MRC/CIHR McGill Group in Medical Genetics
Oral Histories
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Introduction

Dr. F. Clarke Fraser, November 3, 2009

Christopher Canning: My name is Christopher Canning, and I'm here with Dr. F. Clarke Fraser in the Department of Human Genetics on November 3rd, 2009. It is my great honour and privilege to be here with you, Dr. Fraser, to discuss two main themes regarding human genetics. First, I would like to discuss your academic background, which, of course, significantly contributed to the growth of medical genetics in Canada and beyond. Secondly, and perhaps more importantly for this study, I'm interested in your involvement in the MRC/CIHR Medical Genetics Group, which you helped form in 1972 with Dr. Scriver, and which operated until just this past September, also under the leadership of Dr. Roy Gravel and Dr. Rima Rozen. As you know, I've been hired to conduct oral histories of all the members, but first of all, can we just do some background questions about you? Where were you born?

Dr. Fraser: I was born in Norwich, Connecticut.

Christopher Canning: What year?

Dr. Fraser: 1920. I lived there nine months. My father was working there, so I have Canadian roots but I was born there, more or less, by accident.

Christopher Canning: And then, where did you live after those nine months?

Dr. Fraser: My father worked for a while in St. John, and then in Montreal, and then he finally got a job as a Canadian trade commissioner, and his first posting was in Dublin. Then, when I was about seven, he was posted to Jamaica, and I spent the next ten years in Jamaica. I went to a very good public school, which is a private school, Munro College. I think I got a very good basic education there. By the time I'd finished form 6A, I entered Acadia as pre-med, and I was sufficiently advanced that they put me in sophomore year, directly.

Christopher Canning: Right out of high school, you went into your sophomore year?

Dr. Fraser: Yeah.

Christopher Canning: And what did you start to major in, then, if you didn't do biology in high school?

Dr. Fraser: I was pre-med and biology.

Christopher Canning: Okay. Do you have any siblings?

Dr. Fraser: Oh, yes. My sister, Mary. She, unfortunately, died quite young of what was then called Alzheimer Pick disease - one of the early pre-senile dementias.

Christopher Canning: Okay. And what year was that, if you don't mind my asking?

Dr. Fraser: It was when she was….let's see, she was about thirty-five and she was born in '22, so that would be fifty-seven, right?

Christopher Canning: Can you tell me a little bit about your parents? What were they like as parents?

Dr. Fraser: My mother was a very warm, vivacious person who had a beautiful voice. She graduated from Mount Allison University in voice, and sang alto. Although vivacious and gracious, she was also quite a disciplinarian just by personality; no physical punishment or anything like that, but she knew how to teach us what was right and what was wrong and to keep us in line. My father was a quiet gentle man with a good sense of humor, and he loved poetry and he could recite it by the hour. They obviously loved each other very much and they never raised their voices to one another, and I think I got some of that from them. We used to play golf together when I was old enough, and I was very much attached to him. What else?

Christopher Canning: Did they have high expectations from you, academically?

Dr. Fraser: They never sat me down and said, "Now you've got to do this and that," but I think, just by example. I mean, they sent me to the good school and I'm sure they expected me to do well. Although it was never formally verbalized, I got the message.

Christopher Canning: Where do you think you got your motivation, then, to go into med school?

Dr. Fraser: Well, I had an Uncle Lew who, actually, was an uncle by marriage. Lew Lovett was a real horse and buggy doctor, literally. I mean, he drove a horse and buggy, and did appendectomies on the kitchen table, sort of thing. I admired him very much, and I think, probably, that was one of the reasons I wanted to go into medicine, and you know, I had a…somehow felt I wanted to help people, and I went to Acadia. In Biology 1, they had two lectures in genetics given by Muriel Roscoe, who later became Dean of Women at McGill, incidentally, but at that time she was a professor of biology. She gave these two lectures in genetics, and I just fell for it. I knew right away, that's what I wanted to do.

Christopher Canning: How old were you then?

Dr. Fraser: I was seventeen. So instead of going into medicine, I applied to McGill…the genetics department at McGill for graduate work, and somewhat to my surprise, well they said I could come if I got a scholarship, and somewhat to my surprise, the NMRC gave me a scholarship; I think it was six hundred dollars, which was quite a lot of money in those days. And I came to McGill

to their genetics department, which had been newly formed; it was just a few years old, actually. The story goes, and I can't vouch for it but…that the genetics department arose because of botany and zoology, and McGill couldn't decide who should give the course of genetics, and Leonard Huskins, who was one of the professors in the department said, "I'll do it," and he went to Rockefeller Foundation and got a grant to start the department of genetics. It was only three or four years old at that point.

Christopher Canning: Was the focus mainly on plant genetics?

Dr. Fraser: There was trillium because it had large chromosomes, and wheat because they were studying the genetics of wheat rust, I think. But there was also drosophila and mice, and as soon as I entered the mouse room, I knew that's what I wanted to do because it was the closest to medicine. But the first year, I couldn't do that because there were already two students in the mouse room and that's all it could handle. So I got to do drosophila – the fruit fly – and did a study with Arthur Steinberg who had just come to the department. I think that was probably good for me because we could do really rigorous genetic analyses, and so I didn't suffer from that, and then I got my masters. The next year I went into the mouse room and started working with mice and got my PhD that way.

Christopher Canning: Can you just give a brief description of what your PhD research concerned?

Dr. Fraser: There was several mouse mutants that had arisen in the lab that involved hair loss. One of them was called 'hairless', and another called 'rhino' because it had a wrinkled skin, and I studied their histology and tried to find how the gene worked. I did skin transplants to see whether there was some agent that would go from the normal skin into the hairless skin graft that would allow hair to grow. I think I got my PhD on two false assumptions. I actually did get some hair growth along the line…along the interface, and I used color differences so you could really tell which hair was coming from which source. But, I think, really, it was because there was scar tissue at the edges of the grafts; and that was allowing the hair to stay in. And then I decided, because vitamin A was good for some human keratoses, that I'd try that, and I gave the rhino mice large quantities of vitamin A, and it smoothed out the skin very nicely. Again, in retrospect, I think that's probably because it was toxic.

Christopher Canning: In the offspring of the mice, it would smooth out the skin?

Dr. Fraser: No, the mice themselves, yeah.

Christopher Canning: How did Steinberg influence your work at the time? Did he encourage you to stay there and do your PhD? Did you do your PhD with Steinberg?

Dr. Fraser: Yes, I did. Yeah, we didn't hit it off at first because he thought I was lazy,

and the first – I hope I'm not getting into too much detail.

Christopher Canning: The detail is perfect.

