So maybe I got into what I did at the right era and I would have difficulty doing what I'm doing now.

Anyway, I graduated from school. I went to McGill University. I took a degree in arts, all arts and humanities, and I thought I was going to become a geographer. We had a brilliant geography teacher in school, and when I came to McGill, McGill had the best geography department, linked to meteorology, probably in the world at the time. I think that had an influence on me because I've become interested in population genetics and the geographic diversity of alleles at particular loci in human populations.

Anyway, McGill was doing some really interesting stuff with aerial photography and new technology for mapping, so that, I think, maybe penetrated me subconsciously. Technology can do things.

The other thing that happened while I was an undergraduate student is I took a course from the great Jack Berrill. **Endnote 2** For him, I had to write his memoir for the Royal Society, so I learned a lot about him after he died. He was one of these extraordinary teachers who would stand there and sometimes just look at the class and say, "Well, what do you think about that?" And then just stand there and wait for an answer. Very unsettling when you're the type of undergraduate student that I was. But I realized with hindsight this guy is pushing me in a direction that I'm not sure where I'm going, but he's saying there's some interesting questions to ask in the scientific world, and you can get answers to them, by measurement, by observation, by experiment.

With hindsight, he turns out to have been an important influence on me, and he was very kind to me. He was a mentor in the sense that he recognized that he had a student that was interesting. He happened to know my parents, that's the other thing. There are such things as small worlds. So that type of networking was helpful. He kept nudging me all through until he died, actually, about how things were going.

It came time to decide what I was going to do, and I thought, Well, I could apply to be a graduate student in geography, but maybe I should apply to medicine. My parents were good role models. They were really happy in what they were doing. They loved what they did. The joke was at our table that there were all these things at the table. There were the grandparents, there were the parents, there was the kid, and there was the telephone, because my parents took calls from their patients, and they made house calls. After supper they would go out and see their patients that needed to be seen.

All of that was, for me, a set of models, and they were comfortable, good models. So I applied to medicine. In those days you didn't apply to sixteen or twenty-five schools. At least I didn't. I sent in one application to McGill, and I was accepted. When I got into medicine, I said, "Hey, this is kind of exciting stuff. The facts are interesting, and there are inspiring teachers out there, and it seems to be --" I'd already sort of got an unrecognized vestigial interest in biology. I enjoyed the labs, I enjoyed the idea of biological systems, and so on. And here I was studying human biology. Some of it was pretty dry and categorical, but there were things beginning to percolate.

I wasn't very good in biochemistry, which is an interesting thing to say. But we had a teacher, whose name was Esau Hosein, who came from the Caribbean and who was a faculty member and was in this rather extraordinary biochemistry department that was chaired by Thomson. **Endnote 3** He recognized that there were a lot of us who were struggling in biochemistry, so he put on night classes. I was one of the thirty or forty others in a class of a hundred who signed up for the night classes. Esau made it exciting, and suddenly this world of biochemistry was something different than just formulas on a page. Anyway, that was, I think, a formative experience.

I was a good student. I graduated at the top of my class, or somewhere near there, and came away with a couple of medals. Again, in terms of an only child who might have been insecure, and so on, to have recognition like that was helpful. So where did I apply for my internships and residency? I applied to McGill because that was the place I knew, that was the devil I knew, and I'd been on the wards and clinical clerkships and so forth, and I liked the people there.

While I was an intern, someone else thought it would be interesting if we had evening classes, if you could possibly organize your time. A guy by the name of Martin Hoffman **endnote 4** said, "I will put on classes in which I will tell you what I think the exciting things are in the medical sciences. It's the future for you guys who are going to practice medicine. Listen to it now." Hoffman was one of these absolutely inspiring teachers. There would be twenty or so of us who would go and listen to the things, and then we would go off to the library and get the journals and read the papers. This was not very usual in those days. But, again, it made an impact on me. Then the other thing I found when I was doing my internship – my internship was a rotating internship and then a residency in medicine, and I was one of the first people at McGill to say, "Look, I don't want to do a whole year in that direction. I want to do two things. I want to do medicine and pediatrics," which reflected my parental models. I found that what I wanted to do was spend a lot of time with a single patient, if I could possibly do it, so that I could find out why this person was sick. So I was interested in the person with the disease, I was also interested in the history of the disease, and I wanted to begin to answer the question, "Why is this person sick now?"

NC: Individuality right from the get-go.

CS: Well, I didn't recognize that's what it was at the time, but yes. And where did that come from? I don't know. But I think it was because my parents practiced medicine with the patient with the disease, not the disease the patient had, and that just sort of seeped through. For instance, I got my driver's license when I was sixteen, and there were intervals of time between classes at McGill, and my mother had a practice all over the city. It was really interesting what her practice was like. I mean, she could be looking after the grandchild of the president of the Bank of Montreal, and then she could be

attending an immigrant who had just arrived from Europe at the other end of the city.

I was driving her one day, and she was climbing these famous Montreal stairs to see the family in some walk-up flat. When she came out and got in the car and I drove down, I looked in the mirror, and here was the mother and the father standing in the street with their hands like this. I said, "What did you do, Mother? They look like they're blessing you or something." She said, "Well, he was a professor of microbiology in an Eastern European university and his whole world was torn apart, and his wife and he made it into Canada. It's pretty tough, but he's washing glassware at the University of Montreal, and anything we can do to help." I thought, you know, that's the sort of awareness that I would like to have about the whole situation, because she said the circumstances of life and the experience is going to have some role to play in the disease they have.

She was also, I should explain, the first person to do an in vivo experiment on sickle cell disease. She put a rubber band – this is an interesting story. There was probably one sickle cell [anemia] patient in Montreal at that time. He came into the emergency, as I recall the facts. I may make them better than they actually were, but it's a good story. She was looking down the microscope doing her own blood work and noticed that the cells were sickling. She said, "I wonder why that is."

So she arranged – the van Slyke apparatus was brought to Montreal, the van Slyke apparatus, which measures gas pressure [in blood]. And she, with – I think it was a woman called Eleanor Venning – learned to run the van Slyke. She put a rubber band around the kid's finger, she took the oxygen tension values and plotted them against the degree of sickling, and showed that the lower the oxygen tension, the higher the sickling count. This was an in vivo experiment to say that this is one component of the phenotype for sickle cell disease, and she published it in the *Canadian Medical Association Journal*. [endnote 5](#) People said to her, you know, why don't you get out and do something practical, Jessie? What's that got to do with medicine? But that sort of thing, I think, rubbed off on me. I learned about that. These little anecdotes serve to say that they helped probably get me focused on the person with the disease, and the history of that person and the history of the disease.

NC: What year was that, your mother's experiment?

CS: Nineteen twenty-nine, before I was born.

NC: I'm just trying to place that in the history of sickle cell disease.

CS: It's quite early. She probably did the work in '28. Anyway, I enjoyed my time in internal medicine. Some people got impatient with me when I was wanting to take a long time to try and understand why this person had this disease at this time. I also had the unique experience of probably one of the last patients in my era to ever have classic lobar pneumonia with diplococcus [endnote 6](#) and go into vascular crisis, hemodynamic crisis. And it was my job, using new pressor agents and IV, to keep up that lady's blood pressure, and she survived.

My senior and I were invited to give grand rounds, and we were just astonished because it turned out that everybody and his uncle came to the grand rounds, because what we were talking about was what all those old guys who were our teachers and chiefs of service and so forth knew from their days before antibiotics that this is what pneumonia

was and this is what killed people. We had done these little technical things, kept the patient alive, and everybody wanted to hear the story. So that was interesting.

When I, later on, read McCarty's book on the transforming principle [endnote 7](#) and read that he had gone into working with Avery because he wanted to know why the diplococcus had its effect and what the difference between a benign and a pathogenic strain of diplococcus was, there was a context for me because I actually had been involved in keeping a woman alive, who was going to die of lobar pneumonia if we hadn't had the newer technology of keeping the blood pressure with the chemical agents that use adrenalin and so forth that you could use in those days.

2. Choosing A Direction; Inborn Errors of Metabolism; Training at UCL and at Harvard and back to McGill

When I came down to the Children's [Hospital] to be a resident in pediatrics, I really felt comfortable. Internists are aggressive and competitive, and sometimes they don't have as much time for the patient as the pediatricians seem to have. Pediatric rounds were beautifully chaotic here. The kids would be under the bed, the chief would be wandering around and he'd hold the kids, and so forth. Yet the science, the medical information flowed just as well. And nobody wore white coats. (chuckles) Some people did but not everybody. I liked that. That was comfortable. Alan Ross [endnote 8](#) was the Chief of Pediatrics and he turns out to have been one of the key people in my life, in my career.

The internist people had shown an interest in some of us who -- were interested in what we did -- so I got called into the Chief of Medicine's office. He'd been recruited by my father to restore the dynamics of the Department of Medicine at McGill, which had been quite famous in the past. They were going through a difficult period, and my father, as Chief of Medicine, said, "We've got to do something." He recruited Ronald Christie [endnote 9](#) from England to become Chief of Medicine at the Royal Victoria Hospital.

Ronald Christie had a very bright colleague, whose name was John Beck. [endnote 10](#) John Beck was one of the formative people in Canadian medical science for his influence on people. These two lofty gentlemen called me into the office, and they looked at me and they said, "Dr. Scriver, what is it you want to do when you finish your training?" I said innocently, "Well, I'd like to do what my parents are doing. They're happy, they like what they do, I'd like to be an academic physician." They looked at me and said, "Well, that's very interesting.

What specialty will you bring to the faculty that would make you interesting to us?" (chuckles) I said, "I don't know." They said, "Well, maybe you should go and find out." This is a true story. They said, "Come back in two weeks and tell us what you want to do."

So I went to the library, which was a very good library in the Royal Victoria Hospital in those days, and the journals were all laid with their covers exposed, like here behind me. Right in front of me was a journal that had a red band, a white band, and a red band. It caught my eye. I was, by the way, interested in art and so forth. I thought, well, let's pick up and see what's in this journal. It was the British Medical Bulletin, and it was a quarterly journal.

The theme for this issue was chromatography. The opening article as I remember was written by Martin and colleagues, who got the Nobel Prize. [endnote 11](#) There were a whole bunch of highly technical things, a lot of physical chemistry, a lot of equations, and so forth. I said, "Gee, I don't think I'm interested in that." I turned to the back and there was an article by Dent and Walshe that said, "You can use this new simple technology to examine the composition of body fluids, and it will be of interest to understanding diseases," and they named a couple of inborn errors of metabolism and so forth. [endnote 12](#)

I stopped there and said, "This is good enough for me." (laughs) "I'll go back and tell them this is what I'm interested in." It was partly the chromatograms that had a nice sort of aesthetic appeal. And it was the idea that you could use a tool that I thought I could

work with to study why this person had this disease now.

So I went back to Christie and Beck and I said, "This is what I'd like to learn. This is the gimmick you want me to learn." Because there was no one else at McGill doing this that I knew of at the time. So Beck turns to Christie, Christie looks at Beck, and they said, "Will you call Charlie Dent or will I call him? Or do you think we should send Scriver to the Rockefeller to work with Stan Moore?" I said, "Who's Stan Moore?" They said, "Well, he's doing some very interesting work with column chromatography." [endnote 13](#) I said, "Will I see patients at the Rockefeller?" And they said, "No. You'll have to take a Ph.D. if you're going to go there." So I just clicked off and said, "No, I don't go there. I'll go to London, England, and work with Dent if that's where they want to send me."

Isn't it interesting how chance things influence you? Because I got to know Stan Moore. He taught me to wash resin, because he'd come to visit Dent lots of times. He was working on the material that gave him the Nobel Prize at the very time that I would have been in the lab. But that's not what interested me. It's the fact that I went to work in London because it was tied to the healing dimension with patients. When I got to London, Dent said, "I'd like you to work with me in the clinic," and I said, "Actually, sir, I would like not to do too much of that." I was getting very brave now. "I'd like to see how you do your clinic, and I'd love to know more about your patients and their problems, but I really want to learn chromatography and I want to learn about amino acid metabolism." So he said, "All right."

There were guys in the lab -- was Mary Efron in the lab, who became quite famous, [endnote 14](#) and we can come back to her. And there was Stan Wright, who came from California. [endnote 15](#) He had been working with Linus Pauling, [endnote 16](#) and we can go back to him. And we took, over our sandwich lunches, seminars in amino acid metabolism with Roland Westall, who was Dent's right hand man, colleague. University College London was across the street and giving this extraordinary course in biochemistry, and the answer was, "If you're here, sign on and just audit the course, it's wonderful."

Some of these famous guys, who later went on to their careers, were teaching the course. Suddenly Esau Hosein's imprinting comes back, and I sit there and I listen to Baldwin [endnote 17](#) talking about comparative biochemistry, and I hear Shooter [endnote 18](#) talking about this. I don't remember all the professorial names, but they lectured with enthusiasm and I was an enthusiastic student. And Roland Westall brought it all down to the practical things. What is the difference between L and D amino acids, and so on.

NC: This is 1958?

CS: This is 1958. I competed for a McLaughlin Traveling Scholarship. [endnote 19](#) McGill put me up. I got it. And I spent two years in London. At the end of six months, I was really depressed because I felt I hadn't achieved anything. I'd learned a lot of new stuff, and I'd learned to make chromatograms, and I knew how to read them and interpret them, but I felt I wasn't going anywhere.

I've left you a window empty in this story, so I have to go back now. After the interview with Christie and Beck, and after my exposure to pediatrics, I discovered I would like to go in the pediatric direction rather than the internal medicine direction. But I now have

three mentors at McGill. I have Beck and Christie over here planning to send me away, and I have the Chief of Pediatrics here, who is making pediatrics a very interesting experience.

NC: And remind me who the Chief of Pediatrics is?

CS: Alan Ross. So Alan Ross says to me and two or three other people, "I think you should get additional training and you should go to Harvard, you should go to Children's Medical Center. [endnote 20](#) I suggest you go down and be interviewed, find out whether they will take you." So I do what I'm told. I go down, and the interviewing team meets all of us wet behind the ears guys, and I'm one of the ones who's picked to become a junior resident in pediatrics.

I marry my girlfriend of ten years in 1956 after she graduates from nursing. You'll meet her tomorrow. She had a degree from the university, she got tired of waiting for me for medicine, and I had a father-in-law who said you can't marry my daughter until you complete your medical studies, school. So she went into nursing, in the old style of nursing where you live in. We were finally able to get married in 1956. Our first house was here in Montreal, our first home. Then we went down to Boston and we lived in Boston on the Larz Anderson estate, in an interesting Baroque building which is now the Antique Automobile Association of America's main museum. [endnote 21](#)

At Harvard, at the Children's Medical Center -- I thought I [had] worked hard in Montreal. We just worked our asses off. And it was exciting. But it was every second night, and we were tired when we got off, especially as the year went by. But it was hugely exciting, because Charlie Janeway ran the service. [endnote 22](#) Janeway was the chief of pediatrics. And these patients came from all over the world to be "solved" at Harvard on Janeway's medical service. He had a faculty which was inspirational in their approach to how things were done.

Two things happened there. A woman came in, her name was Mrs. H, and she sat down and I sat down with her, and she said, "Doctor, please listen to me. It happened again." With hindsight, I say to myself, Isn't that what doctors are supposed to do? Why does she invite me to listen to her? I thought that's what the profession did. And the second thing was, "it happened again". Is she saying something about heredity? There's nothing concrete but just sort oscillating there.

So I worked up this little girl, infant girl, who had seizures that just refused to respond to any of the anti-epileptic medications.

NC: It was the mother that said it happened again.

CS: Yes.

NC: And bringing in her little girl.

CS: Yes. She then went on to tell me that the first child, the older sibling, who was a boy, had died with his seizures, and no diagnosis. I listened to her story, and I wrote it up very carefully, and when we did our rounds I presented this thing. We thought maybe there's a genetic problem. Two very young kids starting this illness. When it happens in siblings, they tell us that there's things like recessive inheritance and so on, even though the

parents aren't affected.

That night, or sometime right about that time -- Janeway and the seniors and everybody encouraged us to read the literature. I had a subscription to Pediatrics. I opened the journal and here was an article by Bessey et al. that talked about pyridoxine dependency, susceptibility to seizures due to abnormalities in vitamin B6 metabolism.

[endnote 23](#)

NC: What year was this?

CS: This was 1957. So I thought, I wonder if there's any correlation. And again, if anybody thinks they plan their lives, there's no such thing as forward planning. So I went to rounds the next morning, and I said, "Look, there's this interesting article, and maybe we should give this infant pyridoxine." The seniors said, "That's an interesting idea." Because it was giving something to a child under unknown circumstances, before the IRBs [endnote 24](#) of today, there was the idea that you might get an additional opinion. It was appropriate to call in Sydney Gellis, [endnote 25](#) who was the head of pediatrics at the Boston City Hospital and who was a greatly respected pediatrician and teacher. Sydney came in and did a consult, and his consult was written in his famous handwriting. "I think Scriver has an interesting idea. Try B6."

So we took [the child] to the EEG room; we hooked her up to an electroencephalograph; we put an IV [intravenous line] in her, and I gave her a dose of pyridoxine. Over the next ten minutes, the electroencephalograph just got absolutely normal, she stopped convulsing, and we had demonstrated she had pyridoxine responsive seizures. I was encouraged by Janeway to then follow up to understand why this child has those seizures and why they respond to vitamin B6.

That was my first encounter with the discovery that you could really ask an interesting question, you could do an experiment, and you could get an answer. I have to tell you that it was my first paper. I wrote the paper while I was in England. It eventually got published in 1960, I think, and I put forward some ideas. [endnote 26](#) We then went on to show that this was definitely an autosomal recessive condition, it's in the McKusick catalogue, [endnote 27](#) et cetera.

What's really fun to tell you in an interview like this is, fifty years later, Peter Clayton in London, England, discovers what the actual cause of the pyridoxine dependency I was studying is. [endnote 28](#) It's an inborn error of amino acid metabolism, it's an inborn error of lysine metabolism. The block leads to the accumulation of an interesting molecule, which has got a name this long, and it undergoes spontaneous chemical reorganization and produces a particular fragment with a funny name, which I can give you later if you need it. It sticks on to pyridoxine in its phosphate aldehyde form and depletes the body pool of the molecular form of vitamin B6 that's needed to drive enzymes. So the inborn error of amino acid metabolism creates an associated deficiency of this vitamin.

I don't know where Peter Clayton got the idea, but we just published it in our book. [endnote 29](#) It's now a new chapter in the book. And it took almost fifty years to get there -- 1957 to 2006.

NC: Like Vernon Ingram and sickle cells. [endnote 30](#)

CS: Yeah.

NC: In 1957.

CS: Anyway, I enjoyed trying to discover why this child had this vitamin B6 responsiveness. None of us discovered this, that worked on it. It was somebody from out of the blue, Peter Clayton, who comes up with the discovery and comes up with it very much later.

A second thing happened in Boston that conditioned me. Irwin Schafer [endnote 31](#) and I were working one night in the ER and a boy comes in and he's got meningitis, we decide it's viral meningitis. He's deaf. We do all our own lab work in those days, and I'm looking at the urine specimen and it's full of blood. He doesn't have any injuries. He's got hematuria. [endnote 32](#) Somewhere along the line the penny drops that he probably has Alport's syndrome, which is deafness and glomerular insufficiency and nephritis. [endnote 33](#) So we keep in touch with [the patient]. We work him up for his kidney function. He was eligible for renal transplantation, and I think he got transplanted later on and then he went on to die.

But we puzzle about all of this, and nobody knows much about the cause of Alport's syndrome. As I recall, this was about April that this child came in and we worked him up, and then I went in June to England. Schafer and I kept in touch with each other, and he said, "You're over there, you're doing chromatography, supposing I send you some blood and urine from [the child] and see if you find anything."

So he sends it over and I find something. I find that he has proline in his blood in excess, and in his urine he has three amino acids: proline, hydroxyproline, and glycine. [endnote 34](#)

The discovery of proline in his blood leads to our discovery of hyperprolinemia as an inborn error of metabolism, and the discovery of three amino acids in the urine leads to a hypothesis that by now I'm beginning to be interested in the transport of amino acids and how do water soluble substances leave one water soluble phase and get across the lipid phase into the cell and back into the body. [endnote 35](#)

So it's the patient with the problems who leads me to give myself a proline infusion in Dent's lab, produce hyperprolinemia in myself, and collect my urine and show that I produce the triple aminoaciduria, and from that, hypothesize that it's the shared transport system that sees proline, hydroxyproline, and glycine. And that fits in with the idea that there's a shared transport system for another group of amino acids which have cationic charges on them and are involved in cystinuria. [endnote 36](#)

While I'm in London and working on things like this, I meet the famous patient of Dent whose name is Hartnup. [endnote 37](#) I'm talking to Dent, and Dent says, "I think this may be a disorder of tryptophan metabolism." Roland Westall had penetrated my skull enough with his wonderful teachings to say, "You know, the Hartnup urine pattern is of a group of neutral amino acids, and the cystinuria group aren't in it." By this time I know this. "And the proline glycine group are not in it. And glutamic acid and aspartic acid aren't in the Hartnup pattern, and they're anionic amino acids. So maybe the Hartnup story is in fact a transport disorder that's affecting a particular group of amino acids." Well, Dent doesn't think much of that idea. Maybe he was just being a good mentor. He

says, "Go and prove it."

So how does Scriver prove that one? I thought, well, I'm not sure which amino acid I would infuse to displace everything else. But if it's in the kidney, the tubule does the same job that the intestine does, so if it was an inborn error of a transporter, that transporter should be in the intestine as well as in the epithelium of the renal tubule. So why don't you look in the intestine?

How do you do that? What I did was, I collected feces. I collected normal feces and I collected Hartnup feces. (chuckles) Westall and my colleagues in the lab said, "Please, never do this experiment again." (laughs) Anyway, I did the chromatogram and there was the Hartnup amino acid pattern in the feces, the way it was in the urine.

It took me three years to publish that one. I was working with an interesting colleague of Stan Wright, who was Ken Shaw, [endnote 38](#) who was in California. I thought that he'd done some really interesting work on tryptophan metabolites in Hartnup urine and I should publish with him. But Ken Shaw turned out to have been one of those colleagues who never publishes because he's never got it perfectly right, and he very kindly, after about two years, said, "Why don't you just go ahead and publish it yourself." So I sent the Hartnup interpretation, that it's an inborn error of a transport system that's expressed in the intestine and the kidney to the New England Journal, and they published it. [endnote 39](#)

Going back to the proline story, my other great mentor in these days was Harry Harris. [endnote 40](#) I phoned up Harry Harris when Dent wasn't terribly enthusiastic about the Hartnup hypothesis, and Harry said, "Go for it! Do it. It sounds like an interesting idea, and it doesn't require anything except holding your nose while you're working up the samples." (chuckles) Then I told him about the proline story and my hypothesis, and he said, "I think that's possible." Harry Harris was working on cystinuria, and he was one of the early people to see it as an inborn error of transport rather than metabolism. Dent had done those experiments where they infuse lysine and produce the aminoaciduria. So I was working in an environment that helped me to pursue my hypothesis.

But it was Harry Harris who said, "Yeah, go ahead and infuse the proline and find out. You'll never answer your question until you do." We could have done it in animals, but I said I think proline is a pretty safe amino acid, et cetera. So I did.

In this narrative, I should comment on the famous moment. Ideas come with absolutely no overt rational context. I can tell you where I got the idea, "I have to infuse myself, because the explanation is the proline sitting on a carrier and displacing the other two shared substrates." I was walking down the corridor in Dent's lab from where I sat at my desk thinking and where I did the chromatography and the analyses with column ninhydrin reactions. [endnote 41](#) I walked past the glass cupboard, I was turning left around the corner, and suddenly the idea was there. Infuse yourself. That's the answer. That's the experiment you need to do. And it was from one step on my right foot to one step on my left foot that it was there.

NC: Was there any precedent in your experience for self-experimentation? Did you have professors who did that, did you read other papers that involved self-experimentation?

CS: I don't remember. If there were precedents, I don't remember them now. But it

seemed perfectly normal to do. I knew something about proline. I knew that it was a gluconeogenic amino acid. [endnote 42](#) It was important. I also learned that quantitatively in the blood, it's one of the second or third most important amino acids in terms of quantity. So it must be good for you. (laughs) And, after I did the experiment, there was another guy in the lab by the name of Bob Denman and he says, "That looks like fun. When are you going to do me?" (chuckles)

When I came back to Montreal, I had had the taste of three thoughts -- the B6 story, and I worked with some English people trying to pursue that story further. I'd had the excitement of discovering an inborn error of amino acid metabolism. And it was Harry Harris who said, "For God's sake, put that together with your transport hypothesis. Put a new amino acid disorder [in] and a new transport system, consider writing that up and sending it to Nature." So we did, and that was my first big, exciting paper. [endnote 43](#) Then I'd had the excitement of arguing with the top guys about the Hartnup [disease] and getting support for that hypothesis.

So I came back to Montreal, and I was scheduled to be Chief Resident in Pediatrics. That was nice, the idea of being here was nice. But Alan Ross looked at me and said, "You're unhappy, aren't you?" I said, "Yeah. I've got a paper that we want to write about the proline story and the inheritance of Alport's syndrome and the fact that it's a very complicated pedigree in which there are two alleles, two different genes segregating their mutant alleles, et cetera." He said, "There are a lot of other people on the house staff who are very competent, and they would love to look after things if you take a week off, maybe." So we spoke to one of them, Leonard Langlois, and Leonard said, "Sure, I'll cover you while you do that." I went down to Harvard and we worked on our paper and we eventually submitted it.

But it was Alan Ross saying, "You're not very happy. What do you really want to do?" And I said, "What I would like to do is to do what I was sent away to do, to bring my gimmick back to McGill and use it. And I discovered something about inborn errors in metabolism." He said, "Well, it just so happens we thought it might work out and we put aside space for you to have a lab. Why don't you go down and begin to design it." This was the name -- the deBelle lab [Laboratory for Biochemical Genetics] is named after the administrator [John deBelle] who said, "Why don't we put Fraser [endnote 44](#) and Scriver together and create a bigger Department of Medical Genetics?"

So I was able to produce my -- create the laboratory while I was the Chief Resident of Pediatrics in 1960, and the lab opened in '61, and the rest is history, as far as here is concerned.

It was Alan Ross who put me up for a Markle Scholarship, [endnote 45](#) and I succeeded in that daunting interview process that the Markles had. I ended up being one of twenty-five people picked that year from all across North America. That was important because the Markle people wanted to make deans and chair people, but while they were funding you for five years, they wanted you to be left alone. And I was protected. I was given an envelope that Alan Ross could say, "I don't have to worry about you. If you want to work in the clinic, that's okay, but if you want to develop your lab, and you want to develop these new ideas about genetic screening of newborns, and if you want to figure out how to treat the patients you find, that's what I want you to do."

The other thing that was key about him was, he was the only chair in the country who

would appoint people in Canada to the faculty without the [Canadian] Royal College of Physicians' branding. [endnote 46](#) He said, "You don't need to get that for you to be a member of my department," and he did that with three other people. He was really quite something. As a result of him, the way in which the Royal College Fellowship had to be part of your acceptability to be in the department disappeared. Department chairmen began to say, "We'll take you for what you bring to the department, regardless of your initials after your name."

NC: What was involved in getting that Royal College of Physicians stamp?

CS: Oh, five years of committed training, including a year of research. The training was a procrustean affair. You had to do certain things. I mean, there's nothing unusual about it. Every country has it, and it guarantees the public has a reliable person who says "I'm a pediatrician." But it doesn't say that you're a great person to be on the faculty because you may never have been encouraged to go in that other direction that allowed me to join Clarke Fraser. When we started teaching genetics, this room was – you couldn't get another body in here [endnote 47](#) because everybody wanted to hear about that. And what we talked about was something that wasn't on any Royal College list.

Alan Ross was very important because he sent my name in for a Markle, but he also allowed me to be protected. He came to me with a smile on his face about three years into my Markle and he said, "My department isn't so happy about you." I said, "Gee, what have I done?" He said, "Well, you know, you don't work in the emergency, and you don't do service on the wards, the way most of those people do." I said, "I understand that, and if you would like me to do that, I'll go and work in the emergency on the weekends when I'm scheduled to do it, if one of them will go into the lab and keep things going, which is what I do. I do that every night and I do that on the weekends. Would they do that?" (chuckles) He smiled and said, "That's a good message. I'll go back..." He came back a little while later and said, "You don't have to think any more about this." (laughs)

What a mentor. He kept saying, "I don't understand what you do." And I said, "You do understand what I do. Just look at what you do for us." I just hope that people who are starting out in their careers will have people looking after them like him.

NC: Not an intellectual mentor so much as a kind of guiding force and a protector.

CS: Yeah, and who instinctively understood what could be done to help somebody who was starting out in a new area and needed to be protected or looked after. So that's surely a long enough narrative up to this point.

NC: Well, it is. I have a lot of questions that I'd like to double back on and ask you about. [pause; tape off]

3. Family Values and Early Influences; Religion, Literature, and Music

NC: I want to go back to the beginning a little bit and fill in a couple of gaps that I have. You mentioned that your parents were role models for you as far as going into medicine. Did you have a sense of their expectations for you?

CS: No. They bent over backwards to say you don't have to do medicine just because we've done it. My wife and I did exactly the same thing with our children, and we ended up with four children who are in law, architecture, ballet and publishing, and music.

NC: What about general kinds of aspirations? Was it expected that you would go to college, for example?

CS: Not that I'm aware of, no.

NC: You don't recall any sense of pressure that you had to --

CS: No. I think the maxim at home was, whatever you do, do it to the best of your ability. And the other thing was definitely part of their life, and it was do unto others as you'd like done unto yourself. A golden rule which turns out to be a universal human thing, but which is so seldom practiced.

NC: Were they religious?

CS: Not particularly. We went to church. Actually, it was an interesting church. It's defunct now but it was right down in the middle of town. It was sort of the university, the academic church. Going to church for me was an interesting experience because here were all these members of the faculty of religion who were historians more than they were ministers, and the sermons and the services could be really interesting, full of information. And it was a great church for music. We had one of the great choral directors, one of the great organists in the country. And one of the great mezzo-sopranos of Canada's music community was the soloist in our church. [endnote 48](#)

NC: What denomination was it?

CS: Protestant. What's called the United Church of Canada. This particular church was [the] Erskine and American. [endnote 49](#)

NC: So you absorbed kind of moral values, but without a lot of explicit biblical references.