Dr. Fraser: We were studying the effect of inversions in one chromosome on crossing over another, in the X chromosome.

Christopher Canning: This was your first publication?

Dr. Fraser: Yes. And nobody understood what this was, so we used inversions of different lengths and different break points to try to figure out what it might be about the inversion that would do this, and my first series of experiments gave absolutely ridiculous results, and Steinberg thought I was screwing up somehow, so he…the next time he and I ran parallel experiments and he got the same screwy results. And it turned out there was an inversion in the control stock, which buggered everything up. So during the time when I was messing up, he was not very impressed with me, but we eventually got on the same wave length and he was very good for me because he was rigorous and….so.

Christopher Canning: Did you collaborate on anything else with Steinberg after that?

Dr. Fraser: No. As soon as I got my thesis done, I joined the air force because we were still at war.

Christopher Canning: I guess this would have been in '43?

Dr. Fraser: '45 maybe.

Christopher Canning: Okay.

Dr. Fraser: Yes, it was earlier than that – '43, I think, because I got back to the medical school in '46.

Christopher Canning: Yes, it would have been '42 or '43.

Dr. Fraser: So, Major General McNaughton, who was head of the NRC, had told students, at the time, to at least stay in their studies rather than joining up because Canada needed the scientists for the war effort. So I stayed on until I got my thesis done, but then I joined up and I was in the air force for three years and never got over, but when I was let out, I was able to use the veteran's allowance, and that allowed me to go to medical school; that's how that worked out.

Christopher Canning: So you finished your PhD after you came back from the air force – or right before?

Dr. Fraser: Actually, I turned in my thesis. I turned in my thesis before, but then I went through their exam - I guess it was a ritual – when I got back, and then I went right into medical school.

Christopher Canning: You say in your memoir that a few times in med school you felt like dropping out. Can you explain what was going on here?

Dr. Fraser: Well, I thought when I went in that I'd just do…take from my medical studies what I needed for genetics, you know, so I didn't do very well. I flunked anatomy in the first year and had to write a supp. In third year, I flunked obstetrics and pathology, third year special pathology, mostly because I wasn't really paying attention to the….I didn't like things that involved rote learning, like anatomy which involved…. and special pathology, in fact, which you had to learn a lot of stuff which didn't…or wasn't logically hung together; so I didn't do well in those things. In obstetrics, I probably flunked because I was what might be called 'insolent.' See, in the oral exam, the professor said, "You've got this pernicious lady with pernicious vomiting and what are you going to do?" He said that, so I suggested a few things like soda crackers and whatnot, and he said, "Well okay, but she's still vomiting," and I suggested a few more things, and then he said, "She's still vomiting, doctor, in your face," and then he said, "What would you do then?," and I said, "Wipe it off, sir."

Christopher Canning: And that didn't get you a pass? [laughs]

Dr. Fraser: No, strange to say. [laughs]

Christopher Canning: So there were a few bumpy times but you stuck through it.

Dr. Fraser: Yeah. Well, at that point, I got very discouraged and thought I might quit altogether, and wrote to a number of people who gave me very encouraging replies -- Jim Neel who was one of the first medical geneticists, who I knew by then quite well; J.S.L. Browne who was an outstanding biochemist, or endocrinologist, I guess, who was a fraternity brother and I knew him quite well. He wrote back saying, don't be silly. So I took a year out, at that point, to sort of get it together again, and then I went through the final year and I did a lot better paying attention to medicine rather than genetics. And during my pediatric rotation, I got to know Alton Goldbloom, who was the professor of pediatrics, and made myself known to him and what my aims were. He was one of the few people who saw how important genetics might be in medicine, and pediatrics in particular, so he was really the one that organized my going to the [Montreal] Children's [Hospital] -- at that point, instead of doing a regular internship, you were allowed to do a year of research. And Alan Ross seized on this, so he…Alan Ross was Goldbloom's successor, and also a very important person in my life, besides taking care of my kids. He arranged it so I could take this year of so called 'research,' and start the division of human/medical genetics at the Children's.

Christopher Canning: That is a nice segue into my next question. Why the Montreal Children's hospital then? Was it based on these folks?

Dr. Fraser: That's why, yeah. McGill was a reasonable place to start genetics, anyway, but these two very far-seeing individuals were the main reason.

Christopher Canning: Can you recall any other centers, either in Canada or in North America, that were doing the same thing – merging pediatrics with human genetics? Was there a spirit in the air?

Dr. Fraser: Not at that time, really. There was Norma Ford Walker in Toronto, but she was PhD in Zoology; she worked there at the Children's Hospital and did some counseling and studies of Down syndrome stuff, and dermatoglyphics there, but I don't think….they didn't really get her a formal department for some time, and there weren't any people who had both a medical degree and PhD, in Canada at that point.

Christopher Canning: You stated in your memoir - and this is a really interesting line and I pulled it out just to see if you can elaborate on it for me – you said, just as your interest in medical genetics was growing, you were at the Children's Hospital, you had started this medical genetics unit, and you said that you had an interest in spotting genetically interesting patients, and I'm wondering if you can just expand on that. What did you notice when you said 'genetically interesting'? At the time – in the late forties – what were you seeing?

Dr. Fraser: Well I used to go around the wards and quiz the Residents about the family histories and stuff, and encourage them to ask about consanguinity when they were taking the family history and so forth. Well, there were several that come to mind that I think did make an impression. One was a young lady who came in with an acute abdomen – pains in the abdomen - and nobody could figure out why her belly was hurting. And I took the family history, and she had this family history of drinkers, but they weren't alcoholics; they were water drinkers, and they used to drink enormous amounts of water and then thereby peeing enormous amounts. You know, grandfather for example, said he used to…every night he would take a pail of water in and put it on one side of the bed, and then he carried it out from the other side of the bed, in the morning. And so, it turned out that her pain was because her liver was swelling when she drank so much, and I think that diagnosis impressed people a bit. And there was another boy who came in bleeding from his intestine, and they couldn't figure out why that was, and they were running all sorts of tests and so on. I took a family history, and found that that the father had nose bleeds. It turned out that they had a thing called 'hereditary hemorrhagic telangiectasia,' which is a weakness of the blood vessels, so the capillaries sometimes are fragile and will break on insult, and sometimes it happens in your nose and sometimes

it happens in your gut, and that was the cause of the little boys bleeding. So that sort of interesting patient is what I had in mind, I guess.

Christopher Canning: So at the time, obviously, the genetic diagnosis was a family history.

Dr. Fraser: Exactly.

Christopher Canning: And then, obviously, it wasn't until the molecular scientists came into the field, where you started collaborating and saying, "What are the actual molecular mechanisms behind these genetic diseases?"

Dr. Fraser: Yeah, well that was a long time the biochemical stage. I got a little frustrated toward rounds and case conferences and saying this patient has a recessive disorder, and the chances of it happening again are one in four to subsequent siblings, and that's as far as you could go. If you knew what the gene is doing maybe you could do something about it. So, when Charles Scriver appeared on the scene, I mean, he was just the answer to my prayers. I welcomed him on board because he was….

Christopher Canning: …the much needed biochemist?

Dr. Fraser: He was figuring out what the genes were doing and how you could do something about it. Like, PKU and several of the other disorders that he worked on.

Christopher Canning: I'd like to come back to him in a bit, because I'm going to move into the formation of the group in 1972. Just stepping back one bit, what was the collaboration like between your work at the Children's and the department at the University? Was it a friendly relationship? How was that at the time?

Dr. Fraser: It was kind of ambivalent. [Wallace] Boyes, the chairman of the department of genetics, sort of went along with this development at the Children's, and he sort of regarded this as a laboratory where I could see patients and take graduate students, and so he welcomed that side of it. It was bringing some prestige and some money into the department, but on the other hand, he was afraid that it would overwhelm - that human genetics could overwhelm basic genetics, and so he was kind of – what's the word? Protective?

Christopher Canning: Well it seems like there was a bit of a turf war – was it a turf war?

Dr. Fraser: I don't think it ever got to the point of war, but yeah, I mean, I would say, "It's time to have a course in human genetics." "What do you need a course in human genetics for? You can just put the human genetics examples into the regular genetics lectures." Well, you know, that's not good enough. Human genetics had progressed so far that it had a body of information of it's own, it's own characteristics. So, it took me quite a while to get the course in human genetics going, and then I wanted to bring in staff, and that

was a threat. So there was a bit of competition there, alright. Finally, the principal – Principal James – worked out a solution where he invented the human genetics sector. There were three deans responsible for it – medicine and science and – what was the other one? – graduate studies. Anyway, it was a tricephalic monster, which fit right in with my teratology experience, and which really meant that none of the teams really paid much attention to it, but…..

Christopher Canning: To your teratology work?

Dr. Fraser: Yeah, or to the sector itself. I mean, I didn't have to consult the dean very much. It had a separate budget from the genetics department, so I could hire staff and apply for my own grants without having to go through Boyes' approval, and…but I was still part of the department as far as teaching and training went, which suited me very well because I didn't think we were ready to go into the medical school; we still needed some roots in basic genetics. So that was a very good compromise and it worked very well.

Christopher Canning: At what stage, then, did you go to the med school and say, "We could collaborate here"?

Dr. Fraser: Well, the Dean of Medicine was part of one of the three deans overseeing the human genetics sector. I mean, he shared responsibility for the sector. I don't remember ever actually…well it was much farther on when we….well, you know, I guess the next thing that happened was that there was a recommendation that the genetics department and zoology and botany should give up their individual identities and form a biology department. And there was committees that came, external reviewers and stuff, and they thought that was a good thing and it probably was, but that meant I had to give up my human genetics sector and become a part of the biology department. And it was much, much later on when we started to press for a separate department in the Medical School. Leonard Pinsky started the formal connection with medicine, as Director of the Centre for Human Genetics in the Faculty of Medicine in 1979, which evolved into the Department of Human Genetics in 1993.

Christopher Canning: I think Pinsky would have started the department in 1979, and the group started in 1972, so it was shortly after.

Dr. Fraser: I was…sorry, you were going to say something.

Christopher Canning: That's fine; please continue.

Dr. Fraser: I got to know the MRC pretty well, and I was chairman of the genetics committee of the MRC for seven years, and then I sat on several other committees. So, I knew that group and I guess they knew me. I must say, they treated me very well, and I'm sure, well, when I would apply for funds,

I would say, "This is what I've been doing, and I can't exactly tell you what I'm going to be doing next year because it depends on what I see in the hospital, but I'll probably be doing this and that." They bought that and kept on supporting me - I'm sure, I would never get anything like that today.

Christopher Canning: This was in the early years of your funding, so just after you finished your degree and started practicing?

Dr. Fraser: Well, quite a few years they did that. I got some early funding from the Rockefeller Foundation, so that's twice that they influenced genetics at McGill. But most of it came from…I had a grant from the MRC for the human genetics work, and then I had a grant from the National Research Council for the teratology, and after a while, they cut that grant back so far that I could hardly operate on it, and I went back to them several times and asked why they'd cut me back, and eventually, they admitted it was because I was getting so much money from the MRC, they didn't think I needed this money. So I did stop NRC altogether, and just put the whole thing into the MRC, and the teratology part.

Christopher Canning: That came under the MRC – the teratological work?

Dr. Fraser: Eventually, when the NRC cut me back, yeah.

Christopher Canning: Okay. I noticed looking through your publications and your memoir that the 1950's were an important time for developing your idea of genetic counseling, which became a huge part of your work, correct?

Dr. Fraser: Yeah, yeah.

Christopher Canning: So I'm just wondering, if you could – two things – maybe tell us about the development of your ideas of genetic counseling, and maybe for the lay audience, describe what genetic counseling is and where it came from.

Dr. Fraser: Well, when I started, geneticists without medical training did most of the genetic counseling that existed. The doctor would phone up and say, "This lady has hemophilia and she's got one affected…this lady has a brother with hemophilia. What are her chances of having a child with hemophilia?" There were no genetic tests for her at that time. It was just a matter of knowing Mendelian patterns and being able to predict what the risks [were]. And so, the geneticist would say one in four or one in twelve and a half, or whatever, 12.5%, or whatever, and the doctor would tell the patient. That means you have to decide whether the risk is high enough and the disease is serious enough that you'd like to either terminate a pregnancy if you have one, or not have the babies; that was the sort of choice that they person had. Well, when I came on board, that was the way things were, and I was able to…first of all, my research collected more data – more accurate data – about risks of recurrence. But then I also used to start talking to the

parents, and going beyond these simple aspects, delving into…..well, I published a paper called, 'Genetic Counseling – The Darker Side," I think.

Christopher Canning: I remember seeing that, yes.

Dr. Fraser: One of the ways that…one of the statements – first statements – about how complicated genetic counseling was. It's not just, "oh you've got a one in four risk, go away and do something about it." So I started seeing how some patients…how differently patients can see the severity of a disease. Some people say a cleft lip is a terrible thing and feel guilty about it, and others accept it …or some…even a thing like polydactyly; you have extra fingers. Some people say that's a terrible disaster, and others say, well, it's just trivial. So there is that sort of diversity, and also the way they look at risks. I say, you've got a five percent chance that your cleft lip would happen again, and some people say, "Oh, I'm just the one that'll fall into that five percent," and another one will say, "Well, that's ninety-five that it won't happen; that's great; it's much better than we thought it was." And so, these simple statistical risks got translated into all sorts of angles, and how you look at it, and how you regard what you can do about it. When I started, contraception was illegal in Quebec.