CS: Absolutely. I mean, it would just be the opposite to a fundamentalist family. There was lots of spirit of inquiry, lots of skepticism expressed about determinist events and so forth, and yet, the spirit of inquiry. I had a maternal grandmother who was fairly strong on mission and so forth. In fact, my mother, when she graduated from the university, was scheduled to become a teacher and a missionary. That was what her mother thought would be nice. Her mother was a frustrated Victorian intellect, who had won the Lieutenant Governor's Medal in science and was never able to use it, and I think took out some of her frustration on her daughters, and my mother translated that into medicine. (chuckles) My mother had, I think, no wish to go and proselytize. But she would be happy to -- She was the one who -- so often I can hear her say that the Golden Rule was

the good rule.

NC: Was it your maternal grandparents who lived with you?

CS: No, my paternal grandparents.

NC: Do you recall a moment of questioning God?

CS: You might ask it the other way around. You might ask whether I ever thought much about it.

NC: Okay.

CS: I do believe that all life is connected, and I do believe that one can understand that now in terms of the DNA molecules. I also am perfectly willing to accept the fact that there's mystery and order that we just do not understand. I like the literature, I like the effusions from the human spirit that turn up in literature, that we have a divine component to us, because I think that, if I have five classes of knowledge, I'd say, "I don't want to know, thou shalt not know, I do know, I don't know" -- which is what science is all about -- and "the unknowable". I'm perfectly happy to have the unknowable in there as well. I see no conflict between having a faith, [an] understanding of mystery, and a scientific approach which addresses the rules by which natural orders exist.

I thoroughly believe in Darwinian evolution, and I do not believe in exceptionalism that makes the human species only explicable by intervention by God, because he did a bad job with plumbing, teeth, and backs, and sinuses. [chuckles]

NC: You make that reconciliation sound so easy, and so many people find it so difficult.

CS: I don't know why it's easy for some and difficult for others.

NC: You mentioned that your house was full of books when you were a child. Do you remember any particular books or other people that were of great interest to you or that somehow sparked you when you were a child?

CS: I read a lot of Dumas. [endnote 50](#) (laughs) Happy narratives. I was introduced to good literature. St. Exupery was a writer that my father liked, and I have read about everything by him. [endnote 51](#) We raised all our kids on The Little Prince, which is a nice illustration of what we're talking about.

NC: It is, indeed, yes.

CS: Shakespeare. My father had one of these extraordinary memories. He could read something and then he would just remember it and recite it. He liked poetry. He went off to the First World War. My mother and he met when they were in high school, which is the way my wife and I met in our generation. He survived the war. He got typhoid in the trenches and was demobilized and sent back for recuperation. Then they lost his records. He says, "I don't understand it, but I reenlisted." He enlisted in the navy and went off on a Q-boat [endnote 52](#) that was supposed to be sinking submarines, but usually got sunk themselves, and he survived that. I think that gave him an appreciation of life that he might not have otherwise had. When he came back, he took two degrees

simultaneously. He took his arts degree and his medical degree together. He was very well endowed intellectually.

He took the dean's course in poetry and the big poet was Tennyson. [endnote 53](#) My dad could recite whole pages of Tennyson. It was interesting. Every now and then he'd start doing this at the table in some context. (chuckles) And that instilled in me a love of poetry, so I have -- I'll show you the collection tomorrow, but I have a huge collection of poetry, and still am excited to discover a new poet that I didn't know about and respond to.

NC: You also mentioned in passing that you had an interest in art. When did that start?

CS: That was partly because at home we had paintings on the wall. I was interested in Canadian art. My oldest friend, who I met when I was twelve, became an artist and we used to troll the art galleries and so forth when we were teenagers and look at stuff. My wife and I decided when we got married that, if it was possible to buy a work of art each year, nothing expensive but something we loved, we would do that, and preferably try to do it for Canadian art. So we came back here and started to do that and have things that we like and which happen to be quite decent in terms of what they represent in the way of art.

I find that that, again, there's a mystery and a dimension there. There's order in art, and then there's the whole mystery of the creative aspect of it. (chuckles) And I did tell you earlier that chromatography had an aesthetic dimension to it, so there's something in there that I don't understand, but it was effective.

NC: You also mentioned that you were kind of a nerdy teenager. Did you have a group of friends, or one or two close friends that were more intimate? What were your friendships like? Were you a loner? Were you gregarious?

CS: I was probably more of a loner, certainly in the school I went to. I didn't want to do the things they wanted to do. When I say nerdy, simply that I enjoyed the things that I did. And I did enjoy learning and the intellectual dimensions, challenge of schooling. But, no, the guy I met when I was twelve and we're still very close friends – My parents were amused. He lived downtown, so we found that playing downtown in the lanes was a good experience, and very different than what one would do in the part of town that we lived in, which was Westmount, [endnote 54](#) which was rather a good district of the city and where the shakers and shapers of industry and business and the government and so forth were supposed to live. So I really enjoyed playing sandlot baseball and roaming the streets and so forth. I actually ended up with one school friend, who was a piano player and an athlete as well. He said, "We're putting together a trio. How about you taking up the bass?" So I did take up the bass. I was never a great acoustic bass player, but I loved the music, and I became interested in jazz and have an abiding interest in it, and played for several years in small groups in the city.

NC: This was like in the early fifties?

CS: This would be in the late forties and into the fifties. I knew I'd really arrived when my musician friends would call up and say, "Say, Doc, do you think you can get me any of that stuff?" [endnote 55](#) I'd say, "No, I don't do that." "Do you think you can help out my girlfriend?" [endnote 56](#) "No, I don't do that." (both laugh) But it introduced me to a life

that I never would have known otherwise. My parents were always thoughtful about it. They said, "Well, we think you'll know what to do. Yes, you can borrow the car to put the bass in."

NC: Were you playing be-bop in the late forties?

CS: No, but I was playing with a really interesting guy for a while by the name of Keith White, who was a student of Lennie Tristano. [endnote 57](#) And I collected well. I collected [Duke] Ellington when most people said, ah, Ellington, yecch. [endnote 58](#) But I'm proven right. The other person that I now resonate to is Bill Evans. I mean, since Bill Evans was always very careful about his bass player, I know why I stopped playing bass, but I can appreciate what they do. [endnote 59](#)

Our youngest son, who became a musician, he had a band here in Montreal, and he had a band in the San Francisco Bay Area. In each place, his band was said to be the best of its class in the area. He's a serious musician. We have a great time talking about music.

All the kids are interested in music. My mother was going to be a musician. Her mother encouraged her, pushed her into that direction. She was always a family musician. We all loved to have her get her fingers working again and play the piano at Christmas and family gatherings and so forth. She decided that she could be a happy amateur musician, but she was not going to be any performing musician. Of course, she gave up teaching, being a missionary, being a musician to become a doctor, and did it very well. When she died--she died at a hundred and five--she was a much revered person.

NC: The narrative I'm getting is that you see yourself as largely being kind of left alone to make your own decisions and being trusted to make the right ones.

CS: And had the opportunities put in my way to make the right decisions.

NC: Is that how you see yourself?

CS: I think so, yes.

NC: And there's a fair amount of serendipity coming up in your stories.

CS: Yeah. But I'd say that the personal life was nurturing, it was -- I have one other thing to tell you. [I and] my wife and three kids, in a Volkswagen Beetle, were driving to Quebec City to write the accreditation exams for pediatrics. You had to do that in order to practice pediatrics. You didn't have to have a fellowship, you just needed to display your competence in this basic area. We were hit by a hit-and-run driver and our car rolled over three and a half times and rolled through the oncoming traffic.

NC: This was when?

CS: This was the autumn of '61. I was sure we were going to be killed. I heard the noise and I said to myself, God, it's noisy along the way to death. I called out and I said, "Zipper, it's been great."

NC: Zipper?

CS: That's her [my wife's] name. When the banging and crashing stopped, we were upside down, the battery acid was leaking on my coat in the back seat. Two of the kids had fallen out the back window, and our older child was going, "Ow, ow." She'd been bruised. That was it, and I realized we were alive. I've lived every day since as if it might be the last.

So the things in the Odyssey and in Gilgamesh that say the importance of death is that it highlights the beauty of life, and if you're in the medical end of things, it's the significance of disease that highlights the importance of health. That was a formative experience, to have that accident and survive it. [endnote 60](#)

NC: Memento mori.

CS: Yeah. I never regretted the experience. I got out of the car and I could see the guy who hit us. He had stopped farther up to see what damage was on his car. And they were building the highway, and there were a whole bunch of people rushed to see what had happened. I can see myself standing there, "Get the bastards!" (chuckles) That's what I shouted out.

NC: But no one got them?

CS: Nobody got them, no. Anyway, there was a car behind us -- again, all life is connected. I had a colleague and friend who had been with me in [Boston]-- Claude Roy [endnote 61](#) was his name, and he'd been with us in Boston, and he'd been at the Children's Hospital here. He was living and working in Quebec now. It was a friend of his who was coming to visit Claude, who was in the car about three cars back behind us and saw this whole thing. He rushed up to the car, white as a sheet, and when I climbed out of the car, he looked at me and was absolutely astonished. He said, "I thought I was going to find you all dead." We got into the car and he drove us down to Quebec City, and I went and wrote the exam, because I'd already paid two hundred bucks for it. (chuckles)

That probably says something about me. How can that guy go and write an exam? I have no idea whether it was a good exam or not, but I passed it. Or maybe the rumor got out that this is what happened and they just passed me.

NC: What do you think it says about you?

CS: I must be stubborn about some things. (chuckles) Or relatively neutral about events that happen to me, because I was able to do it. I don't know what it says about me, but it does say something. Maybe it's just my Scotch ancestry comes in to play. Since you paid all that money for the exam, don't waste it, laddie.

NC: A couple of questions about your early interest in science. I gather that when you were in high school and college, I understand that you had several possible paths. Medicine was not -- you were not a kid who saw yourself following your parents. That happened, but --

CS: No, no. I did not take courses that made it certain I would get into medicine.

NC: What was your major as an undergraduate?

CS: Geography.

NC: And did you take much biology?

CS: No. I took this course by Berrill, and that was more or less it.

NC: That was basically a survey kind of course?

CS: Invertebrate biology, yes.

NC: So no genetics as an undergraduate.

CS: No.

NC: And in medical school?

CS: No genetics.

NC: You started medical school in the early fifties?

CS: Fifty-one.

NC: Clarke Fraser came to McGill and started the medical genetics clinic in 1950.

CS: Yeah. He may have given us one or two lectures, but I don't remember them.

NC: You don't remember them. So maybe one or two lectures. Didn't make a big impression. So you were not, as a medical student -- at that time McGill was well out in front in terms of medical genetics. Hopkins didn't have its program yet, Seattle didn't have its program yet, Wisconsin didn't have its program yet, Michigan basically still had a heredity clinic and it was sort of tied to the old eugenics days.

CS: Clarke Fraser was way out there in front. And furthermore, putting his clinic into the Montreal Children's Hospital was a unique event. Norma Ford Walker [endnote 62](#) had a clinic, but it was sort of at the university.

NC: At Toronto University, right.

CS: So Clarke was -- we haven't got there yet in this narrative, but he turns out to have been the perfect colleague because he had all of this infrastructure, and things were happening here. He had courses at McGill that he wanted me to teach in, but he also said, "You do what you do and I do what I do and let's see what happens."

NC: But that didn't happen until later.

CS: He was right behind the development with setting up a biochemical genetics laboratory. It was predicted that Scriver and Fraser wouldn't get along. Alan Ross said, "We'll see." And Fraser was wonderfully supportive of what I was trying to do. He said, "I don't understand what you're doing," and I said to him, "I don't understand syndromology

at all. [endnote 63](#) How does your brain work for that?" (chuckles) But we were complementary, and we liked what we were doing together.

NC: But that wasn't until 1960 or so.

CS: That's right. But in medical school, I had no awareness of what he was doing. I knew he had a cleft-palate clinic when we were here at the Children's and that that was multidisciplinary. But that was about the extent of what I encountered.

4. University College London; Learning Chromatography and Biochemical Genetics in Dent's Laboratory; Harry Harris

NC: I don't yet have a clear picture of how genetics came into your --

CS: Harry Harris.

NC: It wasn't really until Harris and Dent, when you went to London.

CS: That's right.

NC: There was a glimmer of hereditary patterns when you were at Harvard at the Children's Hospital.

CS: Yeah. But I think it was being connected to chromatography by some fluke that took me to Dent, by that fluke that opened up the idea of the inborn error of metabolism, which of course then led me back to Garrod. [endnote 64](#) But it was Harry Harris who really animated that part of me.

NC: Do you want to get into that now, or do you want to save that? How are you doing?

CS: I'm doing fine. We can go till six. Is that all right with you?

NC: Yeah. Let's talk about your time at UCH and UCL [endnote 65](#) across the street.

CS: [Lionel] Penrose [endnote 66](#) was there.

NC: Okay. So paint the picture for me. First of all, I don't understand completely the relationship between UCH and UCL. If you could sort of paint the picture of who's there, what does it look like, what is the space like, what are the interactions among people?

CS: Okay. The McLaughlin Traveling Fellowship was to work with Dent in his lab. Dent was a big presence in that world of chemistry coming into medicine, developing the techniques of chromatography, et cetera.

NC: Chromatography was pretty new and hot.

CS: Yeah, a big tool and a Nobel Prize-winning technology. I went to his [Dent's] unit, which was called the Metabolism Unit, and it was in the medical school, which was on the corner of Gower Street and -- I'd have to look at the map to remember the names. I can walk down them, but I can't remember them. The University College Hospital was across the street in a strange Edwardian building. There was a guy in Dent's unit who used to have a telescope so he could read blood pressure readings so he didn't have to go down the stairs, across the street, and up the stairs. (laughs) These were old buildings. When I went back to the lab at night and turned on the light, the floor moved. It was cockroaches. That didn't worry me, but it was interesting. Everything was old and simple, and a good place for me to feel comfortable in and learn.

The University College Hospital Medical School was on that side of the street, the Thames side. That would be University Street. I'll look up the map and tell you later on. On the opposite side of the street was the hospital. Then across -- did I say it was

Tavistock? Anyway, the north-south street-- was University College, the campus that appeared in the movies *Carry On, Doctor*, and so on. [endnote 67](#)

It was the college founded by Jeremy Bentham, [endnote 68](#) and when I was there, Jeremy Bentham was still being carried in his sedan chair, his stuffed body, fully dressed, with his head between his legs, and he was carried into the [university] senate meetings. Because when he had endowed that university, he was not sure that his executors were to be trusted, so he insisted on being present at the meetings. (laughs) Because this was such an interesting, eccentric ceremony, when I went back in 1970 and took our kids, I took them across the street, into the building, and I went to the beadle and I said, "I'd like my children to meet Mr. Bentham, please, sir." He recognized me and he smiled and he said, "Oh, yes. We can do that." So we went down and, "We've moved Mr. Bentham. He's in a special place in a cabinet." So he rattled his keys and he opened the door to this cabinet and he swung them open. And there's this glass thing, and there's Mr. Bentham sitting there. My kids go, "Ooooh!" And just at this point, E. Zed [E.Z.] Young is walking by, the great biologist, and Young looked at the kids, looks at me, and calls out, "And don't forget his head's between his legs." (laughs) And then the beadle goes through the whole thing, telling them what it's all about. And they still remember this.

Anyway, the University College. And over on the left of the famous stairs with the pillars and everything, behind which is the senate, was a quadrangle with a series of buildings, and in the left was the Galton Laboratory. [endnote 69](#) The Galton Laboratory was the place of Lionel Penrose. I knew -- I was very comfortable with Harry Harris because Harry made you feel comfortable. He had sort of taken me under his wing, and he gave me encouragement. But Penrose was something else. I mean, he was a tough guy. He had a dragon lady who looked after him, and you didn't get in to talk to Penrose unless you really knew what you were talking about and you had something to talk about. I was given encouragement to go and meet him by Park Gerald, [endnote 70](#) who was doing an overseas year. He said, "Why don't you come over and meet the man?" So I did. I met him twice. And one of those things that I will give you, unless you have it already, is Penrose's inaugural address as Galton Professor in 1946. [endnote 71](#) I keep reminding everybody in my field, "Have you read Penrose's paper on phenylketonuria?" Most people haven't, but everything we do today was thought about by Penrose, including that it was a treatable disease that had a chemical cause for mental retardation, it was inherited, it was autosomal recessive, the distribution of the disease in human populations was not uniform, et cetera, et cetera, et cetera. My respect for Penrose is, again, retroactive, because I never spent time with him, except to say I've been in the great man's office. But I've read his paper and I keep reading it, because it's so amazing.

Anyway, the lab [at UCH] was on the fourth floor, and it was full of glassware, and it had the first Moore-Stein column in the U.K., and it had the first mechanical calculator. David Cusworth, who was my other mentor and who ran the Moore-Stein column [endnote 72](#) and [knew] everything about it, and had gone over to New York to learn the details from the folks there.

NC: What is the Moore-Stein column?

CS: This was the long resin column that you pumped down through it the buffer that would elute the various amino acids in a sequence, and then it dripped into a tube and you then added ninhydrin to the reaction and you counted -- you used a colorimeter and

you read the tube and you had a quantitative estimate of the amount in that tube. And since the amount in the tube depended on the flow through the column, you had peaks, and the position of the peak was determined by the chemical characteristics of the solute that you were looking at, and since you used ninhydrin, what you were looking at was amino acids. So it was a way of getting quantitative determinations, by elution chromatography, [endnote 73](#) of an amino acid content and composition of the fluid you were looking at. You could do it for plasma if you de-proteinized it, and you do it for urine if you treated the urine with respect.

So that's what I learned to do, as well as partition chromatography so that I could -- Dent used to say, "The pattern of amino acids in two dimensional chromatography, and with the appropriate staining, the position of the amino acids and the coloring is like recognizing a face." He was right. You could hold up the thing and you could say "Hartnup" from twenty feet away, when you knew the language, or you could say whatever it was, cystinuria, and so on. Normal variation.

When we opened our lab, that was what I did. I did that type of chromatography for years and years [partition and column methods]. Then we switched over to quantitative things eventually. But I was never as happy with the column of numbers that would be generated by a computer as I would be with looking at a chromatogram.

NC: Are you good at pattern recognition?

CS: I got to be, for that, and therefore I appreciated what Clarke Fraser was doing with pattern recognition for syndromes.

NC: What was the physical space like then in Dent's lab?

CS: Crowded. I mean, the room I worked in was probably as big as this one. The door would be there. Roland Westall's desk would be there. We had some old antique desks to sit at. There were three of us in the lab. And then there was, over on that side of the room, there was a big apparatus which was electrophoresis, a new idea that you could separate amino acids with electrical charge on wet paper.

NC: Is this starch gel?

CS: No. Starch gel hadn't appeared quite yet.

NC: They weren't doing it there. Smithies' paper came out in '55, so it existed. [endnote 74](#)

CS: It existed.

NC: But I don't know whether they were doing it there.

CS: No, they weren't.

NC: But this was not Tiselius free [-solution electrophoresis]... [endnote 75](#)

CS: No. This was a special type which never got widely adapted, but it was a way in which you could put a lot of stuff on a big piece of paper, turn on the power and let it

flow, and then stain it. And you could separate amino acids by distance in these runs.

NC: You would run them out on filter paper and run the current through the paper.

CS: Yeah. Big Whatman filter paper. [endnote 76](#) I haven't thought about that very much for a long time. But I even bought one of those pieces of equipment and put it into our lab, and we used it when we wanted to do something that might give us additional information from using the solvents, which were fairly potent solvents. We used lutidine, which was terrible smelling, and my wife always knew when I'd been doing the chromatography, because my clothes smelled of it, and phenol. [endnote 77](#) The two dimensional chromatography, with lutidine in one dimension and phenol in the other. The nice thing about the electrophoretic approach was that -- it maybe caught on fire once in a while (chuckles), but it didn't have a terrible odor.

NC: So you had all of that equipment in a room of what? Twelve by fifteen or so?

CS: In London, yeah, I would say.

NC: How many people working in there?

CS: David Cusworth was working in another lab. There were four of us in that room. Mary Efron was one of those people. I think a lot of people thought that she was of genius quality. She really was very bright. She was simply Bob Efron's wife and she was bored at home, so she decided to come and do something. She'd heard about Dent and she said, "Can I come and work for you?" He said, "Yeah, if you want to." So she learned chromatography and she had lots of ideas.

NC: She was a pediatrician, right?

CS: I think that's where she started. Anyway, it was interesting. She was going back to Harvard, she was going back to Boston.

NC: So she was an American?

CS: She was American. Her husband was going to have a lab at the VA [Veteran's Administration] hospital, and she didn't have a job, so -- Park Gerald had gone back to work at the Children's, and I knew from him that he was looking for people to work with him. I said, "What about Mary Efron? Would you like to interview her?" He interviewed her when she got back, and I referred her to him, and she took off like a house on fire and became -- She was in the lab when I was working on the proline thing, and she had lots to say about it, and it seemed the right thing to do, since the conversations had been productive, to have her involved. So she'd done some additional work on the project, as I recall, which is why her name's on the paper in *Nature* and in the *New England Journal*. [endnote 78](#) Then she and I both got interested in using the chromatography techniques that we knew to develop screening tests. She had one approach and I had another. She published hers, in the *New England Journal*, I think. [endnote 79](#)

She worked with [Robert] McCready, who was an old-style microbiologist in public health, who recognized that the world was changing, and said, "Chromatography in newborn screening is a very interesting way of trying to prevent the diseases associated with inborn errors of metabolism," so he supported Mary Efron to develop what became

the Massachusetts newborn screening system. [endnote 80](#)

Whether we were competitors or whether we were collaborators, I don't know. It depends on whether you talk to Mary, who died, or whether you talk to me. But I think we were interested in putting into the health care systems new approaches.

I was working in Quebec, and I was able to develop a 40,000-family study with my colleague, Carol Clow. It's interesting. I said, "We really need somebody to work on this." And everybody said, "I don't want to do that. That's boring stuff." Carol Clow said, "That's pretty interesting." We'd known each other since high school days, and she said, "I'll do that." So we did forty thousand families for first and follow-up tests, first time and second time. That was the pilot study that said we could put this into health care in Quebec. When the new Minister [of Health] came in who allowed us to create the Quebec Network of Genetic Medicine [in 1971], which was that paper in *Science*, [endnote 81](#) there we were with this system all ready to go.

But what we had done was, we had done ours with chromatography, and by that time we were able to sort out what the really important things were in Quebec, what the prevalent things were. So we redesigned the technology and we went to quantitative McCaman and Robins. [endnote 82](#) We did phenylalanine and we did tyrosine, tyrosine because that was important in Quebec for hereditary tyrosinemia. [endnote 83](#)

And we did the PKU story, and because we were in Quebec, the Minister said, "Well, after you've got your positive test, you'll want to corroborate it and do backup investigation, so I'd better appoint four [referral] centers. And after that, I presume you'd like to be able to treat the patients, so we'll put that into the budget, too." We were the first people in the world to do that. The United States couldn't do it because they didn't have health care.

One thing flows into another, and I think the idea that we had learned chromatography and we could see ways to put it to use was one of the foundation stones for the Quebec Network of Genetic Medicine. Thinking medically as well as thinking scientifically, you could see reasons for having technologies and infrastructures that would allow you to have early diagnosis and prevention of the disease, because you had something that you could do in the way of treatment.

NC: And this all grew out of a journal that happened to catch your eye because of its bright red color.

CS: Yeah. (both laugh) Or because people said, "Go and find out something."

NC: That's amazing. Tell me about Dent and Harris. What was the nature of the interaction between the folks at the Galton -- Harris was at the Galton. He was not yet director. Penrose was still there. Harris became director pretty soon.

CS: That's right, he followed Penrose. He was at King's College when I was there.

NC: So he was not located at the Galton.

CS: And he was not located at UC, he was at King's.

NC: So that was a third node in that cluster.

CS: Yeah. I never went to Harry's lab. We would meet in various places, or he would come back to our lab, or it was on the phone. But he did take me out on a field sortie when he was interested in the polymorphism erythrocytes and he wanted to collect blood, so he said, "This is a good time to talk. Come with me."

NC: How did you meet him? When was your first meeting with him?

CS: That I don't remember. As I recall, it was a phone call because I wanted to ask a question and I think Dent said, "Why don't you ask Harry Harris?" But I don't actually remember how that loop started.

NC: Okay. But Dent and Harris published together.

CS: Yeah. And I think it was time for Harry to go off and stretch his own wings. That's what he wanted to do, and he was certainly capable of doing it. Dent was originally a chemist who became a physician during the war and then got this remarkable opportunity to identify inborn errors of metabolism using chromatography. And Harris, who I think was highly trained in thinking genetically -- I suspect that Dent wouldn't have been as interested in Harry's interest, which was, there seemed to be two types of cystinuria, one completely recessive and one that was incompletely recessive, as he called it. And isn't that interesting? That means the heterozygote shows the phenotype, and that's unusual for a Mendelian recessive disorder. So are we looking at two different genes? Are we looking at two different mutations? That type of thinking would be Harry Harris.

Harry Harris was the one who brought Garrod back into visibility after [George] Beadle and [Edward] Tatum said there's been somebody there before us. [endnote 84](#) It was Harris who went and republished all Garrod's famous original papers and then wrote his own appendix to the book, which was this is what we can think about in modern human biochemical genetics. [endnote 85](#) I can show you a couple of those books tomorrow.

NC: That was in '63.

CS: I think so. Then he started his own book called Human Biochemical Genetics, which was published in -- it went to three editions. [endnote 86](#)

NC: So it was Harris who got you interested in genetics.

CS: I would say so. I came back prepared to realize who Clarke Fraser was. (chuckles)

NC: Dent was more on the biochemistry side and Harris gave you the genetics, is that right?

CS: I think that's fair. And certainly Roland Westall was the person who made me learn the biochemistry of amino acids and appreciate what you could know, which is how I got to know Alton Meister and how I probably got introduced to -- Alton Meister wrote the great large book about amino acid metabolism in his day. [endnote 87](#) If you wanted to be serious, you had to have that book on your shelf.

5. Working at McGill; Doing what You Love

So each of these people gave me a perception that there were different ways of doing science, which is probably one of the reasons why I was quite happy to join with Clarke Fraser and the other original members of our group to create what we called the MRC [Medical Research Council] group in Medical Genetics, which was created in 1972, and which put us onto this [the fifth] floor, whereas we'd been over the boiler room and under the cafeteria, and got to be the multidisciplinary, multi-principal investigator group. I'm much more comfortable working that way, with other colleagues, than I am being the only one, even though I may have appeared to have been a loner initially. I have been offered the opportunity to be chairman of this and chairman of that, and do you want to put your name in for dean. The Markle would have been very happy, but that's not what I wanted to do. I wanted to be doing what I'm doing. My dad gave me the most significant piece of personal advice in my whole life. A man by the name of John Evans, who was -- he was really Mr. Big in medical science in Canada, a clinician-scientist, he started up the McMaster School of Medicine in Hamilton [Ontario], and it was the most exciting thing in medical education. [endnote 88](#)

We'd kept meeting at the clinical meetings in the year '62 -'63, and I would present my stuff. He phoned me up one day and said, "I'd like to come down and talk to you about something." So he came down from Toronto, and we went into our old lab downstairs. I said, "What do you want to talk about?" He says, "I want you to come and be my chairman of pediatrics in this new medical school that we're creating." This was 1967 in the spring. Well, John talked at me for two hours, and by the time he was finished, I didn't know what was up or what was down. It was my moral responsibility to leave McGill and go and be part of this exciting new development and so on. My father was at home, he was dying of pancreatic cancer and he was getting yellower by the week. I went to my dad and said, "Look, John Evans has just left to go back and he's absolutely convinced I'm going to be his first chairman of pediatrics. What should I do?" He looked at me and he said, "Do you like what you do?" I said, "I love it." He said, "Do you think you'd be able to do that and be the chairman of the new department?" I said, "I don't know, but I see what you're getting at." He said, "Do you think you'd be as happy doing that as what you're doing now?" I said, "Probably not." He said, "Do you think you would do that as well as what you're doing now?" I said, "Probably not." He said, "Well, then, they might not love you as much as they seem to love you here, so why would you leave?" (both laugh) And I said, "Thanks, Dad." That's a very simple set of questions and the answers are very clear.

So I turned down the offer, and every other offer I've ever had. That woman that you met [Lynne, his administrative assistant], and her former colleague, we worked together for -- we've now been together for thirty-five years. They opened up a file afterwards, starting in the seventies, or late sixties, and the file was, "Offers refused." [endnote 89](#) I've never had any difficulty turning down offers.

NC: Is it a pretty fat file now?

CS: It was. Not many people ask me to go anywhere now. I still give talks, but -- no. I've been very happy at McGill. And McGill's been very good to me. Do what you love.

NC: I get a sense -- as much foreshadowing of the conversation that I want to have as looking back on what we've said so far, but I get a very strong sense of place.

CS: Absolutely. I mean, I started out saying I was born here, I'm going to die here. If you haven't seen the McGill campus, we've got to take you by the McGill campus.

NC: I haven't. I'd like to.

CS: There's no other campus in the world like it. I mean, it's a postage stamp, it's surrounded by heritage buildings that are the finest late Victorian, Edwardian buildings in Canada. The Redpath Museum, which is now reused and houses all sorts of things, [endnote 90](#) was declared the most beautiful building in the British Empire when it opened in 1894 or '97. To have been on this campus as a student was one thing, and to be part of this place, it's persona, really means a lot. Nobody understands how McGill works, but -- (chuckles)

I have to tell you this story. I've been here all my life at this particular institution, and in this particular building, rather like Barton Childs at Johns Hopkins. We haven't got to Barton Childs yet.

NC: No, but we will.

CS: Yeah. A new administrator came into this hospital, with whom I've now developed a very happy, wonderful relationship. But anyway, her job was to solve the problem of genetics, because genetics had been a very high profile thing. We were responsible for something like forty percent or fifty percent of the research that comes through this institution. We'd trained people, they became chairs, et cetera, et cetera. Then I'd done enough of this, and I said, "I'm not going to do this anymore." Then another person took over the MRC group and Clarke retired and went off to Newfoundland and took that, and Gravel left, and came back. So the core, the heart, the momentum was changed.

Then the group was -- they said, "Well, you can't do all the modern molecular stuff here, so we better move some of the people into another place." So physically we were so successful that we metastasized, and when we metastasized, things became different. There was a problem -- we haven't got to the discussion yet. We did the clinical stuff and the research stuff all together. The patients used to come in and ask the graduate student, "How's my problem going?" And I'll tell you about that tomorrow.