Christopher Canning: As was abortion?

Dr. Fraser: Well yes, by all means, abortion for sure, but even contraception was illegal, and in order to have an abortion, the woman had to apply…her obstetrician had to apply to a committee which would decide whether the disease was severe enough and the risk was high enough, and I used to have to write letters to this committee saying that I thought they were or they weren't, as the case may be.

Christopher Canning: As a genetic counselor or because you weren't an obstetrician?

Dr. Fraser: No, I was the geneticist. I was the one who could say what the risk was. So, that was the way things were. Gradually, with the quiet revolution and all, it became a lot easier to get an abortion, but still, an abortion is not a trivial business, and before then, there were…I think I may have referred there to one woman who had three hemophiliac sons, because she tried to apply for an abortion, and one time she was pregnant enough, so she went to the obstetrician and started bleeding in his office. Instead of allowing her to terminate, he rushed her in and stopped the bleeding and preserved the pregnancy giving her another hemophiliac son – that's the hardest thing. So does that make sense?

Christopher Canning: Yeah, that's great. So, in a sense, you had to become somewhat of a psychologist, too, which is intriguing because here, at this point in the mid 20th century, is a sort of a blurring of counseling, psychology, along with genetic medicine.

Dr. Fraser: That's right, absolutely, and I felt very inadequate in that regard. It would have been nice if I'd had some training in psychology, but I had to just play it by ear and talk to psychologist's sometimes, or psychiatrists and…

Christopher Canning: Yes. You collaborated with Abby Lippman for a bit?

Dr. Fraser: Yes.

Christopher Canning: Was she helpful for developing these ideas with you?

Dr. Fraser: She was great, yes. She published three papers with me that were regarded as landmarks in genetic counseling, and she used sit in on my interviews with mothers, usually, or parents, and taped everything, and then she'd go through them and pick up themes, and so she published these papers which really formalized what I've been saying about how people look at risks and severities and how they handle these things.

Christopher Canning: Shifting gears a little bit, one theme I noticed throughout your work is that you always refer to the interaction between the gene and the environment.

Dr. Fraser: Yeah.

Christopher Canning: And you even make reference to epigenetics, which is interesting because the term was coined in 1942….

Dr. Fraser: It was?

Christopher Canning: …by Waddington.

Dr. Fraser: Oh yeah, Waddington, right.

Christopher Canning: And so, you mention it in a '46 publication, which is interesting because it's right after this term comes out. And so, even though you're counseling genetic genetics, you still know, especially in your work in teratology and cytogenetics, that there's an interaction between environmental factors and the gene.

Dr. Fraser: Right.

Christopher Canning: And can I just maybe ask a little bit about your research in that area? What were you doing to understand the mutual interaction between the two?

Dr. Fraser: Well, that gets into my teratology work, right, teratology, being the study of the causes of birth defects, or why malformations happen and how they happen. At that time, when I started at the [Montreal] Children's [Hospital], I still had the mouse room in the genetics department. There was a plastic

surgeon called Hamilton Baxter, otherwise known as 'Happy Baxter,' who was quite a character, and I worked -- he provided families with cleft lip for me to work on to establish the recurrence risks and stuff, and one day he came down and he had some cortisone, and cortisone had just appeared and nobody really knew what it did, except it was a steroid and it was good for arthritis, and he said, "the early embryo has an organizer… an induction agent that induces the formation of the neural tube from the overlying ectoderm. He said, "Well, this is a steroid and the organizer is a steroid (it wasn't as it turned out), but maybe if we put this steroid in to the embryo, it'll mess that up and the embryo will have a neural tube defect." Well, you know, I thought that was kind of crazy, but what the hell, let's try it. So I injected some cortisone into a few pregnant animals I happened to have around, and made some wild guesses as to dosages and times, and to my surprise, some of the embryos had cleft palates, not neural tune defects. So…

Christopher Canning: This was a wild surprise? You had no idea that this….?

Dr. Fraser: Yeah, this was the first time that a drug was shown to be a teratogen in experimental animals. So that caused great excitement and of course people wondered whether it would happen in people. It turns out it's not very teratogenic in people. There's some risk but very little. Anyway, I also noticed that on two different strains of animals, and the one strain – the Ajax - had a high frequency or were quite sensitive to the drug, and the C57 – the other strain – was quite resistant; they had a very low frequency. So well, there's your gene environment interaction. And then one of my students, Bruce Walker, looked at why this was, and showed that, in order for it to close, the palate shelves have to get from the vertical on either side of the tongue, to the horizontal; the shelves have to move up, push the tongue out of their way and meet in the mid-line. And the Ajax were only able to accomplish this much later in development than the C57s. So my idea was that, beyond a certain point, the head is growing so far, so big that…so when the shelves get up, they're too far apart to meet, and that's the threshold beyond which the embryo will be malformed; on the other side, it won't, and in the Ajax strain, the distribution of shelf upcoming is much closer to this threshold, normally, without…it's not a matter of how different they handle the cortisone; it's their normal developmental pattern that makes them susceptible.

Christopher Canning: The gene environment, of course. Great. Did this, then, help with your development of the term 'genetic heterogeneity'? You say that you used the term for the first time in genetics research, and what did you mean by that, and how did this term come about in response to, or in opposition to, simple Mendelian diseases?

Dr. Fraser: Well, it's not really simple…it's not in opposition; it's just that two different genes may cause the same phenotype…the same disease, in this case, which

is understandable in view of the fact that most of these genetic disorders are a result of having a chain of biochemical reactions blocked at a certain point. If you block it, then you don't get the end product, and that causes the disease. So you may block it at point A, in one animal, and block it…or person…and block it at point C in the other person, but they'll still both have the same disease because they've blocked the end point. But they aren't genetically the same disease; they're two different genes that cause the same disorder or trait [to] occur.

Christopher Canning: Or phenotype, yes.

Dr. Fraser: So that was long since recognized. I just coined a phrase. I didn't add anything very fundamental to the knowledge.

Christopher Canning: Was there another movement, at the time, for teratology to merge with genetics? Had it always been teratogenetics, or was there teratology and genetics? And where did you see this starting to merge?