But there was a problem getting somebody to head up the group the way it had been headed up, and with its own motor and energy and so forth. Because I wasn't going to continue to do it, and my successor went somewhere else, and we were fractured, et cetera. So there was a problem in training, there was a problem in looking after the patients that we had acquired, and there was a problem with keeping the momentum in research. So the question was what to do about genetics after Fraser, after Scriver, after Gravel. [endnote 91](#) So the new administrator was handed the job by the chair: solve the medical genetics problem at the Children's Hospital.

She looked at it very carefully and called in a meeting. We were all sitting here -- the people who you'll see tomorrow and around here. She was sitting there, and the only chair left was to sit beside her. Nobody had told me this meeting was taking place, and somebody said, "Aren't you coming to the meeting?" I said, "What meeting?" And they said, "Oh, well -- " So anyway, I came.

She started to talk, and she said, "I've been given this job, and my decision is we'll close the unit, we'll send the patients over to the other hospital, we'll celebrate the excellence that's been here for the last many years. And, Dr. Scriver, we'll ask you to move out, because you're doing research now and you're not involved with the patients. Lynne, you can go into the pool for the institution. Nobody will not be without a job [sic], but it will be different in the future." Well, a shock level went around the room and the faces all looked at me. They all knew that I didn't know about this because I was looking just as shocked as everyone else.

When the meeting was over, I realized that this was something that I could deal with. I went around to everybody and said, "It's not going to happen. Trust me." That famous political phrase, "trust me." (laughs) They said, "Really?" And I said, "It's not going to happen." Then, when I'd gone around to everybody saying that, I thought, Now what do I do? What's my next trick? (chuckles) I started with myself. I said, "God, if they separate me from Lynne, how am I going to work?" Because it was too late in my life to start to learn to type and use a computer and so forth. Can you imagine Barton Childs doing it? I can't. (both chuckle) Well, you can't imagine me doing it. I found that I had her salary money. I got it. I brought it in, but it now had disappeared into the maw of the hospital. Because I was no longer directly responsible for everything, it had moved in another direction. So it was clear I wasn't going to get her salary back; therefore, I might not get her back.

I went to the dean, and I said, "I'm the Alva Professor of Human Genetics. [endnote 92](#) You have an endowment. We've used it to recruit people like Tom Hudson [endnote 93](#) and other people and solve problems. I've never had to draw on that fund because I always had career awards and so forth. Right?" He said, "Right." So I said, "I have this interesting proposal. Can we use the Alva Endowment to pay Lynne and keep me functional?" He said, "You know, that's an interesting request. I've never had one like that before. But then, McGill does interesting things. It solves its problems in different ways." Two weeks later a memo comes, yes, we'll do that. So she gets paid out of the Alva bequest, so every morning I come in and I greet the Alva Professor of Human Genetics. (laughs)

NC: That was the joke that you made earlier.

CS: Yeah. It's my example of how McGill works, nothing categorical, nothing hierarchical, if you can solve the problem to make McGill continue to be what it is. And there's the example in my life. So I'm continuing to work. I send a progress report to my nominal boss, Rima Rozen, [endnote 94](#) who runs the Research Institute and runs it superbly, and who is a former member of our MRC group, and brilliant. I send her a progress report and she says, "Gee, very nice." The reason it's very nice is because I can work, because of Lynne. I can work, because the dean said, "Yeah, the problem's soluble."

And the administrator who was giving us the impossible assignments is just so happy because we didn't disband. There was a colleague of mine from the Quebec Network of Genetic Medicine, by the name of Serge Melançon, who was suddenly without a job himself, because the thing that he'd taken on was closed down by the government. He sent an e-mail out to everybody, "I'm looking for a job." I saw that and I went down to the chairman [endnote 95](#) and I said, "Here's the solution to your ten-year search for the director of the Division of Medical Genetics." Serge came. He's been smiling ever since.

Everyone else has been smiling. The division has gone back up with full momentum, training. Residents are pouring in, they want to study, et cetera. The administrator's just delighted.

NC: Enlightened deans. That's wonderful. Maybe we're at a good stopping point. I've got a whole lot of stuff; I'm a little worried if I open up the next can of worms, we're going to end up cutting off abruptly. So we'll take this up then tomorrow, your coming back to McGill and setting up the units here and so forth. All right?

CS: Yeah.

6. Becoming a Human Genetics Researcher; Charles Dent; Barton Childs; Ideas and Networks

NC: It is Wednesday morning, August 23, 2006. I am here in Montreal with Dr. Charles Scriver. We are in session two of his oral history interview. Dr. Scriver, I wanted to begin this morning with just a couple of fact-checking things and fill in a couple of gaps and things we talked about yesterday, and then press forward with how you became a human geneticist. One thing if you could clarify for me, you were telling me yesterday about the Dent and Walshe paper of 1954, which you cited as one of your top ten most influential papers. You said that that was the paper that -- you saw that journal issue. You were told to go and find a gimmick, as you called it, that you could bring to this department, and you saw that journal issue and that led you to the Dent and Walshe paper, and that's how you ended up going to --

CS: To Dent's lab in London.

NC: To Dent's lab in London. I was just looking that up. That paper came out in '54 and you went to Dent's lab in '58. When was this that you went and found that issue? I was guessing about '57.

CS: It would either be -- I graduated in medicine in '55. I would have been doing my internships '55 to '56. I went into the medical rotation in '56, up to December. So it probably was in late '56. I think that must be about right.

NC: So that issue of that journal was about two years -- but it was still about two years old, right?

CS: Yeah.

NC: So it wouldn't have been the top journal in the stack, presumably, right? Were you rummaging through and finding back issues? How is it that --

CS: It's possible that -- that's an interesting question. I don't know. I don't remember that detail. There have been delays in arrival of journals, and as I narrate the experience -- and this is with the beauty of the fallacy of hindsight -- it was the journal that was facing me. But it may have been as you described. I know it was that journal, and I remember the experience of the color bands that caught my eye. But possibly it was as you see here, I pick up one and I say, "Oh, what is in the other articles?" It didn't come out regularly, it wasn't a monthly. It was, I believe, a quarterly. Maybe it was a yearly. We could look that up. [endnote 96](#)

NC: The reason I ask is that it would suggest a somewhat more systematic scanning of the literature than just wandering in and the issue catching your eye and flipping through it. I believe that the issue caught your eye. I'm not doubting that.

CS: It's an interesting point you bring up. I always ask students whether they take a journal, and if not, why not? Especially if they're studying genetics and biology and so forth. I took a journal when I was a medical student. It just happened to be the British Medical Journal; they had student rates. That was a habit that I acquired as a student.

And my parents both subscribed to journals, so the house had piles of journals. So it may have been a sort of ingrained habit to pick up a journal and look to see what was in it and if that British Medical Bulletin pile had an interesting top copy, I might have gone through and come up with that chromatography issue. That's a really interesting forensic question. (chuckles)

NC: Right, because it says something about the appeal of that issue of chromatography to you. There was something about it that made you say this is worth exploring a little bit, and getting to the back articles. Right?

CS: Yeah.

NC: Okay. Also, was it Harry Harris who introduced you to Archibald Garrod?

CS: It would have been at that time if anybody -- it could have been Park Gerald, because Park and I knew each other from Children's Hospital in Boston. He was there working with the hematology group, as I recall, as a fellow. Then he'd gone across the street, and his family and our family kept in contact with each other. Not vigorous, but there was a certain amount of contact. So it may have been him. It could have also been Dent. I haven't highlighted the place of Dent in my career as much as Harry Harris became sort of the opening of the door, but Dent was a really interesting, complicated character. He should have been a member of the Royal Society, but he was one of these pugnacious individuals who alienated a lot of people. And in the British system, I think he may have suffered by being persona non grata, therefore never nominated. But Dent would walk down a corridor and he'd throw out a question. Did you think of this? Did you do that? And you realized, "That's the key that I need to go and look up something." He was an important person. So he may have been the one who mentioned Garrod.

NC: Would you consider him a Garrodian?

CS: Yes and no. I mean, he was the one who realized that if he -- I have to keep stressing the fact that he was trained as a chemist. He was a chemist of dyes, and that was his original profession. For various reasons, he was encouraged to take a medical degree. I think he was non-recruitable for some reason or another and so didn't actually become a combatant in the [second world] war. He was studying medicine, and he realized that there was a staining part of chromatography, because you could identify compounds by using particular stains and the colors would tell you what -- not only the position, but the color would tell you what the substance was. He was very good at that.

So, for him to say, "I've got a little tool that will bring out the chemical composition of this bodily fluid and it's associated with that disease, or that condition, therefore it gives me another way of describing the individual person with the disease." That would have intellectually been in the tradition of Garrod, because Garrod was a side-room man. I mean, they used to make jokes that his rounds were half the time spent looking at urine in the side room and half the time might be with the patient. And Dent was, in a sense, continuing that tradition with a new set of tools. Whether consciously he was doing it, or whether I could honestly say I recognized that association, I couldn't say that honestly. But Harry Harris, I knew, was working his way into reinventing Garrodian thinking, the world of what was emerging as human biochemical genetics.

NC: So Dent, through his interactions with Harris, which you talked about yesterday, would have certainly been aware of that and would have recognized some commonalities, although Dent was not as interested in genetics as Harris. Is that right?

CS: I would think that's a fair summary.

NC: He was more on the chemical side and the relation of the chemistry to the disease.

CS: Yeah. If Dent had been elected to the Royal Society, we'd have a biography of him and you could answer your own questions, because there is a wonderful one on Harry Harris. [endnote 97](#)

NC: So, where this is leading is, I'm wondering if you can reconstruct for me when you began to think of yourself as a human geneticist.

CS: That's another very interesting question. As I said yesterday, when I came back to be the Chief Resident in Pediatrics, I discovered I was not as interested in being the Chief Resident in Pediatrics as pursuing answers that I had got to why does this person have this disease now. And the idea that there was something called clinical investigation that would let me, as a physician, answer those questions in a different way was very exciting.

Again, so much happens by serendipity. I'd made this interesting observation -- new inborn error of metabolism, hyperprolinemia. Didn't have the enzyme defect or anything. Just had the metabolic phenotype. Had made the observation that the proline sat on a shared carrier and that there was, therefore, something that was both separatism in transport and federalism in transport systems, as the terminology became. Here I was describing a separate system, but which was interesting because it was shared. Yet, the body wasn't losing all the proline, even though the carrier was being competed for, et cetera, et cetera.

So what else was in the tubule that was serving the substrate? I went on to discover, shortly after that, an inborn error of transport that affected the proline-glycine-hydroxyproline system. So that, by this time, told me I have identified a carrier at the functional level, and now I've confirmed that carrier at the genetic level because there is a mutation which is expressed as an autosomal recessive. I think that occurred about three years later.

Anyway, somewhere around that time, I was putting all of this together and I was encouraged by Dent, "Why don't you write up an abstract that will be submitted to the American Society for Clinical Investigation?" [endnote 98](#), which was the nirvana of where we wanted to go. We'd talk and present and be heard. These meetings were all held in Atlantic City in the old days, on the Boardwalk in the spring, and it used to be known as the meat market because this is where the chairmen of departments went to find the bright young guys to recruit for their department. My paper, I will never know, but maybe there was a little help, or maybe it wasn't all totally neutral, objective peer review. Who knows what it was? Anyway, my paper got on the plenary session. So here I was, absolutely terrified, presenting the work of Scriver, Efron, and Schafer to the ASCI on the plenary session. By today's standards, it was a very modest talk. By the standards of those days, it was a modest talk, but it caught the eye of other people who wanted me to write reviews about the possibility of inborn errors of transport in a way that had never

been done before, et cetera.

I guess this is when I begin to say, "Hey, I'm not really going to be a [clinical] physician." I have a taste of what it's like to be in that community of peers. They like what I'm doing. And this is when I want to move forward. I'm on the threshold of recognizing that there are things called inborn errors of transport. I've done Hartnup. I'm on the threshold -- I can't remember the sequence of the papers. You'll know them better than I. Somewhere about that time I'm describing a hereditary iminoglycinuria. [endnote 99](#) I'm saying, yes, I'm beginning to think about human individuality expressed through chemical individuality that can be understood in Mendelian terms, and that's human biochemical genetics.

NC: This would have been what year? '64?

CS: In the sixties. We'd have to look up a list of papers. It's one of that set of papers that I gave you earlier.

NC: We'll look on your CV here. What we need to do is look at the list of -- okay. [pause] The Hartnup disease paper was '65. [endnote 100](#)

CS: Was it that late?

NC: That's your paper A16. [endnote 101](#)

CS: That's how long it took to release the paper.

NC: But the work had been done while you were in Dent's lab, right? So that was from '59 or so.

CS: Yeah, the work had been done.

NC: OK, the Nature article was in '64 and '61.

CS: So what's the second one, in '64?

NC: Scriver and Wilson, "Possible locations for a common gene product in membrane transport of imino-acids in glycine." [endnote 102](#) You're talking about a gene product there, so that was your paper A8. Twenty-two is the amino acid transport [paper], that was *Science*. [endnote 103](#) So '64, '65 you're writing specifically about gene transport.

CS: So I would say that by that time I'd become -- I'm also a Markle scholar. I'm being protected. We talked about Alan Ross being the person who was making sure I was protected. I had a lab. I was able to begin to do lab work.

Another person that I should mention who was influential was Peter Scholefield, [endnote 104](#) who was working with Judah Quastel, [endnote 105](#) and he and Rose Johnstone -- Rose Johnstone [endnote 106](#) became the head of the biochemistry department years later and Peter went off to be the head of the cancer institute in Toronto. They said, "Look, you've got these interesting ideas. Have you ever thought of using renal cortex slices to study transport in vitro?" I can remember Peter rolling up his sleeves and taking out a microtome blade [endnote 107](#) and saying, "This is how you do it." I brought that technique into the lab, and with various people, such as Wilson,

[endnote 108](#) we began to work on rats. We took rats and infused them and showed the shared transport interactions, and then we would make slices of kidneys and study transport.

This was all new to me. I have to explain that I'd really had very limited lab exposure, compared to what people do today in their postdoc. I'd had no formal training in genetics. I was learning genetics as I went. Clarke Fraser would say, "Oh, this might be interest you. You can learn some genetics." I was busy reading the transport literature, Christensen [endnote 109](#) and people like that who were telling me how to think about the functions that I was looking at. But it was pretty much a bootstrap type of work and learning that I had.

NC: So a picture is emerging then of you learning your genetics on the side and making that transition from a pediatrician to a clinical researcher. This is in the early sixties. There's a sort of a window here, it's not a single aha! moment. As those things are happening, you begin to think of yourself as a human geneticist.

CS: Yeah.

NC: Am I reading that right?

CS: Or a human biochemical geneticist. I realized there was so much -- By this time I was beginning to realize there was a huge history of Mendelian genetics, and of course it takes a little while longer to realize that there's Darwin behind all of this. I'm not sure at what stage in my intellectual development that I actually went and read the Watson-Crick paper [endnote 110](#) and what it implied. But in due course I picked up these milestones that we talked about yesterday that helped me to go back and read the Avery paper [endnote 111](#) and go back and read the original Watson-Crick and get a grounding in what I was trying to do.

NC: So the tradition that you allied yourself with was the biochemical tradition more than the genetic tradition.

CS: Yes, absolutely.

NC: So at what point did you begin affiliating with the human or medical genetics community? Were you going to the ASHG [endnote 112](#) meetings at this point?

CS: No, not at that time. I was going to the ASCI and the Canadian Society for Clinical Investigation. [endnote 113](#) I think the great moment was, I must have been at something to do with biochemical genetics, and I think it was Silver Springs, Colorado. I can't remember the auspices of the meeting, but Barton Childs was at it. [endnote 114](#)

NC: When was this?

CS: I don't remember. It may have been in the sixties. We think it was somewhere around then. Anyway, this guy who's fifteen years older than me comes up to me at the end of the day and said, "Shall we go for a walk?" I knew something about Barton Childs because he'd been saying some wise things at this meeting.

NC: Hadn't heard of him before that.

CS: Not that I was aware of. Park Gerald, I think, would have mentioned him, because Barton was the first of all of us who went to study with Penrose. Barton, if you really want to know who I am, what you need to know is who Barton is, because Barton was a pediatrician and Barton was interested in why does this patient have this disease now. He went and studied with Penrose. He was the one who, way back in the fifties, wrote a paper saying this will help us to understand our patients and will make diseases understandable, and so forth. I discovered that retroactively after meeting him.

He sort of took me aside and said, "Maybe if you read some of this stuff, it would help you with --" I don't remember the conversation. All I remember is him, as it were, taking me under his wing and saying, "There's some good things for you to learn about." And we've been friends ever since.

NC: This was at the meeting in Colorado sometime in the sixties.

CS: Yeah. It may have been the Biological Sciences Curriculum Study group, but I think that's a bit early for me being involved with them, because he got me involved with them.

I think the other thing that really lit a fire under the recognition of me was this participation, first of all, in the pilot study, saying, "Can I use these little chromatographic methods to develop a method for newborn screening so that we could prevent, through early diagnosis and treatment, a dread disease, like PKU?"

Then, having done this in Quebec and begun to report it, which is what I did -- I look back on it feeling that I really had a moral responsibility to publish everything that had ever been supported by public money. [endnote 115](#) You don't say I'm too busy to write that paper up. So I sweated it out at home, wrote the papers and submitted them. There was a responsibility to try and publish everything that was negative or positive about what we did. There was some opportunity for awareness that I was involved in newborn screening. I was very much in at the beginning.

And Barton Childs, when he pulled together that National Academy of Science committee, before the Institute of Medicine became what it is today, he had a committee that went for three years and published the report in 1975 on genetic screening. [endnote 116](#) I was the Canadian on the committee, and one of the reasons why we were there was because we had solved so many of the problems that beleaguered the Americans because we had universal health insurance. It was a wonderful matrix in which one could do these things. It was part of health care. So we had a lot of experience.

When Tay-Sachs disease had its enzyme deficiency recognized, we were—we had—a very active Jewish community. [endnote 117](#) I had established some awareness here in Montreal that we were doing some interesting things with biochemical genetics and with screening and so forth, so a group of people from the Jewish community came to me and said, "We would like to do this project to see whether we could screen for Tay-Sachs carriers."

I got involved in that, and that brought me -- that was in the early seventies. So Barton knew I was doing that. Mike Kaback [endnote 118](#) was doing it in Baltimore, and I was doing it in Montreal. This sort of consolidated my connection with Barton, and to just leap

way ahead—We were involved in lots of interesting intellectual and pragmatic things.

Then in 1983, was it, his [Childs'] wife was killed in an automobile accident, and my wife said, "Do you think we could do something for Barton?" I said, "Well, maybe we could invite him up to come to Vermont to spend some time with us." We did that, and Barton came up and spent, one summer, about a month with us. It was such a happy experience that we did it again the next year. And out of that experience came these rather landmark papers by Costa and Hayes as the first authors and Scriver and Childs on the impact of Mendelian disease and the treatment of Mendelian disease. [endnote 119](#) So that's the historical narrative of how that connection [began] -- and we've been in contact with each other ever since.

NC: As you said, Barton was older than you. He had worked with Penrose and Harris closely.

CS: More with Penrose, I'd say. His main anchor was Penrose's office and lab.

NC: Did you have a sense of, here's a guy who's found the path that I've been looking for? Did that really kind of crystallize things for you?

CS: I don't think he was telling me this was the path I wanted. He knew that I was on a path that was like his.

NC: What was your mental experience? Did you find --

CS: My mental experience was, wow! here's a whole new set of windows opening. "Have you read this, Charles? Did you read those papers?" Then he was publishing in the PNAS that paper in which he said that glucose-6-phosphate dehydrogenase shows allelic variation and so on. [endnote 120](#) So I was being introduced to things that -- and whether I discovered Harry Harris' paper on acid phosphatase, [endnote 121](#) the qualitative and quantitative variation independently, or whether it came from him, I have no memory of that at all.

But I think it's fair to say that I began to think in terms of individuality within populations, and so frequency distribution curves. There's been lots of quantitative data about what normal amino acid values are and so forth, but I think we were among the first, meaning our lab, to just say, "What does the distribution of amino acid values look like in a group of normal people?" And the normal people were like me and my colleagues in the lab. I decided to look at men and women, and I decided to look at them under fasted and normal dietary conditions through an interval of the day. Out of this we found by doing ANOVA [endnote 122](#) statistics that each person had their own frequency distribution within the population distribution of values. [endnote 123](#)

Now, that type of thinking came naturally to me once I had been encouraged to think that way. But that's absolutely ground zero thinking for Barton Childs. Whether Barton had an influence on me or not -- but I can remember going to Kurt Sittmann in the biology department, who is the statistician for the biology department, and saying, "Kurt, I've got a really interesting idea. There's a student in a course that I teach and she's all excited about working on this problem with me, so we're all empowered to do this. What do you think of looking at the frequency distribution of normal amino acid values? Nobody's done it. And look at gender variation and look at circadian variation." Kurt was German,

and he said, "Ach! That is a good idea." (laughs) He vetted the statistics for us and was, in this case, a helpful colleague.

I go into that story because I think that paper was an interesting paper. [endnote 124](#) But I was at that place and thinking that way because of my initial association with Harry Harris and my continuing association with Barton Childs. And then you read Garrod and you say, "Oh, other minds have thought about these things before." They didn't have the tools, they didn't do it quantitatively, but -- and I know there's a whole body of statistics and literature out there that I'll never accommodate in my practice and work, but nonetheless, I dipped my toe in those pools and found it really interesting.

NC: And you were pre-adapted in some ways. You were already studying urines and the chemical composition of, and interested in urinalysis as a tool for understanding the biochemistry of metabolism. You had so many pieces there.

CS: Yeah. What I had, in addition to the pieces, was the opportunity -- I mean, so many people had their opportunities destroyed by circumstances or something else. I keep stressing -- I mean, we've now created a scholarship in this country to reanimate the clinician-scientist's mode, or the translational scientist as we're called. I keep telling the young scholars that if you could possibly go for one important thing, get yourself a mentor who will look after you when you're in the formative stages. I keep coming back to that -- I may not have recognized it at the time, but I sure recognize it now, the role of those people who looked after me. Although I give the big credit to Alan Ross because he was the one who took me through the Markle years and so forth, there were all those other names that I mentioned, who said "Go," and "How about thinking about this?"

NC: Was there anybody else at that time, in the sixties, who was thinking this way, in terms of inborn errors and individuality and these kinds of Garrodian things?

CS: Oh, yeah. I mean, there were a whole bunch. If you look at the literature of the time, Bill Nyhan in California [endnote 125](#) was certainly thinking that way. Leon Rosenberg, [endnote 126](#) we became good friends after Onslow Wilson made some outrageous comments at a meeting in which he was presenting a paper and he was questioned by Leon. Wilson made these comments, so Leon decided to call me up and he said, "What's going on here?" (chuckles) I said, "I think this is just Onslow. We've been reading your papers and we're both working on similar themes, so let's get together." And we got together. That was in the late sixties.

NC: So Wilson was working with you?

CS: He was a graduate student. And then Leon and I became friends and found we were interested in what each other was doing. Then we ended up getting together and writing the book on amino acid metabolism. [endnote 127](#)

But in terms of other people thinking that way, I'd have to go back and remind myself of who was there. Bert La Du, the pharmacologist, who was definitely Garrodian in his thinking. [endnote 128](#) We became friends, and I visited him and he visited me.

The omission will seem to be -- not naming the names will seem to be unfair, but it's just that there's a lot of them out there. I'm not remembering them all. There was a community of us who -- it was small, it was tiny, but nonetheless we were there.

Another one who -- Donough O'Brien, [endnote 129](#) he had a major lab and program in Denver, Colorado. He was [Anglo-]Irish. He just died a couple of years ago. He and I got along very well because we believed in human biochemical genetics, inborn error screening, diagnostic laboratories, thinking treatment, and so forth. We worked on the American Academy of Pediatrics Committee on Nutrition, and then we were formative in creating the Committee on Genetics. The Committee on Genetics at the American Academy of Pediatrics [endnote 130](#) was the first formal medical organization to commit itself to a theme of genetics.

Pediatrics saw the Mendelian cases with early onset, so pediatrics was aware of this component of medical care in a way that the other organizations might not have been. There were people like O'Brien and Scriver and -- I can't remember -- Rosenberg was an internist, so he wouldn't have participated. But Nyhan and others were part of the American pediatrics experience and would have attended the Society for Pediatric Research meetings [endnote 131](#) of the American Pediatric Society.

We would be submitting papers for the annual scientific meeting to a section that was called either genetics or biochemical genetics. This led to things like the development of opportunities for treatment that bypassed the American system. What we'd done in Canada was develop what we called a food bank system for the delivering of special diets and products that were necessary to treat the patients with the inborn errors of metabolism and should not be on the shelves because they would be harmful for people who had normal metabolisms. That Canadian experience, which we started here out of our lab, got to be known, and the American Academy said this is kind of interesting. Could you work on this committee, and could we talk to the Blue Cross/Blue Shield, things like that. So there was a community emerging.

In answer to your question who were the other people, were there other people? Yes, there were. There was a very small nucleus, but nonetheless we were there. And it started in pediatrics, and that's why Barton Childs was interested in saying, "Let's look at the natural history of Mendelian disorders." What we showed in the Costa paper was ninety percent of the Mendelian disorders that were in the catalogue of McKusick [endnote 132](#) in the fifth edition presented before the age of puberty, which is why, of the ones that we looked at -- we did a randomized troll through the McKusick catalogue of the day, the fifth edition, and came up with three hundred sixty-seven conditions. Then we just asked for age of onset for presentation of symptoms, and it turns out that ninety percent are manifesting themselves before puberty.

Well, that means they were seen in pediatric departments and not in internist departments, which is one of the reasons why there was a preponderance of these interests in pediatrics and why Garrod, as a pediatrician, was seeing them in the Great Ormond Street Hospital [endnote 133](#) in 1902.

NC: In my limited experience of hospital politics, pediatrics tends to be kind of a little brother. It's usually medicine and surgery are like the giants that dominate the politics, they get most of the money, they have the ear of the dean, they get the best space.

CS: The Four Horsemen of yore. [endnote 134](#)

NC: Exactly. And if you're talking about this nucleus of people, mostly physicians -- I

mean, these are not Ph.D. scientists we're talking about, these are almost all clinicians -- and meeting in places like pediatric meetings, most of them with training in pediatrics. This is one of the beginnings -- I think the story has many beginnings, but this was an important beginning for a real transformation in medicine, where this genetic perspective has come to be seen as really fundamental. That permeates all departments of medicine now. And here it starts out in this -- maybe satellite is an extreme word, but the little brother, kind of, Department of Pediatrics. Did you experience anything in the larger meetings -- I don't know if you went to other general medical meetings.

CS: I used to go to FASEB. [endnote 135](#)

NC: Okay. Was there any experience of resistance of this idea of biochemical genetics and looking at comparing the normal with the disease and so forth? Was it difficult to get that across?

CS: That's a rather interesting question. There was a club, called the Peripatetic Club, which was founded by Fuller Albright, and I got elected to it. It was made up of the great and the good from the Ivy League schools, and Montreal was included because [William] Osler [endnote 136](#) came from Montreal. (chuckles) I think it was with sufferance that it was allowed.

Anyway, JSL Browne was one of the first endocrinologists who participated in the clinical significance of cortisone after it was discovered. [endnote 137](#) JSL Browne, here at McGill, was one of the people who got a little dose of cortisone to treat a patient. So he was a very important person in that axis of influence. And again we're talking about things that don't get into the standard histories. He was certainly a later mentor for me. I haven't mentioned him before, but I had planned to bring him into the story somewhere along the line. He took an interest in me. But, for various reasons, he was not the organizing force that Beck and Christie were. But if I was to say was there another influence on me, it was JSL Browne, who was in the back, saying, "What's Scriver doing?" Again my father was the one who had to bail out the Department of Medicine because JSL Browne was not able to do the things that could be done, so the recruitment of Christie was the resolution for that.

Back to the Peripatetic Club. It was a place where you could -- they called themselves that because they had a meeting in each of the places, so it would be Philadelphia, it would be Boston, it would be New York, it would be Montreal, it would be Johns Hopkins. So they came to Montreal one year, and the rule was the old guys didn't talk. The "old guys" being somebody who was over thirty. (chuckles) They didn't give the talks, but they would ask the questions. The bright young guys would get invited to give the talks.

Well, at the Montreal meeting I was asked to give a talk. My talk was, "Rare diseases: why bother?" Something like that. I gave this talk about what we were learning from the inborn errors of metabolism, what the Mendelian -- and by this time I knew enough that one gene made one protein, and that the protein would be part of a complex. So I talked about what I was learning, and I probably gave considerable emphasis to the transport story. Those guys thought that was an interesting talk. There was a certain buzz after it. Instead of talking about the common disease and what was the latest thing in diabetes, or what we were learning about cholesterol, I talked about these rare problems and I got noticed.

NC: The Peripatetic Club was people from all across medicine.

CS: Yes. They were surgeons -- not many, they were mostly internists, but they were endocrinologists, they were cardiologists, and a few pediatricians. Alan Ross was a member at the time, as I recall.

NC: This was a fairly elite sounding group.

CS: Oh, yeah. As I said, I was talking to the good and the great.

NC: So you got a chance then to expose these internists and surgeons, and whatnot to these genetic ideas, and it was well received. That wasn't the exact title because I did a quick search and it didn't pop up, but I remember seeing --

CS: Well, it may not have been published that way, but that was the essence of the talk that I was giving --

NC: I remember seeing a title something like that. I'll dig that out and try to bring that. Do you recall offhand what year that was?

CS: No; probably in the '70s. Can I take a break?

[pause]

7. Building a Program and a Team; Genetic Screening Programs and the Quebec Network for Genetic Medicine

CS: While we're talking about influences, we've been focusing on the people who one might call those thinking about where medicine was going, where genetics played a role, but in terms of my own contributions to that work, you have to think about the people we were working with. It's quite apparent at the time, and certainly with hindsight, that what happens is often related to who's with you at the time. It may be a graduate student or a postdoc and so on.

I have mentioned her name once, but Carol Clow was somebody who I knew from high school years. When I was a resident in pediatrics, the year after I graduated, in training, my mother was Chief of Service of Pediatrics at the Royal Victoria. I was introduced to all the patients on the ward, and I was introduced to Mrs. Clow and her son who's dying of leukemia, in those days. My mother said to me, "Mrs. Clow will teach you about the dying child." And Carol looked at me and I looked at her, and I said, "We haven't seen each other for quite a while. This is rather an unhappy way to renew our acquaintanceship." But anyway, I did learn about the dying child that way. Then I go to Boston, I go to England, I come back. It's about 1962. Carol is walking through the hospital here and she calls out, "Oh, Dr. Scriver, you're back." Something like that. She has an Eskimo child in tow, and I say, "Carol, what are you doing here?" And she said, "Well, I'm a foster mother. I look after these kids when they come down from the Arctic and they can't get back because they're snowbound up there, so they need homes. There's always room for one more." She had several children of her own by this time.

Then one night she phones me up -- I think it was in 1963 -- and she said, "Can you tell me what this means?" And she starts to read something and I recognize a coroner's death certificate. I said, "What happened?" She said, "My baby died." It was a sudden death in infancy syndrome. So leukemia death is one thing, it's chronic, but sudden death is something else, and the legacies of the two are totally different. So I said to Carol, "Let's meet. I'm in the lab."

So we're sitting there talking and I hear these feet coming into the lab and into my office, and I recognized my mother's walk. I said, "Come on in, Mother. It's happened again. Carol needs to hear from you." My mother's advice was exactly what I just said, that the two deaths are very different. She said, "My recommendation is if there's some way to keep yourself busy, and not dwelling on what you didn't do right and so on, I think you should think about that."

Carol had already registered to go back to university. She was very smart. She'd never had the chance to attend university, although the father of one of my school friends had put aside money to send her to college. Her mother was the classic upstairs domestic in the *Upstairs, Downstairs* genre [endnote 138](#). Her mother was famous in Montreal.

But to make that story come to an end, we needed somebody in the lab and I offered Carol the chance to come to work. And she did. It was about the time we were thinking about doing the chromatographic pilot study. We had decided that we really should try all the hospitals in all the regions, and Carol said, "And I know something about the Arctic, so we could even do the Arctic, couldn't we?" [There were these teams going] up north and it was all part of the Quebec emerging healthcare interest and purview.

So Carol came to the lab, and because no one else was interested in doing the tests, she did all the chromatograms for the forty thousand families, and we looked at them together. We became intellectually and personally close, and she was definitely an animating force in what we did. All the stuff that has to do with the screening is as much to her credit as to mine because it takes somebody to have the idea, but it takes somebody to do the work. She did the work. And she liked the idea. She said, "I don't write, but I'll tell you what's wrong in your sentences." So the papers that have her name on them deserve to have her name.

Then we accumulated these patients out of the screening program, and I began to get phone calls from the mothers of the patients that we picked up in our pilot study of screening, and here were anxious mothers. I can remember me saying to this woman, "Your questions are mother questions. It's your first child, you're worried about the child. There's much less to worry about in the PKU side of things than you think. Would you like to talk to a mother who's had several children?" "Oh, I would like that. I'm so sorry to bother you. I should never bother a doctor." You know, it was that old mystique that you don't bother the doctor with common sense questions.

I said, "No, your questions are all important because if you can't deal with them, then that will get in the way of treating your child with PKU." So Carol said, "Sure, I'll be glad to talk to her." It clicked. So I began saying, when these calls were coming in, "Why don't we work out a way that the first call is to you? Woman to woman is comfortable, woman to male doctor is not so comfortable." And it evolved.

Then we got interested in another group of diseases called rickets. [endnote 139](#) I haven't told you that story. The treatment of that became very complicated, so we began to put together a team of a nurse, who was Terry Reade, Carol Clow, who was Carol Clow, and me. We began to work on the hypothesis that the patient and the family already had a big enough problem. They've got a Mendelian disorder that was dealing with normal homeostasis and normal life. They didn't need to have their child all the time in hospital. I mean, the tradition was to treat some of these inborn errors of metabolism for six months in hospital. We said, "We'll do it at home." Terry could drive a car, so she said, "I'll go to the homes," and we'll man the phones, and I'm in the background. So we made a trio of working on this. I even did a Hawthorne study, time and motion. [endnote 140](#) We worked out a matrix of notes, and we kept track of everything we did in looking after the patients. Those were the process variables, and the outcome variable was how good are we at controlling the phenylalanine value in PKU, and how good are we at controlling the phosphate value in X-linked hypophosphatemia? So we kept track of the medication and everything we did. We put it together in a paper and I sent it in to the *New England Journal* and they said, "Oh, we really like this." It's one of the papers I've given you. [endnote 141](#)

We called that the allied health personnel approach. Joan Marks, the lady who runs the program at Sarah Lawrence, which was the first official program, [endnote 142](#) phoned up one day and said, "Would you come and give the first Melissa Richter lecture to our graduating class?" I said, "I will do it, but on the understanding that Carol Clow will give the lecture or give part of it, because what you like is because she was here and we were able to do it."

This again is an example of serendipity. It starts back in high school. A connection. A very smart woman, who by all credentials has no role to play. She didn't even have a

high school leaving certificate, because of economic circumstances during the war. She had to leave and go and work.

Alan Ross, who never missed a trick, one day came into the lab and he said, "I've been looking at your reports and noticing what you're doing." This is just before he goes off to Africa in '67. He said, "Tell me about Mrs. Clow." So I told him. And he said, "All good steel has got to be tempered in a very hot fire. I like what you're doing with her." Because I'd been told by a traditional administrator that I had no business paying her what I was paying her, and she didn't have the right credentials. I said, "I judge people by what they do, not by the initials after their name."

We had a remarkable dean, Maurice McGregor, [endnote 143](#) who said, "Tell me about Mrs. Clow." And when I had told him, "You know, at this university we have a stream where unconventional people can get promoted and can be put on the academic faculty." When she retired, she was an associate professor.

NC: Without even a high school diploma.

CS: Yeah. So that says something about McGill. But she was also the founder and prototype for the foundation of the first professional program in genetic counseling in Canada. I don't know whether it was the first after Sarah Lawrence, but it was based on what she did. She's a very important person in my life.

NC: Okay. I want to back up just a little bit and lay down some of the administrative foundation for some of the things that we've been talking about. Let's go back to '60, '61 and the founding of the deBelle laboratory. How did that come about?

CS: The hospital made it possible. They built the lab with their money.

NC: What was the impetus? You said, "I want a laboratory for biochemical genetics"? Or did this come out of the Markle?

CS: No, the Markle came sort of simultaneously. I was put up for the Markle and got elected. It was John deBelle, who was the administrator of the hospital, who, with Alan Ross, took the administrator's decision with the authority to do it that there should be a lab for this new thing that Scriver's going to do. I was reporting back from London how things were going. I did tell you that at six months I got depressed and thought I wasn't going anywhere. I mentioned that yesterday. And Dent said to me, "So why don't you ask for an extension of your McLaughlin traveling fellowship?" So I got two years, I got a second year. And everything happened, literally, at the end of the first year and into the second year. That's when all things gelled.

I was telling Alan Ross by mail what was happening, and I guess he made up his mind [that] Scriver's going to work out, he'll be in my department, and he will need a lab. I think there was some correspondence about do you need a lab and so forth. They put aside this old cafeteria space, and I was helped in designing it by Claude Giroud, who was a very wonderful colleague who was head of endocrinology at the time. [endnote 144](#) He took a brotherly concern, interest in me and helped me to work in designing the lab. And also this neighbor of mine who was an architect, Jim Melling, who actually did all the design work for the floor you're on now between our lab that we designed in 1972. But between 1961, when the de Belle lab opened in the space over the boiler room and

under the cafeteria, and we were a converted cafeteria. We started out with three or four people in it and we grew to be twenty-five people, and very crowded.

NC: A converted cafeteria sounds like a pretty big space.

CS: Well, I don't know how much of the cafeteria we got. There was a part that was not claimed by anybody, and we got that. But it was a reasonable size. It took the amino acid analyzer, it took the electrophoresis equipment, which was as big as this table. It allowed us to have sitting space and working space. It was big to start with but it rapidly filled up. Because as a new faculty member, I did do rounds, I did attend grand rounds; I did volunteer to do teaching, and Clarke Fraser and I offered to put on a course about what was happening in genetics.

As I mentioned to you, we found the time and people decided they could bring their sandwich or whatever it was and they'd sit on the floor, and we would do what you have as the "soup conference" at Johns Hopkins. We would do it here. Suddenly there were all these guys saying, "Can I do a year with you? Can we work in the lab?" So several people did that, too. People came from the other universities, like Francis Glorieux, [endnote 145](#) who came to work with me on X-linked hypophosphatemia as a graduate student. There was a certain buzz going on, and the space began to fill up. There were graduate students and fellows. It became necessary to expand.

So, in terms of administration, the hospital paid to get me going. The department paid to let me be an assistant professor.

NC: This was the Department of Pediatrics.

CS: This was the Department of Pediatrics. I got a Markle, and the Markle paid me. It was my first career award. And the rest of my life at McGill has been on career awards. So McGill likes me. (chuckles) I haven't cost them a great deal. When the Markle finished, I -- what happened after that? I guess I was put up for a Medical Research Council career award and got that. The rest of my time was as a Medical Research Council scientist.

Clarke Fraser and I and -- I'm trying to remember who the other original group investigator [was] -- I think Len Pinsky, [endnote 146](#) who did tissue culture and had come back from working with Bob Krooth and Jim Neel [endnote 147](#) at Michigan. I think he was one of the people -- I'd have to go back and look at the notes.

Anyway, we proposed to enter the competition to establish Medical Research Council Groups. Up to then, everyone was principal investigators. Groups were interesting because they would help out with the salaries of the principal investigators. They would provide you not with one-year funding. but five-year funding, and that was wonderful. And they would also -- we strongly recommended a training program in which there would be funds -- you guys know all about this at the NIH, but this was new in Canada. There would be committed funds in advance for the very bright students who would apply. We could take them on and then send them out to go and get their own student awards. MRC thought that was a really nice idea.

In the genetics competition alone, there were five separate applications. We looked at our competition and we said, "Well, maybe not that one, but, God, we'll never beat that

one." But anyway, we won. The reason we won was because we were already at that point looking after a lot of patients. We had a clinic, but those patients could be part of the lab, and they would wander into the lab. And we said, "The research and the applications go together like this." We were the only application that looked like that. Malcolm Brown, who was the head of the Medical Research Council at the time, [endnote 148](#) told me that that was one of the things that looked rather good. The fact that it involved Clarke Fraser certainly was very helpful, because he had established his reputation in Canada. And the fact that this young guy Scriver who was doing interesting things was part of it, they liked that. But they really liked the way McGill worked.

Malcolm Brown -- again connections. My parents knew him. He'd call me Charles; I would say, "Yes, Dr. Brown." (chuckles) He was six foot five or six foot six. He was a very austere person, like so many of them with a sense of humor behind it all. He came down to McGill and he walked in and he looked at the lab where we were working, looked at the cubbyhole that Fraser was in, and he said to the chairman of the day, who was Mel Avery -- who went on to be a professor at Harvard. Harvard recruited her from here, and she started out at Johns Hopkins -- [endnote 149](#) He said to Avery and to the dean, "We will not send MRC money to McGill until you give Scriver and Fraser appropriate space." And then walked out. (laughs) Well, there's nothing like a hanging in the morning to concentrate the mind on the beauty of life. (laughs)

So suddenly it was possible to find space. What you're sitting in was the storage space, completely unfinished, not even a finished floor, in the nurses' building, where they put all the beds and all the junk, because they never finished off this floor for nursing accommodations.

Jim Melling came back into the picture. He lived in the block across from us. His wife was dying of breast cancer. And my wife would make a pot of coffee, Jim would put Beth to bed, and he would come over; and about eleven o'clock we would start designing the lab. Every day I came in and talked to everybody and said, "What are your ideas? What do you want?" And I brought everybody up to see this space. I said, "Tell me what you want to do."

We ended up with an open lab design, a central track where we'd run up and down, open bays. Carol and her team had an area which looked across at the research bays and so forth. I had a little cubbyhole office. Lynne and Huguette [administrative staff] worked in the only place that had any sort of surrounding, and it was all glass so that way they could see everybody. It worked. On good days there were fifty to sixty people on the floor, with all the graduate students and fellows and technicians. It was pretty crowded.

NC: So this is Fraser's group plus your group.

CS: Plus our group. Well, Pinsky wouldn't have been here because he was part of the group, but he kept his lab over at another place. But the other investigators in the group would all be here. I can show you a Christmas photo in which some of the people are in cytogenetics, but everybody else was in this group and its appendages.

NC: So there was some cytogenetics going on here, too.

CS: Yes.

NC: We're now talking about the early seventies.

CS: Yes.

NC: So we've got biochemical genetics, clinical genetics, cytogenetics. You're covering the waterfront here.

CS: Yeah.

NC: Full service medical genetics.

CS: Yeah. The other thing I have to tell you, since you're asking about administration, is again typical of McGill. The MRC says we won't do anything unless you build the space, the dean says I have no money. Where do I go? And they go to their board of governors, and Hugh Hallward -- it was John Molson who provided some of the money to get us going the first time. [endnote 150](#) Hugh Hallward, who is on the board of governors of the hospital, said, "Oh, I'll arrange for that." Arnold Steinberg, who's another person who's on the board, arranges for this space and other things. These were serious men who were benefactors and they helped things to happen. Again, the United States knows all about that. It's called philanthropy. It's less prominent in Canada, but it was very helpful and important in our case.

The other thing that you need to know about is, how did all of that Quebec Network of Genetic Medicine occur? When the pilot study was finished and said it is doable, let's do it, a young man by the name of Claude Laberge [endnote 151](#) comes back from working at Hopkins with McKusick. Laberge is a new generation French Canadian who, instead of going to Paris and so forth for his training, goes first to Toronto, then to Hopkins, and comes back to Quebec and said, "I'm the new generation."

Laberge and I hit it off. I don't speak much French, but he's tolerant of that. He had a father, he tells me, who was a civil servant and knew how governments worked. So if I learned things from my parents, Claude learned things from his parents, and he says, "We can put together a proposal that the government will like." My chairman, Mel Avery, and the other chairmen of pediatrics say, "Look, genetics is in pediatrics. You guys have got some tools that will allow newborn screening to happen. We're the places that can look after the patients when you've got the patients. Let's go for it."

There's a meeting of the four chairpersons, and there's a meeting of four or five of us, including the present guy, Serge Melançon, of the people who would call themselves modern medical geneticists. We proposed to create the Quebec Network of Genetic Medicine.

NC: What year was this?

CS: It starts thinking this way in 1968. It follows -- again another one of these serendipitous things. There's a commission called the Castonguay-Nepveu Commission, [endnote 152](#) which is looking into the design and development of health care in Quebec under a new mandate, which will be universal health care insurance. You guys in the United States have a Nobel Prize winner by the name of Kenneth Arrow. [endnote 153](#) He wrote some very influential documents on how to design universal health care

insurance. He's just been elected as a foreign fellow to the Royal Society. Everybody honors what he wrote. Canada implemented it, you guys have still got to implement it. (laughs)

Anyway, Castonguay has gone around the world with his commission. He's gone to New Zealand, he's gone to England, he's gone to the USA, he's gone to Sweden, et cetera, et cetera. He comes back and he has his own commission here in Quebec, and I'm invited by the director of the hospital, Jack Charters, and Alan Ross -- or is it Mel Avery at this point? This commission was about '57 and I think it was just before Alan Ross went off to Africa.

Anyway, I'm there at the commission, and I said, "What am I going to do?" I'm director of the Research Committee and I presume I'm supposed to talk about the place of research in contribution to health, and so on. The director of the hospital turns to me and says, "Tell them about your work with rickets, tell them about your work with the screening program."

My story with rickets was, there's an epidemic every year of rickets. I have used chromatography to find a generalized aminoaciduria. It occurs in infants with French Canadian names who are fed bottled dairy milk that does not have vitamin D. The other kids who don't have rickets every winter are people who get fed on formula, they're usually [from] another culture, and there's no problem. What I want to do to deal with the rickets epidemic every year which puts kids into the hospital and gives them convulsions, and a serious disease, is to put vitamin D into the bottled dairy milk, like in Vermont and Ontario next door, and so on. It turns out to be an anomalous food regulation in Quebec that contravenes the federal regulation, so it never gets done. I say to Mr. Castonguay, "How do I solve this problem?" That's the end of that thing.

Then I describe the newborn screening possibilities to prevent diseases through early recognition and the introduction of treatment. After the commission's hearings, this austere actuarial scientist gets off his platform, comes up to me and says, "I was very interested in your story. How do you think governments work? What do they work with? Is your issue a vote one or a dollar one?" I said, "I don't think it's a vote one for the rickets story." He said, "Do you know what it's costing the government to care for those patients with rickets?" I said, "I haven't done the arithmetic but I could do it quickly." He said, "Go home and do it tonight, rewrite your letter that you've been sending; you say you've been phoning the government and telling them that there's a solution to the problem. And my prediction is they'll change that regulation. It takes more work to unregulate something than it does to create the regulation." So I did that, and I got a phone call from the deputy minister two days later, and the problem got solved. That was my introduction to how governments work.

The screening project really interested him, because he said, "I understand that this is very cheap technology. You can do it universally if we have a health care system in Quebec that's universal. I think we should look into that." I talked to Claude Laberge, we designed the Quebec Network, and Castonguay said, [after he became Minister of Health] "I will give you a protected budget. It will be for screening, it will be for education, it will be to support the laboratory costs that can be appropriately ascribed to this thing, and we will provide treatment." "Really?" He said, "Well, of course. Whatever the cost of those diets and so forth is should be part of the system. We're providing universal health insurance."

And that's Appendix I of the National Academy of Science's report on genetic screening. [endnote 154](#) Appendix I says we were able to do this in Quebec, because what you have determines what you get. Castonguay said, "I will do it this way. You will have a pilot study for two years and if I like what you get out of those first two years -- you must measure everything and so forth," which we did -- "then we will make a decision about the permanent long-term thing."

By that time, I was talking about adding Tay-Sachs screening, and then two years later I talked about adding thalassemia, [endnote 155](#) because Quebec was getting pretty known, which is why the editor of Science calls me up and said, "I want you to write an article for me in my health maintenance issue, the first dedicated theme issue of Science. I want you to write an article for me." I forget who the editor was. [endnote 156](#) I said, "But I've done that. I've written it up." It was written somewhere else. He said, "You didn't write it for me. I want you to write it. It'll be reviewed, but write it." So we wrote it.

That has, I think, been a significant paper, because it was an early paper that also discussed the interface between genetic thinking and medical thinking, and by that time I'm reflecting some of the things I'm learning from Barton Childs.

NC: That's your 119? The paper you were talking about was the 1978 "Genetics in Medicine: an Evolving Relationship"? [endnote 157](#)

CS: Yes.

NC: The paper was 119. Scriver, Laberge, Clow and Fraser. So Clarke Fraser was on that, too.

CS: Yeah.

NC: Listed as the senior author.

CS: Well, I thought that was an appropriate place for him to be because, although he wasn't directly involved in the Quebec Network of Genetic Medicine, the whole idea of putting genetics and medicine together was certainly him. We had been in the MRC group together. But we were talking about this because the Quebec Network provided a global budget for us, to the network, to the four universities. Then it was divided up by this committee of directors, which was ourselves, and we distributed funds in ways that allowed us to evolve and develop.

NC: Administratively, what was the Quebec Network?

CS: Castonguay was very smart. He said, "I will put you in a division called community medicine, and I will give you a protected budget. It will be sent to you and you distribute it to your institutions." So we were in charge of it. Now, it's an unusual relationship, but it sure worked. When the Quebec Network was abolished, for reasons I will never understand, in 1994, they said the budgets would be distributed to the hospitals. Well, of course, they disappear into the global maw of the hospital budgets. As a result, positions disappeared. Lynne's position was originally funded by the Quebec Network.

NC: Okay. So that precipitated the story you told me yesterday about her being the Alva

Professor.

CS: Yeah.

NC: It's called the Quebec Network for Genetic Medicine, not, for example, the Quebec Network for Medical Genetics or any of the other possibilities.

CS: No. I think we might have been the unknowing originators of the term genetic medicine.

NC: Was that term chosen carefully?

CS: Yes.

NC: Tell me about that.

CS: Well, we believed that genetics had a role to play in medicine, and here were shards of technology that showed how that could be. Since there was a counseling component as well, the Carol Clow side of things, this was also part of it. Everything that we did should address the patients with the problem, as well as the technology to find the problem that the patient has. Initially, we thought this was a form of expert technology that would serve medicine, but there had to be a professional awareness behind it that allowed for the interpretation of the test, its implications, why my baby was affected with this problem because of heredity.

We were beginning to recognize, quite strongly, that these problems were not randomly distributed in the population. PKU maybe, but Tay-Sachs, when we wanted to work on that, was in a particular community, also French Canada, a deme [demographic] isolate. And hereditary tyrosinemia, which was a special interest of ours, was a disorder regionally of northeastern Quebec, which reflected the history of the population. So whether we were aware of it when we created the Quebec Network of Genetic Medicine -- Claude Laberge might have been, because he was already thinking in terms of population genetics -- we expected the Quebec community to be different from the Ontario community or the Vermont community, in terms of its genetic makeup. So we were starting on that path that the history of the population is the history of the genes. That's my review paper in Annual Reviews of Genomics and Human Genetics, a late paper, it's 2001. [endnote 158](#) But it's my experience in Quebec that got me into my interest in population genetics.

NC: All right. I want to come back to that; but before we do, I want to back up to your early days again setting up the de Belle laboratory and talk a little bit about the kind of day-to-day practice, your scientific style and your administrative style running this. You told me a little bit about what the physical space looked like. You told me the equipment you had around and the people. And there was something really unusual about this. There were a number of programs, divisions, and departments of human genetics and medical genetics at this point, but this is the only one that I've ever heard of in which the patients are really mingling with the researchers. Hopkins ran a genetics clinic one day a week. McKusick's group ran a genetics clinic.

CS: And Fraser ran a clinic, too.

NC: OK, and that was in a separate space.

CS: We had a clinic where we told the patients, "This is a teaching clinic. You are teaching these new doctors. Because we're looking after you the rest of the days of the week." I mean, we were three hundred and sixty-five days a year on call.

NC: And the clinic was open every day.

CS: And the clinic was essentially open every day. When it was called a clinic, it was for the purpose of teaching residents, and we told the patients that's what you're doing. Then they would come in here.

NC: So the patients would come up here.

CS: Yeah, they would drop in. It could be chaotic in the sense that you might be doing something important, that you thought was important and here was the patient coming to see you. But it was more or less scheduled, come and see us at ten o'clock.

NC: There would be somebody working on the amino acid analyzer, and some mom with her funny looking kid would come in the door and --

CS: Well, the people who came here were the ones with biochemical genetic problems, so we knew what they had, and it would be Carol and Terry who would schedule that. But then Carol and Terry went to the homes. One of the complaints was, we never see your interesting patients, after we stopped having a regular clinic, because the patients were always being seen at home, or in an unscheduled way, as it were. So it is different. And I think it worked for us, but it might not work for anyone else.

NC: And you're being a laboratory administrator and supervising this clinical group, and not just one day, one thing, the next day, the next thing, but sometimes simultaneously, it sounds like.

CS: I laughed when you said, "I want to know about your administrative style." (chuckles) I think there are administrators who know what they're doing, who would not consider that I have any administrative talents. But in terms of the atmosphere and how people felt about it, I think generally speaking it was a place that worked. People liked being here. And that went for the postdocs and the graduate students and so on.

How did we do it? Again, serendipitous moments. One of the guys I was in college with at McGill happened to be a chartered accountant and he was doing an audit for the hospital. We got talking in the corridor and the word was out that I was looking for somebody to come and help with the administration in the lab. He said, "There's a young person on our audit team here, and she's very good. Maybe you should think about her." So this was a connection. Another degree of separation, but a connection. The financial officer of the hospital, who was a wonderful character, told me that regulations in institutions like ours are so often there to challenge you to how to circumvent them honestly. (laughs) Jerry Schwartz said to me, "If you don't take Huguette, I'm going to take her. I've got my eye on her."

So I offered Huguette Rizziero a job, Huguette Rizziero Ishmael. She came, and a year later she interviewed and I interviewed Lynne, and she came. We were lucky in the

sense that we were allowed to have such people. The government was willing to pay for Lynne, and the hospital paid for Huguette. In a sense, administration problems disappeared. Huguette knew what to do with all the accounts. She looked after all the money that came from Quebec, all the money that came from the Medical Research Council, federal money, any donations, gifts, and so forth. She looked after all the studentships. She did all of that, taught Lynne how to do it. Lynne did all the ordering.

When we needed manuscripts typed, they did that. It was wild. I mean, they sat on two desks that were this far apart. I heard it said that Malcolm Ferguson-Smith's CV is like a palimpsest. [endnote 159](#) It's an archeological dig; it goes through all the technologies. We went through all the technologies of word processing. I had the first non-wet-phase photocopier in the lab. We had the first [IBM self-correcting] Selectric typewriter. We got the Selectric typewriter with memory. We got the first word processor, thanks to one of the members of the board of governors and so forth. They just went through them all. That was our administration. For us, it worked. It might have driven an MBA or a formally trained person bananas. But we were able to answer all the accountants' questions. We knew where everything was. The students just loved being looked after by Huguette and Lynne.

NC: And your graduate students, these were Ph.D. students?

CS: M.Sc. and Ph.D. And they would be registered at McGill, in the department at that time of biology, sector of human genetics, but now in the Department of Human Genetics, they would be registered. And again, the registration and everything of that had to start somewhere. It started here and was integrated with the other campus.

NC: Do you know when the section of human genetics started?

CS: It was there right from the beginning with Clarke Fraser. I mean, there was a human genetics sector in the biology department. And then it became a center. We negotiated that with the principal; he liked the idea. Then, eventually, we convinced the university to make us a department, with its pluses and its negatives.

One of the early members of the group when he came back from Harvard was David Rosenblatt. He brought an interest in folate metabolism. [endnote 160](#) He's become a world authority on vitamin B12 and folate. He's now the director of the Department of Human Genetics and very effective at it and making it work rather well.

NC: So, in the sixties when you started the de Belle laboratory, that wasn't administratively partitioned off from pediatrics. Is that right? Was it considered a division or –

CS: It would be a division.

NC: So that's administratively equivalent to McKusick's Division of Medical Genetics at Hopkins.

CS: Yeah. We were not a department, we were a division in the Department of Pediatrics. That was one of our interesting things, because we were anchored in pediatrics. But then we became very successful. David took his lab, which was here, up to the Royal Victoria Hospital and planted himself in medicine. And Pinsky, who was part

of our MRC group and was the first chairman of the Department of Human Genetics, planted himself in the Jewish General Hospital, which was part of the orbit of McGill teaching hospitals. So we were beginning to expand, colonize other places. Then when Tom Hudson was recruited to McGill, and when Narod [endnote 161](#) came back from France and started up the cancer genetics program, and when other people, Roberta Palmour [endnote 162](#) started in neuropsychiatric genetics, et cetera, we had the seed was germinating, and it was very successful. But then it also fractured the identity and the integrity, and as it were, it sort of weakened this part.

When the Quebec Network of Genetic Medicine was terminated in '94, and a source of funding, and there was difficulty in recruiting a successor to the Division of Medical Genetics, which was the home of the MRC group, and all those things were changing, we went through a period that I would say was administratively difficult, and in terms of identity, it was difficult.

8. Students and Other Collaborators

NC: Are you working at the bench during this time?

CS: Yes.

NC: Right through?

CS: Yes. I was slicing kidneys and running amino acid columns and teaching on the campus in the biology department and here and doing my best to understand what administration was going on.

NC: How did you find time to work in the lab?

CS: Well, I don't know. I figure that's what you do. As time goes on, of course, you do less and less of it yourself. It's been a long time. It would have been much rarer -- I retired -- quote, retired -- when I was sixty-five. My retirement meant that I came down to full time. (both laugh) It was clear that I didn't want to stop doing what I was doing, but it had been a long time since I had done any hands-on research. I wasn't particularly good at it. I mean, there were graduate students and so forth.

Rod McInnes, who is now the head [Scientific Director] of the Institute for Genetics in the Canadian Institutes for Health Research, he and I did what I considered some really beautiful experiments where we wanted to look at individuality of amino acid transport. We picked rats. I didn't know that rats were as outbred as they were. There was the Charles River [Laboratories] strain [of rat], and you figured, oh, those are all homozygous animals. And it turns out that they're not at all. They keep outbreeding them all the time to maintain hybrid vigor and strength in the stock. We did these nine rats with these meticulously beautiful infusion experiments that Rod did, in vivo individual rat biochemical genetics. We were able to show with the design of the experiments that each rat had its own profile of reabsorption of this inert substrate testing in the transport system. Well, that was really kind of interesting and I've shown that slide many times since. But I wouldn't have done the experiments nearly as well as he did. They were just meticulously done.

I discovered that, provided you gave recognition to the person, you treated the identity of your colleague with respect, that I could have the pleasure of seeing ideas investigated, and they had the pleasure of doing it, so the paper is McInnes and Scriver. [endnote 163](#) If I had everything to do with it, like the idea of the Hartnup story being Mendelian for the traits but – complex traits – the Hartnup disease, that's one of the few papers my name is on first. And the reason it's there is because it was my idea. I went and dug out the patients, with Harvey Levy's help, from the Massachusetts program, [endnote 164](#) and I did all the quantitative interpretative data, I analyzed the values on our analyzer, and did all the mathematical work, such as it was, and wrote the paper. But if my name's not on it first, it represents the fact that the person made it possible to write that paper.

NC: So you gradually were spending more time on the conceptual side of the science, but you're still doing some work in the laboratory at the bench.

CS: I'm in here every day. I may not be at the bench, but I'm in here every day, in one way or another, keeping busy.

NC: I'm fully aware that you can do science without being at the bench.

CS: And the nice thing about the design of the lab was that it was apparent that you were here, because there were virtually no doors. There was a door on my office, but it was hardly ever closed. It had a great big glass panel in it, so they would come look in if it was closed.

NC: How did projects get assigned in your lab? If you got a new student or postdoc or fellow, would you tell them what to do? Would you hand them a project? Would you give them a choice of projects? Or would they come with something that they wanted to do?

CS: Since we were an MRC group and there were five investigators, they would often pick the person that they would like to be [working with]-- Avihu Boneh [endnote 165](#) came from Israel. He wanted to work with me. After I listened to him, I said, "I really think the person that you should be working with in our group is Susie Tenenhouse." [endnote 166](#) So he took his doctoral degree with Susie.