Dr. Fraser: Well, teratology, before I started, was already going, but mainly Joe Warkany in Cincinnati, who'd shown that vitamin B deficiency in rats – if you got just the right level of deficiency – could cause malformations. And there was the rubella in people that caused deafness and heart malformations and cataracts, and that had just been recognized, and several other examples like that, but nobody, until I got started, had shown that there is a genetic basis to susceptibility. So, I don't think I coined the term 'teratogenetics' for quite a long time after that, but that was where genetics got into teratology in the first place.

Christopher Canning: And you were pretty much the first person, then, who was working on this, in this area related to the cleft lip?

Dr. Fraser: Cleft palate, actually. Well, you could include cleft lip too. Aspirin causes cleft lip in the mouse.

Christopher Canning: Aspirin does?

Dr. Fraser: Yeah.

Christopher Canning: Too much aspirin?

Dr. Fraser: Yeah.

Christopher Canning: In humans too?

Dr. Fraser: No, not in non-toxic doses, anyway.

Christopher Canning: Right. I didn't know that.

Dr. Fraser: Well, it was…I digress again.

Christopher Canning: No, that's fine.

Dr. Fraser: I gave a talk; I forget where – Cincinnati, maybe – to a group of press people. There was a whole meeting developed to educate the press on teratology, and I gave this lecture on drug induced teratogens and drug induced malformations, and I ended up saying, you know, you never can tell, so no woman should really take a drug unless she really needs it. You never know where…

Christopher Canning: What the potential side effects are, yeah.

Dr. Fraser: …and someone said, "Does that include aspirin?" And I said, "Well, I supposed it does." Next, on the headlines all over the country [read] "Aspirin causes birth defects."

Christopher Canning: [laughs] "Doctor claims aspirin causes birth defects."

Dr. Fraser: Or maybe sometimes they didn't have the 'doctor claims' in. Oh, my friend Joe Workany was very angry with me. So I went back and got my colleague, Daphne Trasler, to try out aspirin on mice, and it induced beautiful cleft lips. That was what got me onto looking at aspirin in the first place.

Christopher Canning: And then you were able to locate the gene that led to the susceptibility of the cleft lip?

Dr. Fraser: Well, I didn't, but some of my graduate students have located some of the genes. It's really not just a gene but several genes, and I don't think they've got them all, by any means, yet.

Christopher Canning: But this triggered the idea that there was a genetic susceptibility to the consumption of aspirin?

Dr. Fraser: Yeah.

Christopher Canning: And, of course, this influenced your own work in other areas, like the cleft palate?

Dr. Fraser: Well, I'm not sure it influenced it; it was part of it.

Christopher Canning: Part of it, yes. Again, part of this time, too, I notice in your publications, is the multifactorial threshold model. And this is where you claim, in your research, that teratology met genetics. So, we've sort of talked about that, but what does it mean, if your words, that "specific genes have a role to play in the multifactorial model"?

Dr. Fraser: Did I say that?

Christopher Canning: You did say that, yes. You said, "Specific genes have a role to play in the multifactorial model."

Dr. Fraser: Well, I've told you about cortisone-induced cleft palate, the distribution of liability and the threshold, and that's it. We were able to identify several factors that will change the position of the distribution; that is how late or early the shelves will come up. The shelves have in them an intrinsic force, which makes them overcome the resistance of the tongue, and push that tongue out of the way and get up; it's a real struggle between them and the tongue. So there's the shelf force, and we think, probably mucopolysaccharides, what gives the shelves their flexibility may have something to do with it. Certainly, the cortisone reduced the mucopolysaccharides so that's a reasonable explanation. And then there is the resistance of the tongue. For instance, there's a gene that removes the tongue musculature so it's just a big flab…doesn't move around, and that will stop the shelves coming up. So there are shelf force factors, tongue resistance factors, and there factors involving the threshold. If the head is too wide, then the shelves have to come up earlier in order to make it, and there's the width of the shelves themselves; if they're too narrow then they have to come earlier. So there are all these factors, and each of them has genetic elements or genes affecting them. So you've got, certainly, dozens if not hundreds of genes which are altering the time at which the shelves come up, and that influences risk that they won't come up in time to meet, and then if they don't…

Christopher Canning: This is the formation of the cleft?

Dr. Fraser: Indeed.

Dr. Fraser: And the same applies to lots of other…I think, most of the familial disorders that have a threshold. I'm not sure whether schizophrenia, for example, has a threshold or not, but most familial diseases. Almost any familial thing that isn't a clear-cut single gene disorder falls into this category. And people are now looking at what they're now calling 'complex diseases,' and looking for the genes that underlie them. I told them many years ago that each of these genes is going to have a small effect. If it had a large effect, it would be Mendelian disorder, so all the genes they're looking for have small effects, and there are hundreds of them, and this person may draw six slow, upcoming genes, and have a cleft palate because of that, and the next person draws six other slow, upcoming genes. Some of them may be the same - they might overlap – but they have a different set of genes doing this and they have the same cleft palate, so you know, it's very complex.

Christopher Canning: On different chromosomes?

Dr. Fraser: Could well be, yeah, probably, in fact.

Christopher Canning: So, you are talking about complexity – what is the complexity of development.

Dr. Fraser: And some people are beginning to realize, somewhat to their surprise, that it's very hard to find genes that alter susceptibility, and they're not doing very well at it at all, and that's the reason.

Christopher Canning: It's interesting that you say that because, again, relating back to your reference to epigenetics, this, in my opinion, is where epigenetics research is going now, is moving into the understanding of complexity.

Dr. Fraser: Moving into…

Christopher Canning: Into complexity. What are the complex gene systems and the environment that contribute to the development of disease?

Dr. Fraser: Yeah, well they're just adding more complexity to the system.

Christopher Canning: Yeah, which is challenging to geneticists who are still looking for one gene.

Dr. Fraser: Yeah.

Christopher Canning: But you say that that debate was going on fifty years ago.

Dr. Fraser: The debate was going on, yeah. They didn't have the molecular tools to really do anything about the debate.

Christopher Canning: Yes, really interesting.

Dr. Fraser: So now they've got the molecular tools to find these genes but they're not finding them, probably because, you know, in the family it's one set; in that family it's another set. And even in the one family, the six or seven genes that are involved each have a small effect. It's very hard to find a gene with small effects.

Christopher Canning: Okay. How are you doing for energy? Do you want to take a small break, because I'm going to move into a few questions regarding the group? We can take a five minute break, get a glass of water and come back for about another half hour - is that okay?

Dr. Fraser: Okay, fine.

Christopher Canning: Great.

Dr. Fraser: Well, you say I used the term many years ago in a Waddingtonian sense, but I don't think he really had any idea about this business of genes being turned off when they go through an ovary and not through a testis, that sort of stuff.