NC: There are a lot of citations for Tenenhouse.

CS: She worked with Murray Fraser on the reverse transcriptase, and she wasn't very thrilled about that. [endnote 167](#) She obviously was very bright. She said she wanted to come and work with me, and I was a little frightened of that because I figured she knew a lot more than I did. I think I was candid enough to say, "Well, that's okay, but I think what we can do together is work on phosphate transport, because I'm interested in that, and we'll capitalize on your way of thinking." She emerged -- she was timid at first. She didn't want to have authority and responsibility, but it seemed to me that it was just waiting for the time when she would do that.

She has taken the X-linked hypophosphatemia story, which we broke open as a transport disorder – published in *Science* [endnote 168](#) -- and then worked on that mouse -- and they gave us the mouse from Bar Harbor [Jackson Laboratories in Maine] because we had a reputation for that disease. And that allowed us to do the brush border membrane vesicle preparation, [endnote 169](#) which Susie could do and which I would not have done with her skill. So we began to show that this was a disorder that involved transport. Then we began to be concerned about what was going on. It turns out to be an enzyme defect that cleaves something that acts as an inhibitor; the sequence of events is that there is an inhibitor that should be cleaved and is not cleaved because of an endopeptidase deficiency apparently, so it inhibits transport and you lose phosphate. [endnote 170](#)

The other side of our story, which got a lot of fame, was the fact that if it's a disorder, primary or secondary, of phosphate transport, then don't kill the patient with vitamin D, give the missing metabolite, which in this case was phosphate. So we fed our patients with phosphate, and because that pushes calcium up and down, give the patient enough vitamin D to stabilize the calcium and watch what heals with the bones. That was what we published in the *New England Journal [of Medicine]*. [endnote 171](#) That's what the home visits and the monitoring of the treatment did for the phenotype that was the end variable that you were measuring.

Because we were doing that sort of stuff, Hector deLuca, at that time at Wisconsin, was

aware that there were places that he could go with his new molecular discoveries that vitamin D was actually a hormone -- didn't know that, initially -- and that it was synthesized from a precursor substance made in the skin under ultraviolet light, went to the liver, was hydroxylated, went to the kidneys, was hydroxylated a second time in the mitochondria, and became this molecule that was the hormone. He said, "I can give you the hormone in a precursor form and then in a final form. And I like the way you guys look after your patients and what you're measuring, so can I work with you?" So that's why DeLuca and our lab published papers. [endnote 172](#)

But that's about therapy, and what we were able to show was that there was a better therapy than there'd been up to that time and it allowed patients to grow and stop having orthopedic surgery every two years, et cetera. And we're obviously not at the final stage of therapy because we need to know what that strain of gene product is and what it's doing so that we can manipulate it to do a better job, or a less harmful job.

Susie was all part of that, and she's now retired. She came to the lab and that's how she got to work on that side of things, and I think it gave her an international reputation. She would go to the American Society of Nephrology. In the end, the people who were cloning the genes and everything called her directly, they didn't call me. Which was the right way to do it.

NC: So administratively, were you now kind of the head of the group? I mean, it sounds almost German, with a major professor and then other professors underneath. Is that how it worked, or was it something else?

CS: Certainly not the way I thought it was working. I thought we were all playing on the same team, and various people did different things. I may have been the one who animated and organized the resubmission of the group application every five years, and Huguette and Lynne would make sure it all got put together. One year I drove it up in cartons to Ottawa to make the deadline, because one of our members didn't submit his stuff until the morning of the deadline. (chuckles)

I would not like to think of myself as the German professor because I didn't put my name first on all the papers. But I was the one that they were likely to come to when there was a problem. "Charlie, can you fix this?"

NC: I was mentally distinguishing between the administration and the social dynamics of the lab. I mean, it's clear that you didn't run things in a hierarchical way, but administratively you were the head of the group, no?

CS: If we had to make a progress report about the MRC group, each person might write up their part, but I was the one who would put it together.

NC: That's what I'm getting at. So that was a useful digression from my earlier question about how you assigned projects. You had started to tell me about when students would come in --

CS: Our recent work has been focused on phenylalanine metabolism, phenylalanine hydroxylase activating the gene, databases, and all of that stuff. Three interesting examples. Concordia University [endnote 173](#) has a bunch of interesting students. It's a different type of university from McGill. But we've had several Concordia students.

Somehow or other, there's a guy over there whose name is Peter Nowacki, [endnote 174](#) he's Polish by birth, he's grown up in Kuwait, he speaks English. A colleague over at Concordia University says, "We have a student over here who says he'd like to study with you. He'd like to do a degree." So I interview Peter, and I like him, and I tell him that we're getting into this area of databases. And he expresses an interest in computer science. I said, "Would working on the phenylalanine hydroxylase mutation database be of interest to you?" He said, "Oh, yeah, I'd like that." He turns out to be the first student at McGill who did a joint graduate degree in computer science and biology. He got on the dean's honor list, and he's gone off -- I mean, everybody in the United States wanted to recruit him.

NC: Now he's making a million dollars a year in bioinformatics. (both laugh)

CS: He wrote this wonderful thesis, and we went to some of these interesting meetings where we were putting informatics and population genetics together. There was a European initiative in this area. So Peter got to be known. How did he get to work with me? Word of mouth. How did he work on that? Because he was interested, we thought maybe we should try that.

Another anecdote. Rima Rozen, who is now actually the head of the continuing MRC group in its present incarnation, came to me as a graduate student because she was in one of the courses that I taught. She started out on a thesis project that had something to do with methylmalonic acidemia, [endnote 175](#) as I recall. And it was a bust. It was my idea that she'd work on it and it proved to be either a bad idea or something just wasn't going to work. So she was quite discouraged; I was quite discouraged.

I said, "Well, look, I've been working on taurine metabolism a bit and I'm interested in the transport of it in the kidney. Would you like to do that?" And she said, [endnote 176](#) probably under her breath, "Anything to salvage the situation at this point." Anyway, she goes off and does brilliant work on taurine metabolism. Her paper gets published in PNAS, et cetera, et cetera. Rima captures everybody's notice. She goes down and works at Yale in Rosenberg's lab. It gets her noticed. She's now, as I say, Director of the Research Institute, runs a busy lab, has all sorts of wonderful graduate students, and really probably salvaged herself, but I gave her a problem that allowed her to salvage herself. And she's one of the major people in the world today talking about homocysteine metabolism and cardiovascular risk factors. [endnote 177](#)

I got a phone call from England, from a colleague over there, who says, "I have a very interesting student. She's just finishing her degree in biochemistry at the university. Do you have an opening for a postdoc?" I say, "Let's hear about this person." So I get introduced to Paula Waters. [endnote 178](#) Paula Waters is trained in biochemistry. She comes to the lab. I'm warned in advance that she has a certain set of conditions. She's a fundamentalist in her faith, and she will not work on any problem that could possibly lead to termination of pregnancy or medical abortion. I say, "Well, I don't think I'm involved in any work in that area. I am working on the phenylalanine hydroxylase mutations, and we'd like to know how they produce their effect on the enzyme. Does that sort of work interest you? Because I think it's worth looking at." How I got this idea I don't know, but anyway, this is what we do. She says, "I think we could look at that with expression analysis."

So we set up an expression analysis system and we are amongst the first to show that

missense mutations [endnote 179](#) produce misfolding of proteins, and we published that in 1998 or 1999. [endnote 180](#) I get invited to go to a workshop that Niels Gregerson's [endnote 181](#) running in Denmark, a physical chemistry sort of workshop, mini-symposium. I say, "I shouldn't go to that because that's not me; but, Paula, would you like to go to that and talk their language, because if they get into physical chemistry equations, I won't be any good." So she went, and they appreciated what she had to say and she learned from them.

And we have published a series of papers on misfolding of proteins. We were working with somebody -- I always believe in working with people who are interested and who will help. I'm blocking on his name at the moment, but he became a Howard Hughes scholar on the basis of the work that he'd done. I'll come up with the name in a moment. [endnote 182](#)

The idea was that we got to do this interesting work by sort of falling into it. There was no categorical thing like me saying, oh, if you come and work with me, this is what you'll work on. We talked about what would be interesting.

At that time I was writing an MRC group application and I wanted to discuss the population genetics of PAH mutations, first of all in the Quebec population, but at large. They liked that. I wanted to discuss new approaches to treatment of PKU, using substitution enzyme therapy with phenylalanine ammonia lyase. [endnote 183](#) I did have this idea and was beginning to try and implement it. My third part of the MRC application was, Can we look at how missense mutations, or how mutations produce their effect on the protein? By this time, I'd identified Paula Waters was somebody who could work on this, so it looked feasible. We've done one or two little experiments.

The phenylalanine ammonia lyase was being implemented by another graduate student, whose name was Christineh Sarkissian. She came from York University. I found her file up in the biology department. I went through a whole bunch of files, and here was this interesting sounding student, Armenian from Iran, and her recommendation was being given by somebody who tolerates fools very badly, so I phoned him up and I said, "Tell me about Christineh." He said, "She's a real original. Some people will not think they want to take her, but I know you and I think you two would get along just fine."

Sarkissian was interesting because she had trouble with her qualifying stage in her doctoral, and Rima was very tough with her and made her come back and do the qualifying exam again. I said, "Christineh, don't let that worry you. Just do it." One of her troubles is that her mind goes at this pace and her tongue goes at another pace, and they don't always connect, and I got used to the way she works. Anyway, this amazing person has five years postdoc now and has refused to give up the work on phenylalanine ammonia lyase, because Ray Stevens at Scripps has picked it up and says, "I really want to work with you guys at McGill." [endnote 184](#) And by the way, we've just been informed that we ranked number one in the NIH competition and McGill is going to get some money because he's arranged the grant to include a contract that will continue to look after us. And it's on the basis of what we've done, which is what Christineh has been able to do with our mouse colony that's made the phenylalanine ammonia project look interesting, and allowed BioMarin to get interested in us. That's a biotechnology firm in California, a good one. [endnote 185](#)

That's how Christineh got in. I said, "This is what I want to work on," and she said, "I

want to work on that." Ten years later, we're still working on it, with the added joy of the corporate support of BioMarin and the Scripps Institute and Ray Stevens and his team being interested. [Dr. Scriver adds: Christineh went on to complete her PhD, and her exceptional efforts have now translated into an innovative new therapy for PKU. The endeavor brought significant exposure and accolades to both her and McGill University. Based on this and other related experiences, McGill has since restructured the examination process in an effort to be more progressive and to retain the highest caliber of talent.]

Then the other thing that came out of the Waters side of things is, since misfolding proteins are perhaps a major mechanism for genetic disease, could you think of ways to stabilize the misfolding protein and convert a homozygous phenotype, if it's autosomal recessive, into a heterozygous phenotype. In our paper in *Trends in Genetics*, there's one line saying "maybe chaperones could play a role." [endnote 186](#) I was aware that the cofactor for the enzyme phenylalanine hydroxylase may play a role in that, so I asked BioMarin whether they could make tetrahydrobiopterin [endnote 187](#) at a competitive price. They're the only place in the world that made it. And might it play a role as a potential chaperone?

We've just completed an international clinical trial. FDA [endnote 188](#) is really interested in it. They're going to approve it, apparently. And there's a paper being given at the ASHG meetings next month that says this is what we found. And we're doing all the mutation analysis for that, and it all arises out of Paula Waters' work and our interest in tetrahydrobiopterin.

So those are the things that keep me interested now, but they also illustrate the way in which some of the people came to work with us.

NC: It sounds like you listen to what a new student is interested in and you think about how they would integrate within the kinds of things that the lab is doing, and you suggest rather than lay down marching orders.

CS: I've always wanted them never to feel that they were out there on a limb in naked isolation, that there were people around them who would be able to work with them.

NC: Has anybody ever come to you and said, "I really want to work with you, but I'm interested in this totally separate problem"?

CS: Yes, and I would always say, "Well then, I don't think I'm the person to help you with that."

NC: You like to have what's going on in the lab to be integrated in some way.

CS: Yeah. I wanted it to be functioning as a community rather than -- and getting back to networking, that everybody was in some way connected to someone in the group. I might have been the hub or something, but everybody was an important node.

NC: All right. Well, what do you say we stop for lunch?

CS: That'd be a good idea.

NC: Okay.

9. Major Research Themes in Dr. Scriver's Career; Inborn Errors of Metabolism and Transport; Genetic Screening; Management of Hereditary Metabolic Disease

NC: It's still August 23rd, 2006, and this is now session three of the oral history interview with Dr. Charles Scriver. It's now two-fifteen in the afternoon. This session I want to focus on some of the concepts and practices in your science, so we're going to retrace some of the chronological ground we've covered and pick it up through the themes. You gave me, preparing for this interview, this fascinating document on what you called hubs and nodes or spin-offs of the seven major themes that you identified in your own career. I want to start with one of those themes and explore the science behind them and also some of the links among them. Your first theme was inborn errors of metabolism and of transport. I think I understand where the transport part came from. The usual phrase is inborn errors of metabolism, and you wrote very precisely inborn errors of metabolism and of transport. Where does the transport part come into your science?

CS: It was in there because up until cystinuria, [endnote 189](#) which Garrod had got wrong, he thought it was an enzymatic disorder, not knowing what an enzyme actually was, Dent's group had shown that it was a transport disorder and I thought -- I had an aha! moment. I said, "How does that happen?" Working and being taught by Roland Westall to remember that amino acids are amphiphilic [endnote 190](#) and they're water-soluble and they have to pass a lipid barrier, which is what the cell membrane is made of. How does a water-soluble molecule penetrate the lipids and get into the cell? And if Mendelian disorders, such as the one producing iminoglycinuria and the Hartnup disorder and cystinuria, encode, tell us that there are proteins encoded by those genes, then the proteins must be imbedded in the lipid perhaps and producing a pore or a carrier or a here-to-there-ase, whatever you want to call it. [endnote 191](#) Maybe if we could work out a taxonomy of transport systems for amino acids, we would then eventually go back and discover the genes, which is what's happening fifty years later.

It was an intellectual paradigm, saying substrates are water-soluble, they've got to penetrate a lipid barrier to get inside the cell. It was a little later -- and I think I must have thought in thinking homeostatically that the membrane and the carriers facing the outside, the lumen of the intestine, the lumen of the nephron, those are topologically outside body spaces -- would the carriers there be the same as the carriers on the basal-lateral membrane of an epithelial cell that faced the *milieu intérieur*, [endnote 192](#) which was controlled in its composition and had a different set of parameters that were quantitative or metrical trait values. OK?

I began, in a very primitive way at that time, but later more sophisticatedly, thinking that carriers on the brush border membrane and on the basal-lateral membrane of epithelial cells would be different and would have a different genetic parentage. And that turns out to be true, too.

That led to something that I did nothing about, because I wouldn't know how to do it, but, for instance, Blobel at the Rockefeller Institute got a Nobel Prize for recently, how are proteins made inside the cell trafficked to go where they go? [endnote 193](#) What are the signals that say, go into the mitochondrial, go to the basal-lateral membrane? And that's a very interesting -- and then to come way up into the future, this is all part of evolutionary biology. Those are modules. How those modules work, how they're engineered, become very important for understanding, so if we want to eventually develop therapeutic targets that modify mutant proteins and so forth, we're going to have

to think of that, too.

That's why I think it's really interesting in modern times, the language of engineering -- modular, robust, efficient -- enter into the language of biology, and eventually into the language of medicine. It's interesting. We had a [post-doctoral] fellow in here who was really a smart lady. She was trained as an obstetrician. She wanted to do genetics and she's redirected her career to do genetics. I was all excited about thinking about this new language, and I went running down the hall and she happened to be standing by the photocopy machine. I said, "Hey, look. When you think about it, it's all modular in biology." She'd heard me say evolution is done by tinkering, which was Jacob's [endnote 194](#) phrase, and the tinkering puts the modules together. I said, "Isn't that interesting? That's totally different than God's intelligent design world, isn't it?" She sort of sat there looking highly amused, and she said, "Do you realize that you're talking to a daughter of two engineer parents, father and mother? And this language was our dinner table conversation. Modules, robust, and efficiency." So I do believe that it isn't so crazy to have engineering language in modern biology. And Barabási talks about modular networks. [endnote 195](#)

How did I get further into transport? I thought that transport systems were not enzymes in the traditional sense. They didn't change the substrates, they moved the substrates. In order to understand more about that, I found the publication by Christensen. I haven't given you that with the articles and publications, all of it, yet.

NC: That great long 1960 article?

CS: Yeah. *Advances in Protein Chemistry*. [endnote 196](#) I read it on a train going to my first Markle meeting. My wife and I took the cross-Canada train, and it was three days and I read Christensen on the train.

NC: It would take about three days. It's a dense, long paper. Lot to absorb there.

CS: Well, it helped me to understand the language, it helped me to understand the principles, it helped me to design experiments, it helped me a lot. So it was a formative paper. It capitalized on the fact that it seemed to be now increasingly relevant to think about inborn errors of transport. When we were doing that work, you could put everybody doing that work into one room at a FASEB meeting. Now it's a huge field.

NC: So that group would be you, Christensen, Dent?

CS: Dent had moved on from that. And Christensen wasn't thinking so much about genetics as much as he was thinking about the biochemistry of transports. Rose Johnstone at McGill was very interested in that, was very intrigued that this enthusiastic amateur was looking into transport, and she was very critical about some of the things I would say or the things I would write.

NC: Who else was in that group?

CS: Leon Rosenberg was another person who was interested and who was sort of like me. There were a huge group of bacterial people. Ron Kaback, [endnote 197](#) Michael Kaback's brother, was an influential person in the field in those days. I got out of the field when it became apparent that I wasn't going to do micropuncture work in rat nephrons,

and I wasn't going to do patch clamp and electrophysiology work.

NC: So are there any other subfields in that vein, inborn errors of metabolism, inborn errors of transport? Is it an historical accident that makes those allied for you to go from inborn errors of one thing to inborn errors of another thing, or were you trying to see a cluster of inborn errors of different systems?

CS: It would be an inborn error of metabolism, in the sense that all metabolisms involved enzymatic chemical conversion here-to-there-ases, things that move and maintain homeostatic systems, that would be metabolism. I never got into mitochondrial metabolism and energy metabolism per se.

NC: So is transport in your mind then kind of a subset of metabolism? Or is it a sister --

CS: Well, it was at that time. And it should be seen that way because -- I mean, I have a diagram in one of my early papers which has lasted a long time. If you look at an amino acid, it starts in protein, peptide linkage. You have to cleave it, you absorb it as dipeptides, oligopeptides, and free amino acids. They go into the body, they're moved around in order to get in cells; to be converted to their enzymatic byproducts, they have to pass cell membranes, so they're carried on transporters. But then there's the enzyme that controls the conversion reaction, and then there's incorporation, and so on. Sometimes too little of the amino acid or too much of the amino acid has a phenotypic effect which you eventually want to understand if you're doing biochemical genetics. So it's all part of the same bag. But nobody had seriously got into the question of how many genes are devoted to the proteins that are part of the transporters, the pores, or the here-to-there-ases, whatever they are.

There was one other area of metabolism that had not been looked at with quite the same zest that I did and Leon Rosenberg did. But my experience with vitamin B6 said to me that I'd better learn what B6 does, and I learned that it's a co-factor and it's a very ubiquitous co-factor for a lot of amino acid metabolism enzymes. Then I thought, well, maybe there're disorders of vitamin metabolism, namely the precursor substance that becomes the vitamin itself or the co-factor itself, and maybe there are also interactions that perturb the association of the small molecule vitamin with the large macromolecule enzyme that is necessary to have a conversion reaction in the substrate.

So then I asked my open-ended question to myself, or anybody who knew how to answer it, what does the co-factor do? And I learned that it's probably a distributor of electrons during the chemical reaction and it'll maybe move it on to the protein and allow that energy to be dissipated in that way, but that's the role it plays. It probably has a very specific relationship to the substrate and a very specific place on the protein. So maybe there are mutations in the protein that affect the relationship, the kinetic energy for binding of the co-factor in the right position to do its work on the substrate.

Then I began to think about that. There's an early paper there, the one about thiamine-responsive maple syrup urine disease. [endnote 198](#) I can remember exactly how that happened. I was in San Francisco at probably the Pediatric Research meetings, and I had a telephone call from the team here. They said, "We've got a new patient with maple syrup urine disease, but she doesn't seem to be typical." I was interested in heterogeneity by this time, well interested in it, and, as I recall it, I said over the phone, "Maybe we should think of giving a pharmacological dose of the co-factor for the

decarboxylation reaction for branch-chain amino acids." We sort of talked over the phone about what that dose might be. The dose was given, the maple syrup urine disease metabolic phenotype went away, and we then reported in Lancet "Thiamine-responsive maple syrup urine disease."

NC: Is Carol Clow the first author on that? Oh no, this reference I have is in Pediatrics. [several pauses here while they look for papers in the bibliography]

CS: She might have been. It should be in Lancet. Let's see if I can find it. It's just possible I didn't pull that one. Oh, here it is. Down under Section 3, "Thiamine-responsive MSUD," paper A181. That's what I have written down. Oh, that's the follow-up paper. A55. Sorry. But A181 is a ten-year follow up on that.

NC: Yes, there it is. "Thiamine-responsive maple syrup urine disease."

CS: Now, somewhere -- and I probably didn't give you the paper -- I wrote a review of vitamin-responsive inborn errors of metabolism, and it's a paper in *Metabolism*. I guess for some reason or other I didn't follow up on that, but that would be sort of a mini-hub paper for a set of work that I did on vitamin-responsive inborn errors of metabolism. I was interested in that because therapy was so easy. Give a pill. Instead of change the food, culture and environment, you give a pill. It turned out to be a good thought, and Leon Rosenberg had the same thought at the time. "Vitamin-responsive inborn errors of metabolism," *Perinatal Pharmacology*. That's C72. Here it is. C69, "Progress in Endocrinology and Metabolism: vitamin-responsive inborn errors of metabolism," and you've got the list of publications. [endnote 199](#)

But that was a paper that I was invited to write on a theme which I see recurred several times, because in '73, I was invited to give the Milner lecture to the Society for Inborn Errors of Metabolism in Europe. [endnote 200](#) It was called Treatment of Inborn Errors of Metabolism, was the theme of the meeting, and I talked about vitamin-responsive inborn errors. So it must have been something that -- anyway, C69 will do, but it's duplicated in the publication list.

I was talking about it in 1971 at the International Congress of Pediatrics. I just thought it was an important theme, and so did Lee Rosenberg, and we got a lot of invitations to talk about it. It was a new way of thinking about inborn errors. And, as I told you, about the B6 story, fifty years later Peter Clayton comes up with the explanation for the pyridoxine responsive disorder. [endnote 201](#)

NC: Your second theme is genetic testing and screening. This is one theme of yours that's not especially Garrodian. It's much more applied. Where does this interest come from?

CS: Medical. Genetic medicine. Instead of waiting for the disease to appear which you then treat, and if you're a pediatrician, you know you can't remake the brain, can you get early warning and deal with it that way? The idea of developing a screening test in the newborn that would see the signal for the disease that's coming, then you could intervene at that time. Castonguay, the Minister, picked that up like that. He said, "Wonderful - prevention." Barton Childs was the first person I ever heard really get up and say, "Genetics is all about prevention in medicine."

NC: Well, there's not much therapy you can do.

CS: Well, that's the next thing. That's why I got interested in PKU, because, for me, PKU is the flagship that changed the paradigm. You just stated the old standard paradigm of medicine, there's not much you can do.

NC: Victor McKusick wrote that in 1963, and he wasn't the first.

CS: Guys like us in biochemical genetics said, "Wrong, and PKU is our flagship." Get it early with a screening test. Start the low phenylalanine diet. In the standard equation $P=G+E$, [endnote 202](#) change E. You can't change G, but you can change E. What we wanted to do was to change the experience.

Penrose talks about this. He said in his inaugural address in 1946 that PKU is a metabolic disorder that's eligible for manipulation of metabolism. He doesn't actually say by diet, but he's implying that if it's metabolism that's associated with a molecule like phenylalanine, maybe you can change it. So we did.

That's why I got interested in screening. The newborn screening test would be done for two reasons in our original pilot study. Barton refined that thinking to a third level, which we then adopted. But you screen for medical intervention, in this case diagnosis and treatment, or you screen to gather knowledge. And in Quebec, we said to Castonguay, you can do two things. You can pick up diseases for which we think we have treatment possibilities, and secondly, we'll find out what the burden of these conditions is in the Quebec population, by counting cases, so we get prevalence rates.

The third rationale for screening was for reproductive counseling. You can't treat but you could avoid through reproductive counseling. That's when we added Tay-Sachs, beginning in 1969, '70, when we developed our enzyme test. Since we had the Quebec Network in place, it was easy for us to pick up and launch a project that was parallel to what Kaback was doing in Baltimore. [endnote 203](#)

When we did the Tay-Sachs story, we did it from the bottom up. The community wanted us to do it. We said our top-down role will be to provide expertise in the test. We developed our own automated system, and we did the program with the willingness of the community to participate. That was part one of it. Part two was, how efficient is it if we do it in the standard medical paradigm, and we published in the New England Journal of Medicine the paper by Beck and others, who was a medical student at the time. We said, "Look, the doctors are lousy at referring or thinking of asking the patient to have the test. You're Jewish, you're at risk for having a child, if you're a carrier. Do you want to know if you're a carrier?" [endnote 204](#)

We went to the high schools. We had a teacher -- our kids were all going to the same high school. The teacher knew who I was. Again, you know, the structure of the community, chance, degrees of connection, separation. She said, "I hear you're thinking about Tay-Sachs screening. I'm Jewish. I'm the only Jewish teacher in the school, by the way, but I'm thinking about what you're doing. Would you ever think of going to high schools? Do you want to try it on my class, see how they are? Because we've got some Jewish students in this class and we can do this and do that." So we went and talked to people and they said, "Hey, that's an interesting idea." We put it into the school system, because we had an enlightened school board.

Again, the rest is history. Twenty years later the incidence of Tay-Sachs has virtually disappeared from the community. It started with the high school students. They remembered whether they were carriers. They took it into their life when they started their reproductive lives. Nobody was abused, nobody committed suicide.

I had a really amusing incident. We were talking about this at an ethics session about ten years ago here in the hospital, and the question came up, Was it the right thing to do, working with high school students? I said, "I think the paper says the proof of the pudding is in it -- so word went through the community and everybody participates in this now." Two of the residents put up their hands and they said, "We were found to be carriers, we told everybody. We thought it was a badge of honor." (chuckles) Completely opposite to what the top-down finger-waggers and opinion-makers thought would be the case. Now, that may be peculiar to Montreal, I don't know, but these two now-adult women said, "We told everybody we thought it was just fine."

NC: Interesting. You began publishing articles having to do with screening in the early to mid-sixties.

CS: That was a technical paper, the first paper. [endnote 205](#) Then in the later sixties, we published the results of the study in the *American Journal of Diseases of Children*. [endnote 206](#)

NC: That was the time when -- in 1963, Robert Guthrie came out with his new easy test for PKU. I'm wondering whether that had an impact on you saying, well, can we extend this to other inborn errors?

CS: No, because I was doing a test that covered a whole bunch of inborn errors. Admittedly, they were all amino acid disorders, rather than the inhibition assay that he describes, which was substrate specific. We were looking at, with chromatography, a bunch of substrates.

NC: Right. The test is very different, but -- was it '65 that Massachusetts began its mandated PKU screening?

CS: Probably, because Efron had set it up on a chromatographic approach also. [endnote 207](#)

NC: All I'm saying is that genetic screening was kind of in the air at that time.

CS: Definitely in the air. I think I mentioned to you, McCready was the old-style public health microbiologist who said, "I see a new approach and a new reason for keeping a lab like this going. Change the technology and we can continue to prevent disease." And it was in the air because that was why it was no hardship to get Castonguay to think about it.

The thing we did in Quebec that was rather unusual was, here we'd done all this chromatographic work to show it works, and we decided that maybe Clow and Scriver could read the chromatograms and [if] they did it on half the population, as it were, do you think you could get somebody in a provincial lab doing a hundred thousand of those a year and how many mistakes would you make? So we did something that was very

unconventional. We switched to a McCaman-Robins method to measure the phenylalanine, which would also give us tyrosine in the province, because we were interested in heritable tyrosinemia. [endnote 208](#) It was a quantitative assay down to zero. It also, because we were collecting the blood on filter paper, which was easier than collecting it in the capillary tubes that we were using for our project -- there was seasonal variation between the cold dry and the wet hot months in Quebec -- so the size of the punch-out spot would vary. This was all part of the technology of screening in those days.

So we had a quantitative down to zero method where we could have statistical analysis of the data for the seasons, summer and winter. Therefore, we were very confident about where the cutoff point could be to say this is an abnormal value. That's different than the threshold value of the Guthrie method, below which you didn't know what the actual value was. It's always dangerous to say this, but as far as I know, since 1970 roughly, when we started it, we have not missed a case. The only other place that has that record is North Carolina, where they also use the McCaman-Robins method.

It became very important, as part of the malpractice suit business in the United States, if you missed the test. And I'm being called right now, would I please offer an opinion about whether somebody did the right thing or not. So often it was on false negative test results. We spent a lot of time in the Committee on Genetics for the American Academy of Pediatrics trying to deal with that. Ed McCabe [endnote 209](#) was a big voice of sanity in all of that.

NC: In the 1965 paper in the *Pediatric Clinics of North America*, you had a review article on "Screening Newborns for Hereditary Metabolic Disease," [endnote 210](#) and you set out some criteria for what kinds of diseases ought to be screened, and you wrote that --

CS: This could be dangerous. (chuckles)

NC: I was struck -- let me find it in the actual paper. I don't think this is dangerous. You said that [reading] "Screening is undoubtedly worthwhile for heritable metabolic diseases with the following characteristics: (a) the natural history of the disease is well understood and, with few exceptions, it can be reliably detected early in life." Okay, you have to understand the disease. "Once identified by a screening procedure, the disease can be confirmed by specific methods." That's what you were just talking about, eliminating false positives and negatives. And "(c) a therapeutic regimen is known which will alter the course of the untreated disease, and (d) the therapeutic resources are easily available to the patient."

So the (c) and (d) struck me as very cautious. You have to be able to do something about it, and that's not the case with all diseases for which there are tests today. It seems to me that, for example, the Huntington's disease controversy over --

CS: This was before the paradigm of testing to avoid the disease through reproductive counseling, the Tay-Sachs story. This is before we added the dimension, screening generates knowledge where you learn about the natural history of the disease, or its incidence in the population, and we better learn to do something about it. Yeah, it's pre-it's at the most categorical, most medical orientation way of thinking about it. It's putting genetics into medicine, and what do you do in medicine? You make diagnoses and you treat. And if you can't treat, then you don't want to diagnose, do you? We've changed all

that in two generations of medicine. And we create a lot of un-patients through some of our screening procedures. I found you have this thing, but I don't really know what it's all about.

The big argument that we're just going through in our own group here is to test or not to test for Gaucher's disease, [endnote 211](#) because most of the mutations that are going to be detected are going to be associated with Gaucher's disease under certain circumstances and non-disease under most circumstances, and we don't know what those modifying circumstances or events are.

I predicted early in the beginning that not all PKU would be as harmful as classical PKU might be, could be. And what was that? We noticed that that form of PKU segregated in Mediterranean populations more than it did in northern Europe. Penrose had noted this in 1946, that PKU is a disease of Irish and northern Europeans, but not a typical type of problem in other countries. So we were looking at heterogeneity, and when you deal with heterogeneity, how you deal with each form of it. I think what we were writing there would be the convention of the time, based on the experience we had and what we knew.

NC: So the nature of screening changed -- it sounds like you said that was a very medical approach to testing and screening.

CS: For genetic problems.

NC: So would you say that screening for genetic problems has become less medical and more scientific since then?

CS: More complicated. More stratified in terms of dealing with all of the possible levels of phenotypic significance of the variation that you've got. We always have to ask, now if you've found a mutation, is it non-expressed? Is it disease causing? What's the evidence that it would be?

In my list of informative publications, somewhere very early in my work, I read Wilson and Jungner. [endnote 212](#)

NC: I wasn't able to get that paper. You sent me the reference.

CS: Well, it's a WHO publication. [endnote 213](#) I think my copy has been stolen, or gone missing. It was a discussion of medical screening, and the rationales are not any different when it's a genetic problem, it's just the cause that's different. And Barton Childs' committee -- and I think he would have been the person who spent the biggest effort on writing the report for the National Academy of Sciences book on genetic screening, which is on my publication list, a "C" publication. [endnote 214](#) I think it's still a very sound document on screening.

NC: I need to get that, but I was not able to track it down before I came. Okay. One of your hub papers, our pilot study, 1969; can you tell us about that?

CS: That's Clow and Scriver?

NC: Yes, A037, "Results of mass screening for hyperamino-acidemias in the newborn

infant." It's a link paper in your theme of genetics screening. [endnote 215](#)

CS: Yes, that's right, and I think it's Clow and, or Scriver and Clow?

NC: It's Clow, Scriver, and Davies.

CS: What do you want to know about it?

NC: Well, can you tell us about the screening program?

CS: It was the pilot one. It was the capillary tubes collecting the blood in Papanicalou screening kits. It was chromatography. It was forty thousand families. It was families outside of the city, the city of Montreal, the Arctic. It reported on what we found, and it also had a follow-up component in it. It examined how people felt about the follow-up, and I think, out of three hundred positive tests, one family objected to the fact that we'd ever done anything that disturbed them, and two hundred and ninety-nine people said let's get on with the program. Something like that. That's how I remember it.

NC: We did touch upon this earlier when we were talking about Carol Clow doing all the forty thousand --

CS: Eluned Davies was the technician in Charles Dent's lab who was the hands-on person who taught me partition chromatography. Somewhere in the early sixties after Carol had come, I recruited her and -- or maybe it was before Carol had come -- recruited her to the lab, and she also helped with this study. But it got done because Carol said, "Let's do it." Eluned was very much an important part of the -- and also because she taught me chromatography in the first place.

NC: So you took middle author position in that paper. How attentive were you to the conventions of author order?

CS: Not very. (chuckles)

NC: I mean, Clow was first because she did most of the work.

CS: She did the work and if it hadn't been for her, we would have never done the project. The other thing that was interesting was, that the auxiliary of the hospital took this on, thinking this was an interesting way of serving society. So a group of women gathered once a week and packed these kits, the Papanicalou [screening kits], which could be put through the mail. They put in the plasticine and they put in the capillary tubes and then they closed them up and we sent them out to the hospital, and then the hospital would fill them up and send them back to our lab. For years after that, I'd get lovely ladies of the community who'd come up to me and say, "Gee, we enjoyed doing that. It used to be like a knitting bee. We'd all get together and talk. By the way, what happened with it?" (laughs)

NC: Another community connection.

CS: Yeah.

NC: You may have touched upon this earlier. The hub paper is your third theme,

management of hereditary metabolic disease A54.

CS: That's the one that I did the time and motion studies, and that's Clow, Reade, and Scriver? [endnote 216](#)

NC: Yes. That's the one where you did the time and motion study. That partly answers -- my question was to suggest that this theme emerged directly out of the genetic screening theme.

CS: That's right. The pilot study generated patients. We also began to get patients referred to us. For instance, the orthopedic surgeons heard that we were interested in rickets, and by this time I was in the process of showing the change in heritability of rickets. Change the environment, put vitamin D in the milk, rickets prevalence goes down by ninety-five percent. But rickets doesn't go away. What's left? Hereditary disorders of calcium and phosphate metabolism. The calcium one turns out to be an inborn error of vitamin D hormone synthesis and the phosphate ones turn out to be a set of disorders affecting phosphate transport, of which X-linked hypophosphatemia is the most important one, and, until we got into the act, had been thought probably was a disorder of vitamin D metabolism. And in our paper in *Science*, [endnote 217](#) we showed that no hyperparathyroidism should suggest that there's something wrong with calcium, and secondarily phosphate, and that it behaves like a phosphate transport disorder.

NC: How did you get interested in phosphate transport? Your earliest papers were on transport of amino acids, especially proline and hydroxyproline and so forth. How did you jump to phosphate?

CS: Because I got involved with using amino acid chromatography and looking at urine samples, the story I gave you earlier. Carol and I would look at these chromatograms on a regular basis like reading lab reports, and here were these hyperaminoaciduria people. I'd go and look them up, go on the wards, and I'd find out that they were always infants, with rare exceptions, and the patterns appeared in the winter. The first winter I just noticed this as an observation. The second winter I said, "Hey, this is interesting." I think by about the third winter, I said, "I've got to look at this."

We found that they were infants, their diagnosis was rickets, they were largely from a culture that fed bottled dairy milk rather than something else that had vitamin D in it, and it seemed to be a manifestation of vitamin D deficiency rickets. When we solved that problem by putting vitamin D into the environment, we anticipated the fact that there would be a great improvement in the problem of rickets, but it probably wouldn't go away.

Because I was doing biochemical genetics, and for whatever reason, some of the orthopedic surgeons began to talk to me about the fact that there were kids with hypophosphatemic rickets. I knew something about that disorder because I'd been in England and Dent was a big authority in England on hypophosphatemic rickets and rickets as a general set of disorders. I haven't made any discussion with you about this before, but Dent's clinic when I was there was not just amino acids; actually, a major theme of his clinic was rickets.

So I came back to Canada primed for rickets, got into the vitamin D story, but was prepared to recognize that some of the patients that they had in the hospital here who

kept recurring with their bone disease and didn't do well with vitamin D, and when they had their legs straightened they'd bend again, and so on, that they actually were male patients and had hypophosphatemia without any overt disorder of calcium, and that they probably had X-linked hypophosphatemia.

There's a famous paper by *Winters* that had come out in the *Quarterly Journal of Medicine*, I think it was -- I'd have to look it up now -- where he had dissected the whole problem, one of the great papers in genetic medicine, and shown that this condition segregated as an X-linked dominant. [endnote 218](#) So I was attuned to that, and I began to work with the orthopedic people here and say, "Look, I think you've got a patient with X-linked hypophosphatemia."

When Francis Glorieux came to the lab, and I think he came in about 1969 or so, he came as a graduate student. His thesis was on X-linked hypophosphatemia, and we studied phosphate transport maximums. We did infusions and all of that. We ended up with the evidence that was publishable in *Science* that we were dealing with a disorder that affected the transport of phosphate and that it was not associated with a primary disorder of parathyroid hormone influence on the kidney. That work we were able to do with Claude Arnaud, who at that time I think was at the Mayo. [endnote 219](#) So there'd been a brand new assay for parathyroid hormone, we showed that the assay gave us essentially normal values, and that our data, our second paper supported the evidence that it was a phosphate transport. That caused a real buzz. Suddenly we were being invited everywhere to talk about rickets. I had learned a lot about rickets from Dent, but I'd also done this strange thing.

As we were putting vitamin D into the Quebec environment, we noticed the prevalence of the disease going down, but the disease not going away, and everybody with persistent rickets had a hereditary disorder of phosphate or calcium metabolism. So we had raised the heritability in the persisting phenotypes in the population. Geneticists thought that was interesting. We were dealing with a very expensive, complicated disease, and our *New England Journal of Medicine* paper says if you replace phosphate, look at what you can do to phosphate values. [endnote 220](#) And we then also showed growth rates and rickets x-rays and so forth for the affected patients being treated with phosphate, and everybody said, "Gee, that's interesting." Then we were the group that got the early access to the vitamin D hormone, which made things even better. So that's how we got into that type of treatment, that type of thinking and screening -- population thinking, heritability thinking, transport thinking, therapy thinking, all comes together.

NC: I'm glad you told me that because, it seems to me, in mapping out your papers, that XLH, X-linked hypophosphatemia, formed a kind of a mini-hub within the hub of inborn errors.

CS: And it sort of does.

NC: Would you say that's fair?

CS: Yes, definitely, because it led to all of the work in the group that Susie Tenenhouse then took over. Her first paper with us was -- when she came, we decided to look at phosphate transport in red cells. At that time nobody knew everything about phosphate transport systems, so we showed that the X-linked hypophosphatemic mutation is not expressed in red cells, because it isn't an epithelial transport system. Then when we got

access to the mouse with that disease, thanks to our contact with Jackson Laboratories, we were able to show that the disease expressed itself in the brush border membrane. That came later.

[pause]

10. Major Research Themes; PKU; Haplotypes; Population Genetics; Databases; Observations on Polymorphisms; Career and Community

CS: Your questions are very helpful. They're great.

NC: Excellent, thank you. Okay. I had a couple of questions about PKU. My first one may be a little bit redundant, but humor me and just tell me how you first got interested in PKU. I'm talking about the 1968 paper on heterogeneity in PKU. I guessed to you earlier, I think off tape, that that was, in some sense, a spin-off of your early inborn errors work.

CS: Screening, really. I mean, the inborn errors of metabolism, the prototype disease was PKU. Richmond Paine [endnote 221](#) was a faculty member at Harvard. He was on the wards when I was a resident at Children's Medical Center. He was the Harvard expert on PKU in those days. But there were other people who were in there, like Eugene Knox, [endnote 222](#) who was interested in the metabolism of phenylalanine. PKU was sort of our benchmark for screening. What could you do in identifying the phenylalanine molecule? Why would you want to do it? Because it gave you the clue that PKU disease was coming and what could you do about that? Well, somebody had said you could treat it. I didn't know about Penrose's paper at that time, which is why I arranged to have it reprinted thirty or forty years after it had been published, because it was such a classic paper. There was Bickel, [endnote 223](#) and there were the Americans who had suggested that there was a treatment in the way of a low phenylalanine diet.

PKU was in there at the beginning as a prototype of an inborn error of metabolism. PKU's in there at the beginning because you can detect it with a screening test in a newborn, and the chromatographic methods will do it, and the McCaman-Robins method, which was developed specifically for phenylalanine, will do it. So it's ground base in a nice Bach aria. It's ground base.

Then I'm becoming aware that there are interesting questions to ask about PKU. And Louis Woolf publishes a paper in one of the English journals, I don't remember which one it is. [endnote 224](#) It's probably cited in our Nature paper that you're referring to. He suggests that if you look at PKU and you load carriers with PKU and you load probands [endnote 225](#) with PKU, I think also, you get different decay curves, suggesting that there's different amounts of enzyme activity. Therefore, what's called PKU, because it's hyperphenylalaninemic, is not uniform in its phenotype and therefore would not be uniform in its genotype.

For some reason or other, I thought, I don't want to do loading tests. That's too invasive and abusive. So why don't we take a blood sample at a particular time of the day and fiddle with ways of pulling apart carriers and non-carriers.

NC: What would be involved in a loading test?

CS: Either an infusion, or taking a dose of phenylalanine and then taking blood samples over time, let's say hourly for the next four or five hours. And that's very invasive. It wasn't invasive in those days, but it required a big commitment on everyone's part.

The other thing was that I was aware that there was something called circadian

variation, not formally like we did later on, but just aware. I thought, what is the most convenient time to get mothers and fathers to participate in a study? I thought, well, if they're families and they've got kids, they don't want to come in at eight o'clock in the morning. Would it be possible for them to come in at lunchtime? (chuckles) So we designed a test that was to be taken after normal breakfast, but before lunch. And we got the fathers and the mothers easily this way.

So they came down to the hospital and we took blood at this time. Then I worked through this idea of phenylalanine over tyrosine, phenylalanine squared over tyrosine and so forth, and I developed a two dimensional array. Then I put a line around it and said this is one population and this is the other. I showed it to Harry Harris, and he thought -- I guess I showed it to Harry Harris because I think I wouldn't have thought of sending it to *Nature*. But he said, "Oh, that's interesting. Why don't you send it to *Nature*?" So I did. [endnote 226](#) David Rosenblatt was the summer student when we did this.

Then a guy came along in 1969, a graduate student. His name was Reynold Gold, who was a real eccentric. He wanted to do a Ph.D. with Clarke Fraser and myself, or anybody who would look after him. He was mathematically inclined, so he then put us together with a mathematician, Urs Maag, over at the University of Montreal. We worked with Bayesian statistics, *a priori* and *posteriori* probabilities, and developed the density functions for the phenylalanine values and showed a different relationship rather than the -- the normal values are down here and the abnormal values are up there, except that would give us two distributions to plot, which was the heterogeneity side of it. We put a circle around it and said, "The center of this has the highest probability of being a carrier, or a non-carrier in this case, and anything outside that mountaintop is down on the plateau, or the plains, and it's less likely to be a carrier."

People protested. I mean, this was a single blood test assay, and people said, "It doesn't work." I said, "Did you do it at noon?" "Well, of course not. We never take bloods at noon." I said, "There's a reason -- circadian variations of the two amino acids is different." "Oh, is that important?" "Yes, you're talking about metabolism, aren't you?"

Our test continues to work two generations later. It's not as good as a mutation analysis, but it's still useful. We also showed that it made a difference whether the woman was taking the pill or not.

NC: The birth control pill.

CS: Yeah.

NC: That was a pretty new invention then.

CS: Yeah. That's how I got to thinking that way. And with hindsight, it was pretty subtle thinking, but it just seemed to be ordinary at the time.

NC: Well, it requires a real intimacy with the biology.

CS: Yeah, and I don't know where I learned that. When I look back on it and thinking about all the questions you're asking, those are things you learn by talking. I was always influenced by Leo Szilard, [endnote 227](#) who wrote *The Voice of the Dolphins*.

Somebody said, "How come you know so much?" And he says, "I don't, I just ask people."

NC: He was notorious—or famous, depending on who your perspective—for pestering people with questions. Does this have to do with your being, as you described yourself, a "passionate amateur?"

CS: I think so. I mean, I am a professional in the sense that I have an M.D. degree, but I don't have any other degree, so everything I've learned, I've learned because it was necessary to learn it or because I wanted to learn it. And I learned it by bootstrapping, by reading. And listening. And having mentors. After Harry Harris, Barton Childs has been a continuing important mentor. Then the other important people are all the people I've been working with here. Clarke Fraser would nudge me and say, "You don't know anything, Scriver. Go and read this."

Or a student would come and say, "Hey, have you read Kacser and Burns on the molecular basis of knowledge?" [endnote 228](#) That was Michel Vekemans, [endnote 229](#) and I found that a hugely influential paper. And it turns out to have been of relevance to Hartwell, [endnote 230](#) who got the Nobel Prize recently. And it's been proved to be very useful in network thinking and everybody cites Kacser and Burns now in systems biology.

I think the secret is, if you're shown to be interested in these things, and you are interesting in the way you talk about things, people want to tell you what excites them, especially if you're generous and say, "Well, I got the idea from you to read this thing," or, "Thank you for taking me there." The Golden Rule.

NC: Again on that 1968 paper, as you were just describing, it concerned heterogeneity in PKU. You said it was the hub of your work on PKU, but also there's that heterogeneity idea. That's a very Garrodian theme. It's something that Barton talks a lot about. I'm wondering whether this paper also influenced you in the direction of other Garrodian themes in your work, such as homeostasis and individuality, which you cited as your fourth theme.

CS: Oh, I think so. I mean, if you look at what I've done, I've increasingly narrowed the range of phenotypes that I work on. I've found phenylketonuria to be a wonderful model for all sorts of things. And I give these papers. I mean, the Trends in Genetics paper, I don't know what its citation index is, but all I know is I keep getting asked to give that paper. I say, "Look, I've talked about it so many times," and the answer is, "But not to us." I can keep thinking of ways of expanding the story, all based on PKU, as a model for how to think about things. Like hemoglobin used to be a model for thinking about genetics in the early days.

NC: You've narrowed the range of phenotypes you've looked at and broadened the range of concepts that you apply to it. Those are two inverse trends in your career.

CS: I think so. Your graph suggests that, and I think it's true. I sit around and listen to my colleagues at genetic rounds, and I'm just astonished about what I don't know. But I do know that we are one of the people who said, "Fifty percent of the mutations in the human genome that we know about are missense mutations and look what they do." We've showed they misfold proteins, and that's a paradigm that's susceptible to forms of

therapy. I do know some other things that are interesting, that populations have their own sets of mutations and if you want to deal with them, you should know something about that.

NC: Okay. So that 1968 paper was your only paper on PKU for some fifteen years.

CS: (laughs) Yes, I know. Isn't it interesting? And yet I get invited to write a review for the New England Journal on PKU. I have no idea why, except they must have thought a guy who's interested in biochemical genetics must be able to write about PKU.

NC: All right. So let's hypothesize that, in the sixties, it was one of the many different phenotypes you were interested in looking at.

CS: I was also helped by patients. When I came here I was referred to two retarded young women. And also I got involved in the diagnosis of the disease in one sibling and helped to counsel and to treat the second sibling, who then grew up to become a bride and whose photograph I took. Dan Hartl [endnote 231](#) was so impressed when he saw that slide at a meeting of the American Genetics Society [endnote 232](#) meeting with the Canadians, he said, "Can I use it in my book on human genetics?" So patients definitely helped to focus the mind.

NC: What got you back to it then in the eighties? How did you get drawn back into PKU after this hiatus?

CS: The National Academy of Science book comes out in '75. It's focused on PKU. I guess I just begin to think about the problem of PKU as a paradigm for inborn errors of metabolism. I haven't looked at that paper for a long time. I never read my old papers, really. But I think I actually mentioned phenylalanine ammonia lyase as a treatment possibility in the New England Journal review. Maybe not; I did bring up some problems about it.

I did begin to have to take over the chapter in what was known as Stanbury, the *Metabolic Basis of Inherited Disease*. [endnote 233](#) I was invited to become the editor of it, and I invited David Valle and Art Beaudet [endnote 234](#) and Bill Sly [endnote 235](#) to join me. It was a pretty intimidating prospect, taking over from Stanbury, Frederickson and Wyngaarden. And maybe it was dealing with writing the next version of the chapter, because I know in the fifth edition, Joe Goldstein [endnote 236](#) was not very happy with the chapter he got, and he said, "I think you better plan to take over that chapter." When I was discovering that what their plan was for me to take over the book -- which has been an interesting assignment -- I think it was thought by my colleagues, "You better write that chapter." So I asked Savio Woo [endnote 237](#) to join me and Seymour Kaufman.

[pause]

But I can't actually recall what the threshold event was that took me into becoming involved in PKU. I do know that a graduate student, Simon John, [endnote 238](#) joined me in 1988, or somewhere around there, and we decided to look at PKU mutations in Quebec. That was an early opening of molecular work in the lab.

That proved to be very interesting because of the fact that -- well, this isn't answering

your question for 1980, but it is answering for everything that follows since. I knew about haplotype [endnote 239](#) backgrounds and how they identified the home for the mutation. I asked Simon to be sure that he do the haplotypes. And Simon said, "Do I have to really do the haplotypes?" And I said, "Yeah, I think it's interesting to know the background." So he did the haplotype for this PKU mutation in Quebec. It was the prevalent mutation, the one that occurs most prevalently in Europe, always on haplotype 2 in Europe. We did the haplotype back then, and we did it again and did it again, and it just kept coming out as haplotype 1. We said, "Isn't that interesting? This mutation is on a different background." So we looked at the haplotypes and we looked at the size of the gene as it was known at the time and said it either is recurrent or it's recombination or it's gene conversion. Too big a distance for gene conversion, no evidence of recombination that might really do the story, but it could have been possible, or recurrent mutation. Anyway, we published the paper as mutations are [codon] 408 mutations in Quebec on haplotype 1, et cetera. And the *American Journal of Human Genetics* published it. [endnote 240](#)

That was the beginning of population genetics, because it turns out that this is -- we have a paper that's coming out right now in *Human Mutation*. [endnote 241](#) We have shown that cytosine [endnote 242](#) is methylated and that this is a mutation will occur by spontaneous deamination and conversion to thymine, and therefore it changes the codon from arginine to tryptophan. When you do that, you destroy the hinge region for the tetramerization domain of the subunit of the protein. Therefore, you can't put two subunits together to make a homodimer [endnote 243](#) and you destroy the enzyme. My database information tells me that this mutation has occurred at least four times in European populations over history, so therefore it's a recurrent mutation and it spins itself off, and it's driven to high prevalence in populations, perhaps because it may be advantageous. Who knows?

But, anyway, everybody assumed that because it was a CGG codon, it was methylated. And we were the first people to show that it actually is methylated, so it's an interesting example of epigenetics, modifying a genotype. So that's where my interest in PKU has driven me, and it's always an observation that begs an explanation.

NC: This is very helpful. Now, your next three themes, including PKU, and population genetics, and databases seem to form a cluster.

CS: The population genetics story is driven by PKU, and because I work in Quebec. Claude Laberge is a background voice here. The other key person as a mentor is Kenneth Morgan. Ken Morgan was recruited to McGill by a bunch of us. We were trying to recruit another population geneticist and he didn't come, but he knew and he was a friend of Ken Morgan, and everybody said, "Well, try and get Ken Morgan to move to McGill." So he and his significant other, Mary Fujiwara, came to McGill. In my opinion, Ken Morgan is one of the people who's transformed genetics in Quebec, and also had a big influence across the country. He recently was given the Genetics Society of Canada Award of Excellence. He's kind of like Barton Childs. He's very thoughtful, kind of grumpy. (laughs) And just a beautiful human being. He taught me an awful lot of what I have come to do and enjoy doing in population genetics. But he's taken the Quebec community and everybody recognizes him as the bedrock resource to go to when we want to deal with these fundamental problems in genetics and population distribution, stratification, and so on.

So I can remember when I was writing my last MRC group application, I went to him and

I said, "Look, I'd like to do this with the PKU story. We're beginning to get these things about mutation distribution. What do you think? And by the way, we're also noticing that the thalassemia mutations that turn up here in Quebec are kind of interesting. How do those Mediterranean mutations get into this French Canadian population?"

I was teaching in a biology course, and a young guy -- not so young guy, who took a course every year -- came up to me and he said, "You've been talking about some interesting things. Who should I work with?" And I said, "I think you should go to my mentor on this, and go to Ken Morgan." And this was going back and challenging the old hypothesis that nephrogenic diabetes insipidus in North America, about which Barton has written, is in fact a founder effect mutation [endnote 244](#) and spread through the population. Well, a geneticist is going to say, "But if it's a lethal disorder in the absence of modern medicine and access to water, and it affects males, and it's on the x-chromosome, if the male dies with it and yet the condition continues in the population, isn't this a new mutation every time?" So we did haplotype backgrounds, looking at the Hopewell hypothesis, and it turns out that this is a recurrent mutation type of story. [endnote 245](#)

Anyway, it was Morgan who was the hub of all of that, and he just was my mentor in trying to do some simple population genetics. Because I was doing it with PKU, and because we were beginning to publish information about the non-random distribution of PKU in the population, and I had agreed to sort of host a consortium of PKU investigators, which came out of a meeting in Paris in the early nineties, that was put together by a French individual, Jean-Marie Saudubray. [endnote 246](#) At that meeting, when molecular work by Savio Woo's group was showing promise, I said, "I think we should make a consortium and keep track of all of these mutations the way those guys do it who've just been starting to do that for cystic fibrosis." Everybody said, "Hey, that sounds like fun." So we did it by fax in those days. Now we do it otherwise. We took our database, and it grew as one technician that I had to do it, and then when we created a formal approach, with the graduate student Nowacki.

I began to publish a couple of things about -- well, one thing about that, mutations around the world, but the other thing about mutations in Quebec. So I got invited to the CIBA Symposium on population genetics. [endnote 247](#) Cavalli-Sforza and Bodmer and Weatherall and all those guys were at it. [endnote 248](#) I spoke like a passionate amateur and talked about possible selective advantage for this and that, because of the way in which the mutations presented themselves. Bodmer trampled all over me and said, "Oh, no, it's all [genetic] drift." [endnote 249](#) But it was a wonderful meeting, and I just thought, "How lucky can you be to end up doing stuff that seems so simple and so local, and people are excited about it?"

That introduced me to Ken Weiss, the fellow at Pennsylvania, [endnote 250](#) who is such an interesting thinker. You should go and interview him, if you haven't. He's an evolutionary biologist and really very thoughtful. He drops in every now and then, and I got him to write a paper for our book on somatic mutations, and his latest thought is, don't forget somatic mutations. They modify phenotypes all the time. But the connections are interesting, how they happen.

It started with an interest in it from the point of biochemical genetics, of treatment, improving the diet, thinking about phenylalanine ammonia lyase, then having a very smart graduate student say, "I liked the lectures you gave in the biology department, can

I come and work with you?" And then being very smart and getting us started in molecular analysis of mutations, and responding to the question, do I have to do the haplotypes?

NC: Interesting. And databases.

CS: Simply because we had to keep track of what we were gathering, in the way of alleles at the PAH locus.

NC: OK, I see how that starts. I mean, you've got a bunch of things and you need to be able to organize them. You could make a list, right? But a database is a different sort of thing. It's conceptually a different kind of tool. From the number of papers you've published on this, and the way you've pushed it from a simple database to a relational database to a knowledge base, clearly you've got an interest in the concept of a database.

CS: Yeah. Probably, again, not as professional and as skillful as it should be. I just know what they can do and what they serve.

NC: I think an amateur's interest in something can, in some ways, be the most interesting because you're making the connections at a very high level of abstraction, because you don't have all of the technical detail to get mired down in. What I want to know -- I'm not entirely sure how to phrase this -- but do you see connections between organizing digital information in a database and organizing genetic information in an organism? Are there any parallels in your mind between databases and genomes? Are we talking about a similar kind of concept at an abstract level for you?

CS: No. I haven't formally looked at it that way, but I think I see what you're getting at. I have instinctively responded to Barabási-type thinking, as have a lot of us. I do believe the evidence shows that evolution arrived by tinkering, that you have modules, that what you end up with is networks, that you end up with hub proteins and nodes that talk to those proteins, and that you have the language, if you wish, that we talked about of nodes, hubs, and edges. That's the origin of order in biology, and it may well be the origin of order in the way our mind works. What genetics gave us was a nomenclature, a taxonomy system of naming of parts and that the parts make these proteins which then talk to each other. Genes don't talk to each other directly, they always talk to an intermediate. They're called regulator proteins, etc.

I do think that the genetic information system works that way and that there is a hierarchal approach and that it is relational in that sense. I wouldn't be able to address it beyond that, but my instinct -- when I went to hear Barabási, I immediately said, "Hey, I feel at home with what you're talking about. It isn't foreign to me." When Howard Bussey [endnote 251](#) here at McGill came to me one day, he said, "You know, I have a graduate student who said that you were talking about networks and you were talking about -- " in this human genetics course that I taught -- "You were talking about our work. How did you get on to that?"

I said, "Well, it's because it seems pretty logical to me. They're homeostatic systems, things have to monitor each other, they have to talk to each other. And you guys are looking at yeast and pulling it apart. You've got the yeast genomes and now you're asking how systematic gene arrays in which you work with query proteins, where you

know the knockouts and then you create other mutations and you ask, what do you lose and how does that affect a measurable phenotype? So if you can then say this gene talks to this gene, or if it isn't the gene talking to the gene, it's a protein talking to a protein. So you construct these networks in which you have a hub, you have a whole bunch of nodes, and networks cross over to each other, just like your thing there." I said, "I understand that. It seems so logical. Why would anybody be surprised by this?"

Now, where that easy acceptance on my part comes from, I don't know, but I get into trouble when I get asked to go to an -- Canada has an advanced research system where they work in some stratospheric level, and I was asked to come as an observer and commentator on putting a bunch of these people into the room to see whether we would create an expert group in Canada to look at those ways of thinking, network biology. Another term for it is systems biology, but it's a little different than that. It's the kind of thing that Hartwell, and Hartman, in his famous paper in *Science* about four years ago published [endnote 252](#) saying, when we go back to Kacser and Burns and we ask how mutations affect metabolic systems, maybe we should be thinking about thinking this way. Then Hartwell's team picks that up and says, "These are important ways of thinking. We will take yeast and we will make these mutations, and I'll show you why, when you have two mutations, the animal's dead, but when you have one mutation, it survives," et cetera, et cetera. I read the *Science* paper by Hartman just before going to a Canadian Genetic Diseases Network paper, which is a group of us all across Canada who were supposed to be very smart and doing things in this Network of Excellence. There was a big discussion after the paper, and I put my hand up and said, "Look, there was a really interesting paper in *Science* last week. Some of us may not have had a chance to see it, but it's this paper by Hartman and I think this is really the heart of some of the things we were trying to understand." There was one other person in the room had read it.