Christopher Canning: Methyl tags and…

Dr. Fraser: Yeah, and being replicated to the next generation of…it's a terribly new…I think, that's, to my mind, new in the last ten years, right?

Christopher Canning: Ten years, yes. And that's the most exciting part, is how traits can be passed on intergenerationally without a change to the DNA. So it's almost Lamarckian. It's this…people are saying it's a return to the Lamarckian acquired characteristics.

Dr. Fraser: Well, I don't know how…Lamarck would say there was a selective direction. I don't see that in the epigenetics. It doesn't change in a particular direction, like a giraffe getting a long neck because it's reaching.

Christopher Canning: Right, so it's random, still, in a sense; it's not directive, yeah, right.

Dr. Fraser: So it's not Lamarckian.

Christopher Canning: Yeah, obviously, you would know a lot better than me; I'm still new to the literature, so…

Dr. Fraser: And then there's copy number variants, which is a whole new…another new source of genetic variation.

Christopher Canning: What's it called?

Dr. Fraser: Copy number variants.

Christopher Canning: Okay. I've never heard of it.

Dr. Fraser: Oh, well you will.

Christopher Canning: Okay.

Dr. Fraser: A whole new source of genetic variation – totally unexpected before. So, I went to a Gairdner Foundation meeting in Halifax, where I heard there, I think it was Scherer from Toronto gave a talk on it. Anyway, look up copy number variants.

Christopher Canning: Okay, the last section of questions, which are fewer than the first section, are to do with the origin of the MRC Group. Obviously, I've been hired to conduct oral histories with all thirteen members, who at one time or

another were funded and contributed research to this Group. I have a list with me; we can go over that in a bit. I would just like to first talk about the importance of you meeting Dr. Scriver and what that relationship was like. What did he bring to your work, and how did you two see yourself collaborating at that time?

Dr. Fraser: Well, as I said, I was very glad to see him on board because it opened up a whole new field; [our meeting] opened up the possibility of presenting some of these disorders, or at least treating them in an intelligent way. I guess we didn't really collaborate very much. We just went on our parallel paths, and I confess that I probably don't know as much biochemical genetics as I should, because whenever something like that came along, I sent it up to [Scriver's] lab and let him deal with it. So I guess our main characteristic was getting along together; not competing, but not interfering either with each other. We always had very cordial relationships, and I guess we didn't compete because we were operating in different fields.

Christopher Canning: What do you think he took from your work? You mentioned that he saw you as father figure, and what do you think it was that he took from your own work in genetics and medicine?

Dr. Fraser: I don't know.

Christopher Canning: I guess I'll have to ask him.

Dr. Fraser: Yeah. He seems to have a high regard for me, and likewise, I for him, but I can't think of…he didn't need to take anything from anybody.

Christopher Canning: Okay. Do you think this kind of collaborative work between the clinical and the biochemical was happening in other places in Canada? Did you get the sense that, in the fifties at least, that there was sort of a move towards collaboration between basic science and clinical practice?

Dr. Fraser: Oh yeah, it was coming along. I guess PKU really started things off in large part. Here was a disease you could treat. A genetic disease you could treat; that was really something and it did a lot to boost the image of medical genetics. I can't remember whether there was anybody at Toronto at that time that got into that. Anyway, it was beginning to develop, yeah.

Christopher Canning: And do you recall the first time that you saw the call for this MRC grant – this group application – and do you remember saying to Dr. Scriver, "We need to do this. We need to put something together"?

Dr. Fraser: No. My memory is just very vague. I was having some personal problems at that time, and as I said, I worked with the MRC quite a lot and spent a fair bit of time in Ottawa, and they knew me. I guess, when they first developed this idea of group grants, which is…I think their idea was mainly to provide

stable funding for people who were working in a particular area, and instead of having to apply every two or three years for grants, they were operating on a five year basis so that people could plan ahead, and I think that was really the main idea of the groups. They said that anyone in a group would have to have their own MRC grant, individually, first, and then they would put groups like this together. They had a genetics group and a physiology group and a biochemistry group and so forth, and ours. I don't know whether we actually applied for it, or it might even have been Malcolm Brown said, "Why don't you guys do a group?" I can't remember.

Christopher Canning: Part of what I'm doing is collecting old documents, and Dr. Rosenblatt actually gave me most of the applications. So there was indeed a 1972 application that would have had to be submitted in 1971, I guess, to be funded in 1972.

Dr. Fraser: Oh, good. But who signed it?

Christopher Canning: I haven't seen it yet. So it's in a box and I still need to go through all these materials.

Dr. Fraser: Uh huh.

Christopher Canning: That's going to be another part of this project, to collect as much paper material to donate to the Osler library to showcase this important group that operated for so long. Another question I have is, were the projects or the different areas of research that contributed to the formation of this group – cytogenetics, molecular biology, biochemistry, pediatrics – were these by accident or were they pre-planned? Do you recall saying, "We need to get this crew together," or was it, "There's a scholar over there, there's a doctor over there, lets work together"?

Dr. Fraser: I don't recall ever saying, "We've got to get this." I mean, it was natural to say we needed biochemical genetics, and then it was…cytogenetics, I mean, you just have it. It's not a matter of, "We've got to get this so we can have a group." Molecular genetics, I don't think even existed at that time, did it? Yeah, so no, I think it's just a natural growth, and people like each other and like to interact and work together.

Christopher Canning: Do you remember group meetings? Did you have group meetings when you were working on these projects and grant applications?

Dr. Fraser: I don't remember. Charles [Scriver] will tell you all that.

Christopher Canning: Okay, I'm sure more details will come out there. You mentioned in one of your publications that the hard work of the group helped form the human genetics department in 1979, which Dr. Pinsky helped form. So, who played a role in this, if you can recall? What were the factors, from the group

specifically, that said, "We need our own human genetics department"?

Dr. Fraser: Well, I don't know. By that time, human genetics had a base of knowledge that made it an entity separate, in some senses, from basic genetics, and made it fit in much more logically with medicine than biology. I have to confess that I always avoided administration as much as I could, and I didn't feel like taking on the responsibility for that. When was the Center for Human Genetics formed, '72?

Christopher Canning: 1979, actually. And from what I can tell so far – you're the first person that I've interviewed – that you and Dr. Scriver sort of co-organized it and supervised it, as sort of co-directors until, I think, maybe Dr. Pinsky took over from there in 1979.

Dr. Fraser: Yeah, I guess that's right.

Christopher Canning: Yeah, that's, from what you recall, how it went? I'll have to check as the study progresses. What can you tell me about the overall dynamics of the group?

Dr. Fraser: The dynamics of the group? I'm not a very good psychologist.

Christopher Canning: [laughs] Well you were with your genetic counseling, no?

Dr. Fraser: Maybe I mean sociologist. Well, I do remember having group meetings, probably in [the Human Genetics] office. I don't remember any discords, really. People respected each other and liked each other, and we sat and planned what to do next very amicably. So, I was glad that I was able to persuade Leonard [Pinsky] to take on the responsibility, which I didn't want.

Christopher Canning: In the early eighties, you left and went to Newfoundland, correct?

Dr. Fraser: Right. I was three years away from retirement, and I was beginning to feel somewhat in a rut, and also over worked, over burdened with an increasing number of counseling – families that would be coming back for more counseling, and more than I could handle, and they wanted to start a genetic service in Newfoundland, and they asked me to be on the search committee for a director and then one day they called me up and said, "Why don't you take yourself off the committee and apply for the job?" Well, you know, it might be nice to have something new to end up with, and so I went there and had a great time. We had lots of fun and met good people and had some political difficulties; I never did get a service started, but I think I made it a whole lot easier for the next incumbent to get it going, and they now have a good one. They didn't talk to me about the Emeritus status or what I might do after I reach retirement age. I think it was Charles [Scriver] who persuaded McGill to offer me Professor Emeritus, which I gratefully accepted, and came back here in '85 maybe?

Christopher Canning: 1985, yes, according to your CV here.

Dr. Fraser: So I was able to continue teaching and doing a little bit of research at the Children's [Hospital], and spent a very happy fourteen years after that.

Christopher Canning: As Emeritus, here in Montreal. And then you retired home to your home in Nova Scotia.

Dr. Fraser: Right.

Christopher Canning: Can you tell me a little bit about that home?

Dr. Fraser: You have a picture of it, I think.

Christopher I do, in your memoir, yes.

Dr. Fraser: Yeah, it's a beautiful old frame house that my grandfather bought in 1898, I think. I was only a few years old at that time – overlooking the river, and I spent several happy parts of my childhood in it. And my wife, who was a geneticist and then decided she wanted to be a lawyer, and having gone through law school, she went to Digby to article because she liked Nova Scotia, and articled – Digby's quite near Bear River – and she lived in the house and commuted to Digby, and she actually spent a lot of time restoring the house which hadn't had anything done for fifty years, maybe. She pulled off three or four layers of wallpaper, and remodeled some of it to make it more modern, particularly the kitchen. She did a wonderful job of restoring the house, and I guess she was really the one that…she said it felt more like home than her own home in Winnipeg so…no, Edmonton. So, she made it very easy for me to move back there.

Christopher Canning: And there you've been since there since finishing here?

Dr. Fraser: '99, yeah.

Christopher Canning: '99. And you just read, and you still write; you've published quite a bit since then.

Dr. Fraser: I'm still publishing, yes. I keep up academic contacts. I don't know what I'd do without the Internet. And I write a lot of book reviews. I'm the book review editor of the American Journal of Medical Genetics, and that keeps me…it gives me an excuse to call up old friends. I did a thing on Agent Orange a few years ago.

Christopher Canning: Oh yeah? Okay. You also wrote a small handbook on genetics, didn't you, or sort of a small introduction into basic genetics?

Dr. Fraser: Are you talking about the one on genealogies?

Christopher Canning: Yes.

Dr. Fraser: Yes. It does have an introduction to genetics in it, but it was really written for genealogists, most of which don't seem to pay any attention to genetics. You know, they don't record the important things, like what people died of or the diseases they had. I wanted to encourage them to start doing this, but it also has a lot of information which most people would find hard to get; lay people would find hard to get, about how diseases do run in a family, and what it means to you if you have a near relative with such and such, you know, what's the chances that you're going to get it and what can you do about it. So, it's not selling very well. I wrote it to kind of inform, and that doesn't seem to sell very well, but it's a good book.

Christopher Canning: Yeah, okay, I'll have a look. Where do you see genetics research heading, now?

Dr. Fraser: Genetics?

Christopher Canning: Genetics and medicine; medical genetics. I know that's a very broad question, but especially considering your important contribution to the field, where do you feel it's heading in the next – I don't know, ten, twenty years - from what you have been seeing?

Dr. Fraser: Yeah, well, I guess most people are seeing genetic medicine where you've got a…in the long run, everybody'll get a microchip card at birth with all their genetic susceptibilities and drug susceptibilities and all that on it, and then you'll be able to…the doctor will be able to use that when he's prescribing to you. I suppose that may come, but I think it's going to take a lot longer than some people say, because there are lots of ethical and practical problems with it, and gene therapy is going a lot more slowly than people thought it would. I would see a very few diseases for which there will be a gene therapy for quite some time, I think.

Christopher Canning: Really. They've got to hit a bit of a rut, yes?

Dr. Fraser: Well there's, again, so many practical problems about getting the gene in there and making sure it stays there, and making sure it doesn't turn the cell into a cancer or…so they're not doing at all well with that. But I suppose that will eventually come, but very slowly, that they'll be able to treat at least some of these diseases by changing the defective gene instead of trying to treat it's consequences.

Christopher Canning: Right. So pre-natal diagnosis and treatment.

Dr. Fraser: Pre-implantation diagnosis - well, that's here already. No, I'm thinking

postnatally. I think you might one day be able to find the gene that goes wrong with the retinal dystrophy that a lot of old people get. I think that's one of the likely things they might be able to get at and treat genetically.

Christopher Canning: Right, okay.

Dr. Fraser: Cystic fibrosis is not…they thought it would be natural but it's not working out very well. There's one of the hemophilia's that they found that putting the gene in, also led several of the patients to develop lymphatic cancers. So things are going very slowly, but they'll go.

Christopher Canning: Cancer research – do you think medical genetics is making headway there?

Dr. Fraser: That's one of the encouraging things. They're now, I was reading, being able to look at the genes of a particular cancer. You know, a cancer is the result of usually three or four genes being mutated somatically – not just one. To have so many fail safe mechanisms is useful; if one of the controls of cell division goes, there are several others that will take over, but then eventually they all break down, and then the cell takes off. Now they're getting so they can take the cancer and look at which of the genes is mutated, and then know much better how to treat it.

Christopher Canning: Your most recent publication – you actually started to publish on schizophrenia and neural tube defects, which was published in 2005. What's your next publication, may I ask? What are you working on?