These guys in the Institute of Genetics and so forth saying, "God, you know, you brought this paper to our attention." "Well, all I'm doing is giving back what other people brought to me. It's an interesting paper. Maybe you'd like to read it." I don't go beyond that, I just know that this is an important way to think, and if we can think of the experiments that you can do to test the system -- well, that's what Howard Bussey does. He knocks out genes and he's developed a systematic way of analyzing the phenotypes, so he can look at thousands of mutations interacting in a week. And they end up with these wonderful understandings of how the yeast genome and its expression look after the life of the organism. I don't know whether we can do that in organisms as complicated as ourselves, but I really think yeast is a nice way of going. So am I surprised when... Mark Vidal, is it?... at MIT, the Broad Institute, [endnote 253](#) comes up with doing the same work in *C. elegans*, [endnote 254](#) and suddenly you're moving closer to looking at organisms as complicated as us. So I think human biochemical genetics, network biology, system biology, all of that's coming together in the future, and I will watch it with delight. I won't be doing any of it, but I think that's the next step.

NC: One area that often comes up in these sorts of Garrodian themes that we've been talking about, that doesn't come up all that often in your work, is polymorphism. [endnote 255](#) It comes up some. It appears in a few of your article titles and so on, but not enough so that I would consider it a major theme of your work. Correct me if I'm wrong on that.

CS: That's true.

NC: Yet, another person who I would liken -- Barton talks a lot about polymorphism, Dave Valle talks a lot about polymorphism -- he's very interested. When he teaches history of human genetics, he spends a lot of time talking about Harris' work on polymorphism and the Kan and Dozy paper of 1978 that introduced RFLPs. [endnote 256](#) I'm trying to get a sense of the different flavors of Garrodianism in human biochemical genetics. Is that a little bit of a different tack on some of these themes? Does that indicate more of a genetic as opposed to a biochemical approach to some of these things?

CS: I would think that the biochemical approach would always be dealing with an expressed phenotype, something that was disadvantageous initially, that's where it would be. Harry Harris comes along and is already asking us to think about the evolutionary biology behind these things, how selective are they, and he says, "So there are neutral polymorphisms." You can change one amino acid for another, back in those protein level days, and it doesn't make much difference. But it's there and it's a background noise of variation that we want to pay attention to.

Then we get to the DNA level, and the polymorphism occurs in sites not under selection, but they become useful because they give us RFLPs, and the Kan and Dozy paper is the classic example. I teach polymorphisms too when I taught in the human genetics class.

Now we have to ask our question over and over again is how significant are those polymorphisms in terms of expression? Do they actually modify phenotypes? Or do they simply serve as markers for genes of interest? I think that there are -- And then the other thing is how polymorphic is it? I mean, the PKU allele R40AW is polymorphic in western Ireland. It's more than one percent of the alleles in the population, so it's a polymorphism. What do you mean by a polymorphism? The quantitative term, or the evolutionary selective/non-selective thought? That's where the arguments always [start] - - and if it's a polymorphism within the gene without any apparent effect, how do you know that, in the organism? Does it maybe modify expression and we don't see that otherwise?

Anything that's variant from the canonical or most prevalent form of the gene, I think, will be of interest. I never use the word -- in my own language, I've never used the term "junk DNA", because I don't believe evolution would have wasted any of its energy over time on something that was of no value. My classic example of this is the lactase polymorphism. [endnote 257](#) Lactase expression in the human genome comes in two forms, persistent after weaning and not persistent after weaning. The persistent after weaning happens to segregate with people who drink milk in temperate zone populations.

But how does that come about? Well, it turns out that it's one single nucleotide -- I think it's a C to a G, but I'm not certain -- change, fourteen thousand nine hundred and seventy-five base pairs upstream from the start codon to the lactase enzyme on chromosome two. So what's one nucleotide doing up there? If you think about it, fifteen thousand base pairs, it must be quite a distance along the loop DNA, and there must be a protein that -- everybody's predicting there's a protein that sits somewhere up here that acts on the promoter for the lactase gene, and when you change that nucleotide, the binding site for that protein is modified and something doesn't happen. But it's the spacing, it's the distance, and evolution has kept fifteen thousand base pairs in there to

be copied, seemingly wasting effort and so forth. But it's in there for a reason, the way that gene works. So that's not junk DNA, it's not just fifteen thousand base pairs of junk, it's there for a reason. And that's a module.

NC: I'm going to jump around a little bit. I've just got a few clean-up types of questions. I think we're getting close to done. Again I'm stretching a little bit here. I've been struck through our conversations by -- it's come up specifically a few times -- the way that so much of your work is so anchored in this place. Within McGill, within Quebec, within Canada, within your community here in Montreal, neighborhoods. Some of the themes of your work with genetic screening and testing in particular, some parts of population genetics have, as I'm sure you are well aware, a rather ugly early history, the first part of the twentieth century in eugenics and so forth. I frankly don't see a trace of any of that in your own work.

CS: Do you mean a trace of ugliness or a trace of unawareness?

NC: Of that kind of ugliness. Of that, we need to do this for the good of the race, for our descendants, and so forth. I'm wondering if being kind of grounded in your community as you are has helped you avoid those sorts of directions in some very tricky things. When you're talking about preventive genetic medicine and so forth, that's straight out of the North Carolina programs of the forties and fifties and so on, in some sense. The eugenics offices morphed into preventive genetic medicine. Historically, the connections are explicit, the Michigan department is one example. [endnote 258](#) Does that connection to community help avoid those sorts of negative directions for genetic medicine?

CS: Very perceptive question, again. I've always been comfortable, and I passionately believe it, in being able to say that I think, when we were working in Quebec in the sixties and seventies doing this sort of thing, we were working in probably one of the most modern communities in North America.

NC: How so?

CS: Because we weren't thinking of this in a eugenic sense, we weren't talking about that danger. We said, the community said -- well, first of all, we worked from the bottom up always. Before we did the newborn screening program, we went and consulted the community, we did surveys. We didn't do Tay-Sachs screening from the top down. We waited -- we were asked by the Tay-Sachs community to come to us, to listen to their problem, and could we take this new knowledge about the enzyme and have a program? The Greeks and Italians [endnote 259](#) said, "Hey, look, we came over here and we brought our genes with us, that were great for malaria, but aren't any damn good in Montreal. Can you do something about that?" (laughs)

I sat down with rabbis, with the Board of Jewish Ministers. I sat down with the Catholic priests of the community. It was brilliant. I was referred by the Minister of Health in whose parish -- she lived in Montreal, worked in the federal government of Ottawa, and sent me to her parish priest, Father Duquini [phonetic]. I went with Carol Clow, and I said, "This is the Italian disease, as it's called in Montreal, and these are the things that we could do to help families not have an affected child." I was very uncomfortable, but I went through the whole way in which the program could be done, the rationale for it, reproductive counseling, and to support the birth of unaffected children at the price of

terminating a pregnancy, if the family wished it, to avoid having that baby in this new economic challenge of the new world.

When I finished, I was very uncomfortable. Father Duquini looked at me and he was very quiet. I started to do it all over again, and he stopped me and he says, "I understand, Professor Scriver, it's an option for my families to have babies." And he stopped. And he said, "My fellow priests may not all support me on this, but I will support my families." End of discussion. He said, "I will talk to everybody."

Then when we said we want to go to the high schools -- when Zipper was away for a year, I went out with other girls, and one of them was a woman who I liked very much. We liked each other. But she said, "Charles, don't get serious about me because I'm going to become a nun." Years later, when I was talking about the Tay-Sachs program at a public meeting in Montreal, this woman came up after the meeting and she said, "Do you remember me?" I looked at her and said, "Yeah, you married God." She said, "You've got a wonderful memory." I said, "I remember you." She said, "Can I help you -- you mentioned the thalassemia program. I work in the Catholic School Board and I could introduce you to the chairman of the board and maybe you'd like to talk to them about the program in the Catholic schools, where our Greeks and Italians tend to go."

So I went, and they said, "That's a very nice idea. We would, in principle, support it, but I don't think we should do it until you've talked to the principals." I went and talked to all the principals, and there were three nuns, one of them quite buxom and had a crucifix on her front. The light shone on it. Every time she took a breath, this crucifix would light up. (laughs) Here I am talking to these people about this program. The vote at the end of it was, "I think this would help our community."

We had got it from the bottom up because the patients -- that boy I showed you with thalassemia himself -- I mean, the patients would come, the families would come. They said, "We want you to think about helping us." So we took it to the top level, and then the school principals all said, "But you should talk to the Parent-Teachers group." So we did that. Sixty-five parents turned out, and sixty-four of them said, "It sounds like a great idea." One person said, "This is a search and destroy mission. I don't want anything to do with it." And sixty-four people said, "Well, that's your choice. You don't have to participate, but we think the program should go ahead."

So that's my long narrative to say that's how it happened. It was really bottom up with top down guidance and support, and technical professionalism where it was wanted. So we went ahead and did it. It's interesting that the Institute of Medicine report on "Assessing Risk," that was chaired by Arno Motulsky [endnote 260](#) -- our program got knocked because we dealt with high school students, and it was exceptionalist, et cetera, et cetera. I was asked by Peter Byers if I would like to write a book review of this thing. I wrote a book review, which is one of the publications that's in your list there, that says, well, it may not work in one community, but that doesn't mean to say it won't be respected and doable in another community. [endnote 261](#) What works in Quebec, in the high school system, may not work in the American system. But that doesn't mean to say it shouldn't be done.

It's examples like that that help me to say Quebec was a very modern community. We went to the population at large with the information about newborn screening. When we decided to add the urine screening, we told everybody the urine test may turn up things

that we don't understand what it all means, and you have the choice not to be tested, if you wish, the negative option. But we will find things that could be useful. The population said, "That's okay by us."

Because we had the urine screening program here, it was possible for the NIH to come to us with that big project where they wanted to know whether testing for neuroblastoma [endnote 262](#) by chemical composition of urine was useful. We showed it was feasible with a pilot study, a student and I, and Carol. Then the big study was done. And it saved the world millions of dollars of useless testing because it showed, sure you can pick up a signal, sure it tells you that there's a neuroblastoma-like phenotype. But it's an involuting developmental thing that never becomes a tumor, and if you do that type of screening, you won't pick the tumor up when it appears, because it comes at a later time.

The Quebec community said, "Sure, we'll be part of that, we'll help people to get that knowledge." I don't know where that wisdom comes from, but it's there in the Quebec environment. And it was there in the Greek and Italian communities for thalassemia, it was there in the Ashkenazi communities for Tay-Sachs screening.

It's been a great place to work, but you're right, I don't think I could have done what I've done in other communities. We talked about what we were doing in Quebec, and we talked about it in Ontario, where there was even a larger community of people at risk for thalassemia, in the Italian community in Toronto. Nothing happened for years. I don't know why. I don't know if the advocates were different from us. But I think it had to do with the nature of the community. Also, we had this extraordinary political wisdom in the form of Castonguay, who got us started. So it's a series -- It's a good genetic equation. The E was very good. The G wasn't bad. (laughs) And the P that we got was great.

NC: I thought that your career would be inconceivable anyplace else.

CS: Well, I think that may be true. And that's maybe why I -- my father said, "Would you be happy if they didn't love you?" and I didn't work anywhere else. (laughs)

NC: It's a different place. Well, we could talk forever, but I'm about at the end of my questions. Did you have any other last sort of observations or thoughts that we didn't touch upon? Any important themes that I've missed?

CS: I don't think so. That's why I say your questions have been hugely helpful. You've done your homework. (chuckles)

NC: Thank you very much. This has really been a pleasure. Thank you.

END OF INTERVIEW

Endnotes

1. Jessie Boyd Scriver (1894-2000) is a distinguished figure in McGill medicine. See her biography in the online exhibit put on by the NIH, "Changing the Face of Medicine":
http://www.nlm.nih.gov/changingthefaceofmedicine/physicians/biography_289.html . [return to text](#)
2. Norman John Berrill (1903-1996), English-born embryologist. See: Scriver, Charles R. "Norman John Berrill. 28 April 1903-15 October 1996." *Biographical Memoirs of Fellows of the Royal Society* 45 (1999): 20-34.
<http://www.jstor.org/stable/i231422> . [return to text](#)
3. David L. Thomson (1901-1964) chaired the Department of Biochemistry at McGill from 1941-1958. [return to text](#)
4. Hoffman was an endocrinologist also remembered by David Rimoin. See Rimoin's interview in this collection. [return to text](#)
5. Scriver JB and Waugh TR. "Studies on a case of sickle cell anemia." *Canadian Medical Association Journal* 23(3) (Sept 1930): 375-380. Theodore R. Waugh (1890-1960) was professor of pathology at McGill. Eleanor Hill Venning (1900-1988), a very noted chemist working in the Department of Endocrinology, later Professor of Experimental Medicine at McGill, is not credited in this article.
[return to text](#)
6. A former common name for streptococcus. [return to text](#)
7. McCarty, Maclyn. *The Transforming Principle: Discovering that Genes are Made of DNA*. New York: W.W. Norton & Company, 1985. Experiments by Oswald T. Avery (1877-1955), Maclyn McCarty (1911-2005) and Colin MacLeod (1909-1972) established in 1944 that DNA was the substance involved in hereditary "transformations" or mutations in bacteria. See: Avery OT, McCarty M, and MacLeod C. "Studies on the chemical nature of the substance inducing transformation of pneumococcal types." *Journal of Experimental Medicine* 79 (1944): 137-156 at:
<http://202.114.65.51/fzjx/wsw/newindex/wswfzjs/pdf/24avery.pdf> . [return to text](#)
8. 1903-1998. [return to text](#)
9. Ronald V. Christie (1902-1986) had been a medical resident at McGill. As physician-in-chief at the RVH (1955-64), and then dean of the McGill School of Medicine (1964-67), he is credited with integrating research with clinical care.
[return to text](#)
10. John C. Beck, a renowned endocrinologist, was appointed the first head of the combined division of Endocrinology and Metabolism at McGill in 1957 and, in 1964, succeeded Christie as physician-in-chief at the RVH. [return to text](#)
11. Archer J. P. Martin (1910-2002), Nobel in Chemistry, 1952 shared with Richard L. M. Synge (1914-1994), for their invention of partition chromatography. [return to text](#)
12. Dent CE and Walshe JM. "Amino-acid metabolism." *Br Med Bull* 10, no. 3 (1954): 247-50 at: <http://bmb.oxfordjournals.org/cgi/reprint/10/3/247>. Charles E. Dent (1911-1976) was a British physician and biochemist who published many classic studies of the amino acids and linked hereditary conditions. For a brief biographical memoir, see Neuberger A. (Nov 1978) "Charles Enrique Dent. 25 August 1911-19 September 1976." *Biographical Memoirs of Fellows of the Royal Society*. 24: 14-31 at: <http://www.jstor.org/stable/i231401> . [return to text](#)
13. Stanford Moore, Nobel Prize in Chemistry in 1972, shared with William H. Stein, also of Rockefeller University, "for their contribution to the understanding of the

connection between chemical structure and catalytic activity of the active centre of the ribonuclease molecule." Developed the Moore-Stein column for separating amino acids. See biography at

http://nobelprize.org/nobel_prizes/chemistry/laureates/1972/moore-bio.html.

[return to text](#)

14. Mary L. Efron (1926-1967). See Westall R & Adams RD. Tributes to Mary L. Efron. *AMA Journal of Diseases in Children* 117 (Jan 1969): 1-3. The Mary L. Efron Research Fund at Massachusetts General Hospital is named for her. [return to text](#)
15. Stanley W. Wright, Professor of Pediatrics at UCLA, was one of the pioneers of medical genetics at that institution. He was involved in the assessment of the effects of atomic bomb radiation on pregnancy loss in women at Hiroshima and Nagasaki and in early studies of mental retardation due to PKU and other genetic disorders. See Wright SW and Tarjan G. "Phenylketonuria." *AMA Journal of Diseases in Children* 93 (4) (April 1957): 405-419. [return to text](#)
16. Linus C. Pauling (1901-1994), a double Nobel laureate and one of the most important chemists of the 20th century, laid the foundations of molecular genetics in 1949 with his demonstration that sickle cell anemia, an autosomal recessive disorder, is the clinical manifestation of a hemoglobin variant in red blood cells. [return to text](#)
17. Ernest Baldwin (1909-1967), author of *An Introduction to Comparative Biochemistry* (4th edition 1964). [return to text](#)
18. Eric M. Shooter is professor emeritus of Neurobiology at Stanford University. Shooter was originally interested in the biochemical structure of hemoglobins, but turned his attention to neurobiology where he identified and characterized nerve growth factor (NGF). [return to text](#)
19. The R. Samuel McLaughlin Foundation was established in 1951 by McLaughlin, a pioneer in the North American automobile industry. In accordance with the founder's wishes, the trustees distributed the assets of the Foundation in August, 2001, with the largest grant going to the creation of the R. Samuel McLaughlin Centre at the University of Toronto. The remaining \$50 million was distributed to various institutions, community groups and charities. [return to text](#)
20. One of the leading pediatric hospitals in the US, Children's Hospital Boston was established in 1869. See the website at: <http://www.childrenshospital.org/> . [return to text](#)
21. The Larz Anderson Auto Museum, founded by Larz and Isabel Anderson in 1927, is the oldest such museum in the US. It is currently located on Newton Street in Brookline, MA. Anderson (1866-1937) was a wealthy American businessman and diplomat. [return to text](#)
22. Charles Alderson Janeway (1909-1981) was among the best-known academic pediatricians of his time. He was physician-in-chief at Boston Children's from 1946 to 1974. See Haggerty, Robert J., and Lovejoy, Frederick H. *Charles A. Janeway : pediatrician to the world's children*. Boston: Children's Hospital Distributed by Harvard University Press, 2007. [return to text](#)
23. Bessey OA, Adam DJ, and Hansen AE. "Intake of vitamin B6 and infantile convulsions: a first approximation of requirements of pyridoxine in infants." *Pediatrics* 20, no. 1 Part 1 (1957): 33-44 <http://pediatrics.aappublications.org/cgi/reprint/20/1/33>. Pyridoxine is one of the forms of vitamin B6. [return to text](#)

24. Institutional Review Boards. Institutional review boards (IRBs) are formally convened committees empowered to review, approve, and monitor biomedical research involving human subjects. [return to text](#)
25. Sydney S. Gellis (1914-2002), taught at all three medical schools in Boston, but was most closely associated with Tufts-New England Medical Center, where he worked until the age of 86. [return to text](#)
26. Scriver CR. "Vitamin B6-dependency and infantile convulsions." *Pediatrics* 26 (1960): 62-74. <http://pediatrics.aappublications.org/cgi/reprint/26/1/62>. [return to text](#)
27. See note 132. [return to text](#)
28. Clayton PT. "B6-responsive disorders: a model of vitamin dependency." *J Inherit Metab Dis* 29, no. 2-3 (2006): 317-26 at: <http://www.springerlink.com/content/x5j7762495122123/>. Clayton is now Professor of Metabolic Medicine at UCL and works at the Great Ormond Street Hospital for Children. [return to text](#)
29. Scriver CR, Beaudet AL, Sly WS, et al. *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw-Hill, 2001. A 6000-page book. See note 233. [return to text](#)
30. Referring to Ingram's discovery of the amino acid substitution involved in sickle cell anemia. Ingram, Vernon M. "Gene mutations in human haemoglobin: the chemical difference between normal and sickle cell haemoglobin." *Nature* 180 (1957): 326-28. See the URL at: <http://www.nature.com/nature/journal/v180/n4581/pdf/180326a0.pdf> . [return to text](#)
31. Irwin A. Schafer became a pediatrician and geneticist at Cleveland Metropolitan General Hospital in Ohio. [return to text](#)
32. Blood in the urine. [return to text](#)
33. Alport syndrome is the second most common inherited form of kidney inflammation and failure, caused by the absence or abnormality of a key collagen protein in the formation of the glomerular membranes that filter blood within the kidneys. It was first recognized by William Dickenson in 1875, but definitively described by Cecil Alport (1880-1959) in 1927. OMIM #301050 (<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=301050>). [return to text](#)
34. Proline, hydroxyproline, glycine, and tryptophan are all amino acids active in the body. [return to text](#)
35. Now recognized as hyperprolinemia type 1 (www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=239500). [return to text](#)
36. See note 43. [return to text](#)
37. The Hartnup phenotype, which involves abnormalities of the renal tubules, was first identified in a 12-year-old boy in 1951; studies of his family established that this was an inherited metabolic syndrome. [return to text](#)
38. Presumably Kenneth N. F. Shaw, of the University of Southern California. [return to text](#)
39. Scriver CR. "Hartnup Disease: A Genetic Modification of Intestinal and Renal Transport of Certain Neutral Alpha-Amino Acids." *N Engl J Med* 273 (1965): 530-532. [return to text](#)
40. Harry Harris (1919-1994) was one of the most influential geneticists in postwar England. He spent his career at UCL and King's College until accepting the Harnwell Chair of Human Genetics at the University of Pennsylvania in 1974, a position he held until his retirement in 1990. For his biography, see Hopkinson, DA. "Harry Harris: 30 September 1919 - 17 July 1994." *Biographical Memoirs of*

- Fellows of the Royal Society* 42 (1996): 153-170, at:
<http://www.jstor.org/stable/i231419>. [return to text](#)
41. Ninhydrin is a chemical used to detect primary and secondary amines. [return to text](#)
 42. That is, it generates glucose from non-sugar carbon substrates. [return to text](#)
 43. Scriver CR, Schafer IA, and Efron ML. "New renal tubular amino-acid transport system and a new hereditary disorder of amino-acid metabolism." *Nature* 192 (1961): 672-73 at:
<http://www.nature.com/nature/journal/v192/n4803/pdf/192672a0.pdf>. [return to text](#)
 44. An interview with F. Clarke Fraser is available in this collection. [return to text](#)
 45. The John and Mary R. Markle Foundation (b. 1927) awarded 25 Medical-Scholar-in-Residence grants each year between 1948 and 1974. Scholar candidates were nominated by their medical schools. [return to text](#)
 46. Established 1929. [return to text](#)
 47. "here": the library in which the interview took place. [return to text](#)
 48. Maureen Forrester (b. 1930). [return to text](#)
 49. The United Church of Canada was formed in 1925 by the merger of the Presbyterian Church, Methodist Church, the Congregational Union of Ontario and Quebec, and the Association of Local Union Churches. The church Dr. Scriver refers to was the Erskine and American Church, an amalgamation of two Presbyterian churches. [return to text](#)
 50. Alexandre Dumas père (1802-1870), the author of *The Three Musketeers*. [return to text](#)
 51. Antoine de Saint Exupéry (1900-1944), best known for *The Little Prince*. [return to text](#)
 52. Q-boats were disguised merchant vessels with antisubmarine equipment on board. [return to text](#)
 53. Alfred Lord Tennyson (1809-1892), Poet Laureate of Great Britain from 1850 until his death. [return to text](#)
 54. Westmount is an historic Montreal neighborhood, dating back to French missionaries in 1684. [return to text](#)
 55. i.e., marijuana or other recreational drug. [return to text](#)
 56. i.e., get her an abortion. [return to text](#)
 57. Lennie Tristano (1919-1978) was an American jazz pianist and composer. [return to text](#)
 58. Edward Kennedy "Duke" Ellington (1899-1974), American bandleader, composer, and pianist. [return to text](#)
 59. William John "Bill" Evans (1929-1980), American jazz pianist. [return to text](#)
 60. The *Odyssey* is Homer's famous Greek epic poem of the wanderings of Odysseus, usually dated to about 700 BCE. The Mesopotamian epic of the hero-king *Gilgamesh* is much older, dating to around 2100 BCE. [return to text](#)
 61. Claude Roy is now Professor Emeritus of Pediatrics at the University of Montreal. [return to text](#)
 62. Norma Ford Walker (1893-1968), PhD, became famous for her research on the Dionne quintuplets in the 1930s and subsequently was the first director of human genetics at Toronto's Hospital for Sick Children. [return to text](#)
 63. Syndromology is the taxonomy and etiology of congenital malformations. [return to text](#)
 64. Archibald Garrod (1857-1936), MD, the British physician who introduced the concept of inborn errors of metabolism in 1908. [return to text](#)

65. University College Hospital and University College London. [return to text](#)
66. Lionel S. Penrose (1898-1972), British psychiatrist and geneticist who carried out pioneering studies on the genetics of mental retardation in the 1930s and 1940s. [return to text](#)
67. Scriver is correctly recalling street names around University College London, but the geography is fuzzy. [return to text](#)
68. Jeremy Bentham (1748-1832), English jurist, philosopher, and social reformer. His skeleton, the "Auto-Icon", preserved and dressed in his own clothes, and surmounted by a wax head, is still on display in the South Cloisters of the main building at UCL. Bentham's real head, which was damaged in the preservation process, was kept on separate display for years, but after repeated thefts by student pranksters, was put into storage in 2005. [return to text](#)
69. The Galton Laboratory, named for Francis Galton (1822-1911), was founded as a center for human genetics research in 1904. [return to text](#)
70. Park S. Gerald (1921?-1999?) founded the first research and training program in human genetics at Harvard University. [return to text](#)
71. Penrose LS. "Phenylketonuria: a problem in eugenics." *Lancet* 247, no. 6409 (1946): 949-53 reprinted in *Ann Hum Gen* 62 (3) (May 1998): 193-202 at <http://www.blackwellsynergy.com/links/doi/10.1046%2Fj.1469-1809.1998.6230193.x>. [return to text](#)
72. Developed in 1948 at the Rockefeller Institute by Stanford Moore (1913-1982) and William H. Stein (1911-1980). See: <http://www.jbc.org/cgi/reprint/176/1/367.pdf>. [return to text](#)
73. Elution chromatography involves continuous addition of the mobile solution to be separated. [return to text](#)
74. Smithies O. "Zone electrophoresis in starch gels: group variations in the serum proteins of normal human adults." *Biochemical Journal* 61, no. 4 (1955): 629-41 <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1215845&blobtype=pdf>. An interview with Oliver Smithies is available in this collection. [return to text](#)
75. Arne Tiselius (1902-1971) of Sweden was the first (in 1948) to use an electrical apparatus to separate large molecules in solution. [return to text](#)
76. Whatman paper is an extremely durable paper first developed in England in the 1740s. Whatman paper was used by artists and for important documents, but today is used mostly in the life sciences. [return to text](#)
77. Lutidine and phenol are natural aromatic organic compounds, derivatives of coal production. [return to text](#)
78. Schafer IA, Scriver CR, and Efron ME. "Familial hyperprolinemia, cerebral dysfunction and renal anomalies occurring in a family with hereditary nephropathy and deafness." *N Engl J Med* 267 (1962): 51-60 at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14497974. See also note 43. [return to text](#)
79. Efron ML, et al. "A Simple Chromatographic Screening Test for the Detection of Disorders of Amino Acid Metabolism. a Technic Using Whole Blood or Urine Collected on Filter Paper." *N Engl J Med* 270 (1964): 1378-83. [return to text](#)
80. Instituted within the Massachusetts Department of Public Health in 1962. [return to text](#)
81. Scriver CR, Laberge C, Clow CL, and Fraser FC. "Genetics and Medicine: an evolving relationship." *Science* 200 (May 26, 1978): 946-952 at: <http://www.sciencemag.org/cgi/reprint/200/4344/946> . [return to text](#)
82. A fluorimetric blood assay for phenylketonuria (inability to metabolize phenylalanine) in newborns, developed in 1961. [return to text](#)

83. Like phenylketonuria, tyrosinemia is a genetic disorder in which the subject is unable to metabolize a specific amino acid (tyrosine), leading to a damaging buildup of this compound in body tissues. Type 1 tyrosinemia, which leads to failure to thrive and possible liver and kidney failure, has an unusually high incidence in Quebec. [return to text](#)
84. Beadle G. "Genes and chemical reactions in Neurospora." *Science* 129 (1959) at: <http://www.sciencemag.org/cgi/reprint/129/3365/1715>. Beadle's (1903-89) and Edward Tatum's (1909-75) Nobel prize-winning work of 1941 demonstrated that each of seven genes in Neurospora expressed a specific enzyme. [return to text](#)
85. Garrod, Archibald Edward, and Harris, Harry. *Inborn errors of metabolism*, Oxford monographs on medical genetics. London and New York,: Oxford University Press, 1963. [return to text](#)
86. The 3rd revised edition was published in 1980 by Elsevier. [return to text](#)
87. *Biochemistry of the Amino Acids*. New York: Academic Press, 1965 (2nd ed). Alton Meister (1922-95) was an American biochemist who spent most of his career at Cornell. [return to text](#)
88. John R. Evans (b. 1930) was the founding dean of the School of Medicine at McMaster, in Hamilton, Ontario, in 1965. [return to text](#)
89. Scriver clarifies: The file was for offers to leave and go elsewhere; offers all refused. [return to text](#)
90. The Redpath is an interdisciplinary museum of science. [return to text](#)
91. Roy Gravel is now a Professor of Medical Genetics at the University of Calgary. [return to text](#)
92. The Toronto-based Alva Foundation, established in 1965 by a branch of the Southam newspaper publishing family, supports Canadian research and services that address significant risk factors in early childhood development. [return to text](#)
93. Associate Professor Thomas J. Hudson is founder and Director of the McGill and Genome Quebec Innovation Centre; he constructed the first physical map of the human genome. [return to text](#)
94. Associate Vice-Principal for Research and International Relations at McGill. [return to text](#)
95. David Rosenblatt, M.D., has been chair of the Department of Human Genetics at McGill since 2001. [return to text](#)
96. The *British Medical Bulletin* is a quarterly publication. For the article citation, see note 12. [return to text](#)
97. Dent was elected a fellow of the Royal Society in 1962. His biography is cited in note 12. [return to text](#)
98. The American Society for Clinical Investigation (ASCI), established in 1908, elects up to 80 new members each year among physician-scientists under the age of 45. [return to text](#)
99. Genetic impairment of the transport system of the kidney tubules, which normally reabsorb proline and glycine (see above under Hartnup disease). [return to text](#)
100. See note 39. [return to text](#)
101. Scriver's CV employs a system of numbers and letters to group his papers. [return to text](#)
102. Scriver CR and Wilson OH. "Possible Locations for a Common Gene Product in Membrane Transport of Imino-Acids and Glycine." *Nature* 202 (1964): 92-93 at <http://www.nature.com/nature/journal/v202/n4927/pdf/202092a0.pdf>. For the 1961 paper, see note 43. [return to text](#)

103. Scriver CR, and Wilson OH. "Amino acid transport: evidence for genetic control of two types in human kidney." *Science* 155, no. 768 (1967): 1428-30 at: <http://www.sciencemag.org/cgi/reprint/155/3768/1428>. [return to text](#)
104. Peter G. Scholefield had a distinguished career as a researcher and administrator in Canada since the early 1970s, much of it at the National Cancer Institute. He retired in 1999 but is still active. [return to text](#)
105. Judah Hirsch Quastel (1899-1987) was a founder of modern neurochemistry and made many contributions to the study of membrane transport processes. From 1966 to 1983, he was a professor at UBC in Vancouver. [return to text](#)
106. Rose M. Johnstone, one of Canada's most noted biochemists, was Chair of Biochemistry at McGill 1980-1990 and continues to be a productive researcher as an Emerita Professor. [return to text](#)
107. A microtome cuts biological specimens into transparent slices. [return to text](#)
108. Onslow H. Wilson, who was one of Scriver's postdocs, has more recently been active as a writer on metaphysics and the body-mind connection. [return to text](#)
109. Christensen, Halvor N. *Biological Transport*. Reading MA: WA Benjamin, 1962. Christensen was Chair of Biological Chemistry at the University of Michigan from 1955 to 1970. [return to text](#)
110. Watson JD. and Crick FHC. "A Structure for Deoxyribose Nucleic Acid." *Nature* 171 (April 25, 1953): 737-738. [return to text](#)
111. See note 7. [return to text](#)
112. The American Society of Human Genetics was founded in 1948. [return to text](#)
113. The Canadian Society for Clinical Investigation, founded in 1951, is open to all Canadians active in clinical research. [return to text](#)
114. An interview with Barton Childs is available in this collection. [return to text](#)
115. Scriver clarifies: grants and agencies. [return to text](#)
116. National Research Council Committee for the Study of Inborn Errors of Metabolism. *Genetic Screening: Programs, Principles, and Research*. Washington DC: National Academies Press, 1975. [return to text](#)
117. Tay-Sachs is a rare autosomal recessive disorder, first described in the 1880s, in which the enzyme that biodegrades the fatty acid derivatives called gangliosides is absent or malfunctioning. The infantile form is generally fatal before age 5. Tay-Sachs is most prevalent among Ashkenazi Jewish, French Canadian, and Cajun populations. [return to text](#)
118. Michael Kaback helped to develop the enzyme assay method for detecting Tay-Sachs carriers and to develop the first large-scale screening program in the US, in Baltimore, in the early 1970s. He is currently Chief of Medical Genetics at the University of California San Diego. See Kaback MM, et al. "Approaches to the control and prevention of Tay-Sachs disease." *Prog Med Genet* 10 (1974): 103-34. [return to text](#)
119. Costa T, Scriver CR, and Childs B. "The effect of Mendelian disease on human health: a measurement." *Am J Med Genet* 21, no. 2 (1985): 231-42 at <http://www3.interscience.wiley.com/cgi-bin/fulltext/110518375/PDFSTART> ; Hayes A, Costa T, Scriver CR, and Childs B. "The effect of Mendelian disease on human health. II: Response to treatment." *Am J Med Genet* 21, no. 2 (1985): 243-55 at

- <http://www3.interscience.wiley.com/cgi-bin/fulltext/110518369/PDFSTART> .
Teresa Costa is now in the Department of Human Genetics at the University of Montreal; Andrew Hayes is at the University of Manchester. [return to text](#)
120. Davidson R G, Nitowsky HM, and Childs B. "Demonstration of Two Populations of Cells in the Human Female Heterozygous for Glucose-6-Phosphate Dehydrogenase Variants." *Proc Natl Acad Sci U S A* 50 (1963): 481-5 at
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=14067093>. [return to text](#)
 121. Possibly Spencer N, Hopkinson DA, and Harris H. "Quantitative differences and gene dosage in the human red cell acid phosphatase polymorphism." *Nature* 201 (Jan 18, 1964): 299-300. [return to text](#)
 122. Analysis of variance. [return to text](#)
 123. Scriver CR. "Normal distributions of amino acids in body fluids." *Pediatrics* 42, no. 3 (1968): 391-92 <http://pediatrics.aappublications.org/cgi/reprint/42/3/391>.
[return to text](#)
 124. Scriver CR, Gregory DM, Sovetts D, and Tissenbaum G. "Normal plasma free amino acid values in adults: the influence of some common physiological variables." *Metabolism* 34 (Sep 1985):868-73 at
[http://www.sciencedirect.com/science doi:10.1016/0026-0495\(85\)90112-X](http://www.sciencedirect.com/science doi:10.1016/0026-0495(85)90112-X).
[return to text](#)
 125. William L. Nyhan (b. 1926) is Professor of Pediatrics at University of California San Diego. [return to text](#)
 126. Leon E. Rosenberg (b. 1933) was the first Chair of Human Genetics at Yale and Dean of the Yale School of Medicine 1984-1991. More recently, he has worked in pharmaceutical and biotechnology research. [return to text](#)
 127. Scriver, Charles R., and Rosenberg, Leon E. *Amino acid metabolism and its disorders*, Major problems in clinical pediatrics. Philadelphia: Saunders, 1973.
[return to text](#)
 128. Bert N. La Du (1920 – 2005) was a pioneer in the field of drug metabolism and pharmacogenetics. His research focused, among other things, on genetic variants of the serum cholinesterase enzymes. [return to text](#)
 129. Donough O'Brien (1923-2004) was Professor of Pediatrics and the head of the Stolinsky Center for Metabolic Diseases and the Barbara Davis Center for Childhood Diabetes at the University of Colorado Health Sciences Center. He retired in 1991. [return to text](#)
 130. The American Academy of Pediatrics, founded in 1930, is the professional organization of American pediatric professionals; in addition to representing their interests, it disseminates information on child health, helps to set standards for medical education in pediatrics, and promotes research into pediatric health problems. [return to text](#)
 131. The Society for Pediatric Research, founded in 1929, works to encourage young investigators to work on research problems that will improve children's health. [return to text](#)
 132. *Mendelian Inheritance in Man: catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes*. The 5th edition was published in 1978. An interview with Victor McKusick is available in this collection. [return to text](#)
 133. The Great Ormond Street Hospital for Children, founded in London in 1852, is thought to be the first inpatient facility for children in the "western" world.
[return to text](#)

134. Referring to a famous painting of William Osler, William H. Welch, William H. Halsted, and Howard Kelly, which hangs in the Welch Medical Library at Johns Hopkins. [return to text](#)
135. The Federation of American Societies for Experimental Biology, a collaboration of 21 constituent research organizations, was founded in the US in 1912. [return to text](#)
136. Sir William Osler (1849-1919) became a legend of early 20th-century medicine. He was the first chief of medicine at Johns Hopkins (1889-1905), and Regius Chair at Oxford from 1905 until his death. Fuller Albright (1900-1969) was a noted American endocrinologist, who worked at MGH. [return to text](#)
137. Cortisone, a hormone of the adrenal cortex, was discovered by the American chemist Edward C. Kendall (1886-1972) in 1949. John S. L. Browne (1904-84) was Professor and Chair of Medicine at McGill from 1948 to 1955 when loss of eyesight forced him to give up clinical duties; he was made Chair of Investigative Medicine and continued teaching until his retirement. [return to text](#)
138. *Upstairs, Downstairs* was an award-winning British drama series of the 1970s that dramatized the life of an aristocratic family and their “downstairs” servants from the 1890s through 1930. [return to text](#)
139. Rickets is a nutritional disorder caused by the absence of vitamin D in the diet, and causing bone pain and weakness. Scriver has also studied a rare X-linked dominant disorder, in which the body is vitamin-D resistant, leading to low levels of blood phosphate, bone pain and softening, muscle dysfunction, and weakness. [return to text](#)
140. Scriver here is conflating time and motion studies, in which jobs are broken into basic tasks and each task is timed and observed to see how it can be done more efficiently, and the “Hawthorne effect”, a temporary behavioral change in response to any environmental change or to experimental observation itself, an effect observed in studies at the Hawthorne Works near Chicago in studies conducted 1924-32. [return to text](#)
141. Clow, C. L., T. M. Reade, and C. R. Scriver. "Management of hereditary metabolic disease. The role of allied health personnel." *N Engl J Med* 284, no. 23 (1971): 1292-98. [return to text](#)
142. Melissa Richter, professor of biology, developed the first formal genetics counseling training program in 1969 at Sarah Lawrence; her colleague Joan H. Marks, a social worker, took over the directorship after Dr. Richter died in 1972. Dr. Marks is currently director of the New York Breast Cancer Study with Mary-Claire King. [return to text](#)
143. Maurice McGregor, a cardiologist, was physician-in-chief, succeeding John Beck, at the Royal Victoria Hospital 1974-1979. He became emeritus in 1985. [return to text](#)
144. Claude J. P. Giroud was a professor of experimental medicine at McGill University. [return to text](#)
145. Francis H. Glorieux is now in the Genetics Unit in the Shriners Hospital for Children at McGill. [return to text](#)
146. Leonard Pinsky, currently Emeritus Professor of Human Genetics at McGill, established a research program in human somatic cell genetics there and was named the first director of McGill’s Centre for Human Genetics in 1979. [return to text](#)
147. Robert S. Krooth was somatic cell geneticist in the Department of Human Genetics at the University of Michigan. James V. Neel (1915-2000), was the founder of medical genetics at the University of Michigan and the first scientist to

- recognize the genetic etiology of sickle cell anemia. For a brief biography of James Neel, please see Morton NE. "Recollections of James Neel." *Mutation Research/Reviews in Mutation Research* 543(2) (2003): 97-104. [return to text](#)
148. G. Malcolm Brown (1916-1977) was the first full-time president of the Medical Research Council of Canada, from 1965 to 1977. [return to text](#)
149. Mary Ellen "Mel" Avery (b. 1927) became the first woman to chair a major department at Harvard Medical School when she was appointed the Thomas Morgan Rotch Professor of Pediatrics in 1974. [return to text](#)
150. Hugh G. Hallward was president of the Southam publishing corporation. John Molson is part of the Molson Brewery and banking family. [return to text](#)
151. Claude M. Laberge moved to Laval University in Quebec City in 1975 as Chief of Medicine, and is now Professor of Medicine and Pediatrics there. [return to text](#)
152. Claude Castonguay (b. 1929), later Minister of Health, Family, and Social Welfare (1970-73) and Gerard Nepveu chaired this 1960s Commission which produced a report recommending a new health and social service network providing greater access to health care for the Quebec population. Castonguay also headed the more recent Castonguay task force which in 2008 recommended health care user fees. [return to text](#)
153. Kenneth J. Arrow (b. 1921) is an influential American economist, joint winner of the Economics Nobel in 1972 and a convening lead author for the Intergovernmental Panel on Climate Change, which shared the 2007 Nobel Peace Prize. [return to text](#)
154. See note 116. [return to text](#)
155. Thalassemia refers to a group of inherited autosomal recessive blood disorders, in which the synthesis of either the α or β globin chain of the hemoglobin molecule occurs at a reduced rate, leading to anemia. It is most common in Mediterranean countries. [return to text](#)
156. The physicist Philip Abelson edited *Science* from 1962 to 1984. [return to text](#)
157. See note 81. [return to text](#)
158. Scriver CR. "Human genetics: lessons from Quebec populations." *Ann Rev Genomics Hum Genet* 2 (2001): 69-101 at <http://arjournals.annualreviews.org/doi/pdf/10.1146/annurev.genom.2.1.69> . [return to text](#)
159. Malcolm Ferguson-Smith (b. 1931) is a noted geneticist, currently Research Professor of Veterinary Medicine at the University of Cambridge. A palimpsest is a manuscript where old text has been erased and new text superimposed. [return to text](#)
160. Folate is the anion form of folic acid, or vitamin B9. [return to text](#)
161. Steven A. Narod, currently Canada Research Chair in Breast Cancer at the Centre for Research in Women's Health at the University of Toronto. [return to text](#)
162. Roberta M. Palmour is Professor of Psychiatric Genetics at McGill and studies addiction and alcohol abuse. [return to text](#)
163. McInnes RR and Scriver CR. "Net reabsorption of alpha-aminoisobutyric acid by rat kidney in vivo." *Am J Physiol* 237(4) (Oct 1979): F274-84. Professor Roderick R. McInnes is an international expert on inherited eye diseases and eye development. In addition to his post at CIHR, he is University Professor of Pediatrics and of Medical Genetics at the University of Toronto. [return to text](#)

164. Harvey Levy is a pediatrician and geneticist at Children's Hospital Boston. [return to text](#)
165. Avihu Boneh is now at Royal Children's Hospital/University of Melbourne in Australia. [return to text](#)
166. Harriet Susan Tenenhouse is Assistant Professor of Human Genetics at McGill. [return to text](#)
167. Murray J. Fraser was a professor of Biochemistry at McGill. [return to text](#)
168. Glorieux F and Scriver CR. "Loss of a parathyroid hormone-sensitive component of phosphate transport in X-linked hypophosphatemia." *Science* 175(25) (Mar 3, 1972): 997-1000 at <http://www.sciencemag.org/cgi/reprint/175/4025/997> . [return to text](#)
169. The brush border membrane is the highly specialized intestinal mucosa adapted for the absorption of many nutrients. [return to text](#)
170. Tenenhouse HS and Scriver CR. "The defect in transcellular transport of phosphate in the nephron is located in brush-border membranes in X-linked hypophosphatemia (Hyp mouse model)." *Can J Biochem* 56(6) (Jun 1978): 640-46. [return to text](#)
171. Glorieux F, Scriver CR, Reade TM, Goldman H, and Roseborough A. "Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia." *New Engl J Med* 287(10) (Sep 7, 1972): 481-87. [return to text](#)
172. For example, Scriver CR, Reade TM, DeLuca HF, and Hamstra AJ. "Serum 1,25-dihydroxyvitamin D levels in normal subjects and in patients with hereditary rickets or bone disease." *New Engl J Med* 299(18) (Nov 2, 1978): 976-79. [return to text](#)
173. Concordia University is a private university in Montreal, formed from the amalgamation of a Catholic and Protestant college in 1974. [return to text](#)
174. Peter M. Nowacki created the online Phenylalanine Hydroxylase Locus Knowledgebase. He works in Bioinformatics at the Genome Centre at Montreal General Hospital. [return to text](#)
175. A rather rare genetic disorder in which the body is unable to metabolize certain proteins and lipids. [return to text](#)
176. *Proceedings of the National Academy of Sciences*. [return to text](#)
177. Homocysteine is an analog of the sulfur-containing amino acid cysteine (of which taurine, a major component of bile, is a derivative). High levels of homocysteine in the blood are linked to increased cardiovascular risk. [return to text](#)
178. Paula J. Waters is now Clinical Assistant Professor of Pathology and Laboratory Medicine at UBC in Vancouver [return to text](#)
179. A type of point mutation in which a variance in a single nucleotide results in the expression of a different amino acid. [return to text](#)
180. Waters PJ, Parniak MA, Nowacki P, and Scriver CR.. "In vitro expression analysis of mutations in phenylalanine hydroxylase: linking genotype to phenotype and structure to function." *Hum Mutat* 11, no. 1 (1998): 4-17 at <http://www3.interscience.wiley.com/cgi-bin/fulltext/5001296/PDFSTART>. A missense mutation is where a variant in a single nucleotide causes the expression of a different amino acid. [return to text](#)
181. Professor of Human Genetics at Aarhus University in Denmark. [return to text](#)
182. Michael Parniak. [return to text](#)

183. A lyase is an enzyme that catalyzes the breaking of chemical bonds, but not through oxidation or hydrolysis. [return to text](#)
184. See for example Wang L, Gamez A, Sarkissian CN, Straub M, Patch MG, Han GW, Striepeke S, Fitzpatrick P, Scriver CR, and Stevens RC. "Structure-based chemical modification strategy for enzyme replacement treatment of phenylketonuria." *Mol Genet Metab* 2005 Sep-Oct; 86(1-2): 134-40. Raymond Stevens is Professor of Molecular Biology at the Scripps Research Institute in La Jolla, California. [return to text](#)
185. BioMarin Pharmaceutical is located in Novato, California. They emphasize development of innovative biopharmaceuticals. [return to text](#)
186. Scriver CR, Waters PJ. "Monogenic traits are not simple: Lessons from phenylketonuria." *Trends in Genetics* 15 (7) (July 1999): 267-272. at: [www.sciencedirect.com/science doi:10.1016/S0168-9525\(99\)01761-8](http://www.sciencedirect.com/science?doi=10.1016/S0168-9525(99)01761-8) . Chaperones are proteins that assist in protein folding, assembly of large macromolecular structures, and other tasks within the cell. [return to text](#)
187. A naturally occurring essential cofactor of phenylalanine-4-hydroxylase for the conversion of phenylalanine to tyrosine. [return to text](#)
188. The US Food and Drug Administration. [return to text](#)
189. The formation of cystic stones in the kidneys, ureter or bladder. [return to text](#)
190. Amphiphilic substances are both attracted to and repelled by water under specific circumstances. [return to text](#)
191. "Here-to-there-ase" is a playful way of referring to an enzyme that moves another molecule from one place to another within the cell. [return to text](#)
192. Claude Bernard's term for the interior environment of the body. [return to text](#)
193. Günter Blobel (b. 1936) won the 1999 Nobel "for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell." See http://nobelprize.org/nobel_prizes/medicine/laureates/1999/ . [return to text](#)
194. François Jacob (b. 1920) shared the 1965 Nobel Prize for his work on the role of feedback in DNA transcription and enzyme expression. [return to text](#)
195. See Barabási, Albert-László. *Linked: The New Science of Networks*. Cambridge, Mass.: Perseus Pub., 2002. Barabási (b. 1967) is a Hungarian-born American physicist, a major contributor to real-world network theory. He is currently Director of the Center for Network Science at Northeastern University. [return to text](#)
196. Christensen, Halvor N. "Reactive sites and biological transport." *Adv Protein Chem* 15 (1960): 239-314. [return to text](#)
197. Professor of Physiology at UCLA. [return to text](#)
198. Scriver CR, Mackenzie S, Clow CL, and Delvin E. "Thiamine-responsive maple-syrup-urine disease." *Lancet* 297, no. 7694 (1971): 310-12 at [http://www.sciencedirect.com/science doi:10.1016/S0140-6736\(71\)91041-5](http://www.sciencedirect.com/science?doi=10.1016/S0140-6736(71)91041-5) . Maple-syrup-urine disease (MSUD) is an inherited and potentially fatal deficiency of the metabolic enzyme BCKDH, leading to a buildup of the branched-chain amino acids (leucine, isoleucine, and valine) in the blood and urine. [return to text](#)
199. Scriver CR. "Vitamin-responsive inborn errors of metabolism." *Metabolism* 22, no. 10 (1973): 1319-44 at [http://www.sciencedirect.com/science doi:10.1016/0026-0495\(73\)90276-X](http://www.sciencedirect.com/science?doi=10.1016/0026-0495(73)90276-X). [return to text](#)

200. The Society for the Study of Inborn Errors of Metabolism (SSIEM) was founded in the United Kingdom in 1964. Mr. J. Milner was a major supporter of the group in its early years. [return to text](#)
201. See note 28. [return to text](#)
202. P= G+E: Phenotype equals genes plus environment/experience. [return to text](#)
203. See note 118. [return to text](#)
204. Beck E, et al. "Advocacy and compliance in genetic screening. Behavior of physicians and clients in a voluntary program of testing for the Tay-Sachs gene." *N Engl J Med* 291, no. 22 (1974): 1166-70. Ellen L. Beck is now in the Department of Family and Preventive Medicine at the University of California San Diego. [return to text](#)
205. Scriver CR, Davies E, and Cullen AM. "Application of a Simple Micromethod to the Screening of Plasma for a Variety of Aminoacidopathies." *Lancet* 284, no. 7353 (1964): 230-2 at [http://www.sciencedirect.com/science/doi:10.1016/S0140-6736\(64\)90183-7](http://www.sciencedirect.com/science/doi:10.1016/S0140-6736(64)90183-7). [return to text](#)
206. Clow C, Scriver CR, and Davies E. "Results of mass screening for hyperaminoacidemias in the newborn infant." *Am J Dis Child* 117, no. 1 (1969): 48-53. [return to text](#)
207. See note 80. [return to text](#)
208. See note 82. [return to text](#)
209. Edward R. B. McCabe, chair of Pediatrics at the University of California Los Angeles and a leading medical geneticist. [return to text](#)
210. Scriver CR. *Pediatric Clinics of North America*. 12 (Aug 1965): 807-821. [return to text](#)
211. Gaucher's disease, the most common of the hereditary lysosomal storage diseases, is a deficiency of the enzyme glucocerebrosidase. It was originally described by Philippe Gaucher in 1882. [return to text](#)
212. Wilson JM and Jungner YG. *Principles and practice of screening for disease*. Geneva: WHO Public Health Report, 1968. [return to text](#)
213. World Health Organization. [return to text](#)
214. See note 116. [return to text](#)
215. See note 206. [return to text](#)
216. See note 141. [return to text](#)
217. See note 168. [return to text](#)
218. Winters RW, Graham JB, Williams TF, McFalls VW, and Burnett CH. "A genetic study of familial hypophosphatemia and vitamin D resistant rickets with a review of the literature." *Medicine (Baltimore)* 37, no. 2 (1958): 97-142, reprinted in the same journal 1991 May; 70(3): 215-17. Robert W. Winters was in the Department of Pediatrics at the University of North Carolina and later at Columbia. [return to text](#)
219. Arnaud C, Glorieux F, and Scriver C. "Serum parathyroid hormone in X-linked hypophosphatemia." *Science* 173(999) (Aug 27, 1971): 845-47 at <http://www.sciencemag.org/cgi/reprint/173/3999/845>. "Our second paper" is cited in note 168. [return to text](#)
220. See note 171. [return to text](#)
221. Richmond S. Paine (1920-1969) was a leading pediatric neurologist. [return to text](#)
222. W. Eugene Knox (b. 1918) was in the Department of Biological Chemistry at Harvard. [return to text](#)

223. Hörst Bickel, in Germany, who helped develop the first low-phenylalanine diet in the 1950s. [return to text](#)
224. There are two, published back to back in *Nature*: Woolf, L. I., W. I. Cranston, and B. L. Goodwin. "Genetics of phenylketonuria. Heterozygosity for phenylketonuria." *Nature* 213, no. 5079 (1967): 882-83; ———. "Genetics of phenylketonuria. Third allele at the phenylalanine hydroxylase locus in man." *Nature* 213, no. 5079 (1967): 883-85. The 1968 *Nature* paper by Rosenblatt and Scriver (see note 226) cites the first. Louis I. Woolf was then in the Population Genetics Research Unit at Oxford; he spent his later career at University of British Columbia. [return to text](#)
225. A proband is the first member of a family to seek treatment for a genetic disorder. [return to text](#)
226. Rosenblatt D and Scriver CR. "Heterogeneity in genetic control of phenylalanine metabolism in man." *Nature* 218 (5142) (May 18, 1968): 677-678 at <http://www.nature.com/nature/journal/v218/n5142/pdf/218677a0.pdf>. [return to text](#)
227. Leo Szilárd (1888-1964) was a Hungarian-born physicist who first conceptualized the nuclear chain reaction in London in 1933. He later worked on the Manhattan Project in the US. *The Voice of the Dolphins* (1961) is a book of short stories dealing with moral and ethical questions. [return to text](#)
228. Kacser H and Burns JA. "The control of flux." *Symp Soc Exp Biol* 27 (1973): 65-104. [return to text](#)
229. Now in the Department of Genetic Research at the Hôpital Necker-Enfants Malades in Paris. [return to text](#)
230. Leland H. Hartwell (b. 1939) is director of the Fred Hutchinson Cancer Center in Seattle. He shared the Nobel Prize in 1981 for his work on genetic control of the cell cycle. [return to text](#)
231. Daniel L. Hartl is Higgins Professor of Biology in the Department of Organismic and Evolutionary Biology at Harvard. [return to text](#)
232. The Genetics Society of America, founded in 1931. [return to text](#)
233. The first edition of *The Metabolic Basis of Inherited Disease* (McGraw-Hill, 1960) was edited by John B. Stanbury, James B. Wyngaarden, and Donald S. Frederickson. Scriver became the lead editor for the 6th edition in 1989 and the 7th in 1995 (now renamed *The Metabolic and Molecular Bases of Inherited Disease*). Stanbury et al remained as consulting editors. The online edition, with David Valle as lead editor and Scriver as an emeritus editor, appeared in 2007. [return to text](#)
234. David Valle is Henry J. Knott Professor and Director of the Institute of Genetic Medicine at Johns Hopkins. Arthur L. Beaudet is professor and chair of the Department of Molecular and Human Genetics at the Baylor University College of Medicine. Interviews with both will soon be available in this collection. [return to text](#)
235. William S. Sly is professor & chair of the departments of Biochemistry and Molecular Biology at St. Louis University School of Medicine. [return to text](#)
236. Joseph L. Goldstein, is Regental Professor, the Julie and Louis A. Beecherl Distinguished Chair in Biomedical Science, and Paul J. Thomas Chair in Medicine at the University of Texas Southwestern Medical Center and shared the 1985 Nobel Prize in Physiology or Medicine with his long-time collaborator, Michael S. Brown. [return to text](#)
237. Savio L.-Y. Woo is University Professor of Bioengineering at the University of Pittsburgh. [return to text](#)

238. Now a researcher at the Howard Hughes Medical Institute at the Jackson Laboratory. [return to text](#)
239. Haplotypes are combinations of alleles (genetic variants) at multiple linked chromosomal loci that are transmitted together to the next generation. [return to text](#)
240. John SW, Rozen R, Laframboise R, Laberge C, and Scriver CR. "Novel PKU mutation on haplotype 2 in French-Canadians." *Am J Hum Genet* 45, no. 6 (1989): 905-09 at <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=2574002> ; John SW, Rozen R, Scriver CR, Laframboise R, and Laberge C. "Recurrent mutation, gene conversion, or recombination at the human phenylalanine hydroxylase locus: evidence in French-Canadians and a catalog of mutations." *Am J Hum Genet* 46, no. 5 (1990): 970-74 at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=1971147> . [return to text](#)
241. Scriver CR. "The PAH gene, phenylketonuria, and a paradigm shift." *Hum Mut* 28(9) (Sep 2007): 831-845 at <http://www3.interscience.wiley.com/cgi-bin/fulltext/114211626/PDFSTART>. [return to text](#)
242. c.12226 in the PAH [phenylalanine hydroxylase] gene. [return to text](#)
243. A molecular unit formed of two identical subunits. [return to text](#)
244. Founder effect mutation refers to the loss of genetic variation when a separate new group is formed by a small number of individuals from a larger population, as in a colony. [return to text](#)
245. The Hopewell hypothesis holds that nephrogenic diabetes insipidus arrived in North America in the genes of Ulster Scots on the ship Hopewell, which landed in Nova Scotia in 1761. See Bode HH, and Crawford JD. "Nephrogenic diabetes insipidus in North America. The Hopewell hypothesis." *N Engl J Med* 280, no. 14 (1969): 750-54. The disease is characterized by the insensitivity of the kidneys to ADH (antidiuretic hormone) or vasopressin, resulting in the excretion of highly diluted urine. [return to text](#)
246. Jean-Marie Saudubray is a geneticist at the Hôpital Necker-Enfants Malades in Paris. [return to text](#)
247. From 1949 to 2006, the CIBA Foundation (later the Novartis Foundation), funded by a Swiss pharmaceutical company, sponsored several well-regarded scientific symposia each year with published proceedings. CIBA-Geigy and Sandoz merged in 1996 to become Novartis; and as of February 2008, Novartis has withdrawn support for the Foundation; the future of the symposia is therefore uncertain. [return to text](#)
248. Luigi Luca Cavalli-Sforza (b. 1922) is one of the world's leading population geneticists. He is Professor Emeritus of Genetics at Stanford University. An interview with Cavalli-Sforza is available in this collection. Sir Walter Bodmer (b. 1936) is the Head of the Cancer and Immunogenetics Laboratory in the Weatherall Institute of Molecular Medicine at Oxford University. Sir David Weatherall (b. 1933) is the founder of the Institute; he left the Regius Professorship of Medicine at Oxford in 2000 to become Chancellor of Keele University. Interviews with Bodmer and Weatherall are planned for this collection. [return to text](#)
249. Genetic drift refers to purely random changes in the frequencies of alleles in a population. [return to text](#)
250. Evan Pugh Professor of Anthropology and Genetics at Penn State. [return to text](#)

251. Professor of Biology at McGill, a researcher in yeast genomics. [return to text](#)
252. Hartman JL IV, Garvik B, and Hartwell L. "Principles for the buffering of genetic variation." *Science* 291, no. 5506 (2001): 1001-04 at <http://www.sciencemag.org/cgi/content/full/291/5506/1001>. [return to text](#)
253. Mark Vidal is Associate Professor of Genetics at Harvard Medical School and Director of the DFCI Center for Cancer Systems Biology. The Eli and Edythe Broad Institute is an Massachusetts Institute of Technology-Harvard research community collaboration in genomic medicine, founded in 2004; Vidal is part of that community. [return to text](#)
254. *Caenorhabditis elegans* is a nematode or roundworm often used as a model organism. [return to text](#)
255. Polymorphism: multiple alleles of a gene within a population, often expressed as different phenotypes. [return to text](#)
256. Kan YW and Dozy AM. "Polymorphism of DNA sequence adjacent to human beta-globin structural gene: relationship to sickle mutation." *Proc Natl Acad Sci U S A* 75, no. 11 (1978): 5631-35 at <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=281713>. RFLPs are restriction fragment length polymorphisms, short gene sequences detected by restriction enzymes that vary between individual organisms. An interview with Y. W. Kan is available in this collection. [return to text](#)
257. Lactase is the enzyme essential for the digestion of lactose in milk; its deficiency results in lactose intolerance. [return to text](#)
258. In 1956, the University of Michigan Heredity Clinic, which had its origins in eugenics, was reorganized as the Department of Human Genetics. The Eugenics Board of North Carolina, which authorized the sterilization of individuals with mental illness or mental retardation, was in operation from 1933 to 1974. [return to text](#)
259. Scriver here begins to talk about thalassemia and sort of mixes that disease and Tay-Sachs together in the next paragraphs. [return to text](#)
260. An interview with Arno Motulsky is available in this collection. [return to text](#)
261. Andrews, Lori B., et al., eds. *Assessing Genetic Risks: Implications for Health and Social Policy*. Washington, DC: National Academy Press, 1994. Scriver's review is in *American Journal of Human Genetics* 56: 814-816, 1995. Peter Byers was the editor of the journal. [return to text](#)
262. A neuroendocrine tumor of the sympathetic nervous system, the most common cancer in children under 2 years of age. [return to text](#)