Dr. Fraser: Well, I went to a meeting of neural tube defect people, in Burlington, and one person reported that anencephalics have an access of females, and they reported this series of anencephalics where there's not only the access of female anencephalics, but in the normal sibs there was an excess of females, which was quite puzzling; and I had the idea that maybe there's a subset of anencephalics where there's a single gene which is lethal in males and causes anencephaly in a minority of the heterozygous – the carrier females – and if you worked that out, it would work…it would cause…there would be normal 25% unaffected males that would not be there, so that leaves an excess of females, so that would be one reasonable explanation. And I'm trying to set up at the Children's Genetics Department and get back to the old records and see if this occurs in our families and whether it's real or not, and if it is, we can do some additional analyses that might either prove or disprove this mechanism. Then you might be able to go and look for this subset and find a gene there, because that would be a major gene. I've also taken on…there's a thing called the Lincoln Reference Library, which is a sort of encyclopedia, I guess. They've asked me to update the genetics section. So I'm about to start working on that.

Christopher Canning: Lincoln Reference it's called?

Dr. Fraser: Lincoln Reference.

Christopher Canning: Is it a science database kind of encyclopedia?

Dr. Fraser: Sure, but it's more of a general reference library

Christopher Canning: OK, that concludes my questions for the day. Thank you very kindly, Dr. Fraser.

END OF INTERVIEW

Dr. David Rosenblatt, December 1, 2009

Christopher Canning: My name is Christopher Canning, and I'm here with Dr. David Rosenblatt in the Department of Human Genetics on December 1, 2009. It is my great honour and privilege to be here with you, Dr. Rosenblatt, to discuss two main themes regarding human genetics.

First, I would like to discuss your academic background, which of course contributed significantly to the growth of medical genetics in Canada and beyond. Secondly, and perhaps most importantly for this particular study, I'm interested in your involvement in the MRC/CIHR Group in Medical Genetics, which you joined in 1975 and were a member until 2009, making you the longest standing member of the Group.

Before we get into the group questions, though, and these are open ended and you can respond as long as you want, I'd just like to ask a few introductory questions about where you've come from: where were you born, where did you grow up and where did you do sort of your early years, where did you do sort of your early years of schooling?

Dr. Rosenblatt: I was born July 14, 1946 in Montreal and both my parents were born in Montreal, one in 1909 and one in 1911. Their parents were of Ashkenazi Jewish origin; my mother's family was from Lithuania, with my father having come to Canada from South Africa. There was a family rumour of his having been jilted by a woman in South Africa and then coming to Canada. My father's family was from Galicia. My mother grew up on Notre Dame Street near the Atwater Market. My father's family grew up on Rachel, what's now the Plateau. My mothers' family moved to what's now NDG around 1921, 1922. My parents married in the early 30s and I had two older siblings, my sister who was 12 years older than I am and my brother who was six and a half years older. Both are now deceased; they both died around the age of 58. , We're sort of a war family and a depression family- my sister was born in '34 I believe, my brother in '39, and me in '46--you can see it sort of captures the war. My mother was one of four sisters, all of whom had one boy born in 1946, in different cities, two in Montreal, two in New York, so I guess with the demographics of the baby boomer. I grew up in NDG; my mothers' father died in 1948 and my parents eventually moved into my grandparent's house with my grandmother and stayed there until 1963. So I am very much Montreal based. I did my grade school in one of the early Jewish Parochial schools-Shaare Zion Academy; I don't know if you want to know everything – you have lots of space on the recording device, I take it.

Christopher Canning: Please, speak for as long as you wish.

Dr. Rosenblatt: Okay. I don't know if you know something. Montreal is an interesting Jewish community because the school system for many years was confessional.

There was a Catholic school system and a Protestant school system. The Jews were immigrants who didn't speak English or French, but Catholics wouldn't allow Jews into to the Catholic school system, so by default they went to the Protestant school system- that's why the Jewish community ended up being mostly English speaking. I entered into the Parochial school system. I am not sure why there was no Jewish school system when the Parochial school systems were set up. It was around the time of the rise of Fascism and the politics was difficult in terms of setting it up. By the time they got into the '50s, the government was prepared to set up ethnic schools where it would be sort of quasi private but the secular part of the education was paid by the government and the additional religious education was paid for privately. Montreal also has Greek and Armenian schools for the same reason. I went into the Jewish Parochial day school system in elementary school and then did my high school in the public school system at Westmount High School. Westmount High in the early days consisted of Westmount Junior High and Westmount Senior High – Westmount Junior High was a school that is on Westmount Park in Lower Westmount and Westmount Senior High is in the building that Selwyn House is now in, and they…

Christopher Canning: This is still NDG, right?

Dr. Rosenblatt: Those are Westmount actually.

Christopher Canning: Westmount.

Dr. Rosenblatt: I lived on the border of Westmount and both my elder siblings had gone to Westmount High, but I was in the first class that moved into the merged Westmount High School, on St. Catherine Street. Now, so that was in, oh, God, I don't know, what was it – maybe '59, '60, you can check the records of when Westmount opened, so it was in the first year in that school and graduated Westmount High. Now, this was before, I don't know if you know about the CEGEP system in Montreal, so this was before there were CEGEPS. So they had a program at McGill, which they called the Seven Year Medical Program. What they have now is about half the medical class comes in after CEGEP. CEGEP is a two-year program. Today at McGill, these students take…I think it's probably a six year program now where they do two basic years and four years of medical school. You can check what it is now, but they end up just getting an MD degree and they don't end up getting a Bachelor's degree. In my day we had what was called a Seven Year Med Program, where the first two years was the undergraduate science curriculum with one additional course, the third year you had four courses, where you took first year medicine anatomy with the medical class and then you got into the medical class into the second year and you graduated in seven years with both a BSc and an MD.

Christopher Canning: Got you. Okay.

Dr. Rosenblatt: So that ran from '63 to '70. I was in the graduating class of 1970. One of my classmates was the ex-Dean, Dean Fuks, who was also part of the seven-year program.

Christopher Canning: OK.

Dr. Rosenblatt: Twenty-five of us, in the 1970 class.

Christopher Canning: It says here that you were part of the Faculty of Arts and Science.

Dr. Rosenblatt: Because you got a BSc as well as an MD, it's an equivalent of now the CEGEP Program, before there was CEGEP and the differences now they don't get the BS.C, they just get the MD, so they're always undergraduates, you know, until they get the MD degree.

Christopher Canning: OK, got you.

Dr. Rosenblatt: And there's no BSc today, so it makes it difficult in terms if they want to go on to graduate studies of anything if you, if you get the drift.

Christopher Canning: Yes.

Dr. Rosenblatt: My mother's sister was married to a general pediatrician in Montreal by the name of William Gavsie and just sort of an aside, he and his brother were from the Maritimes. My wife is also from the Maritimes so it's very funny, from Glace Bay and his brother, Charles Gavsie at one point was head of the, the uh, I forget what it's called, not the mint, but the guy who signs the bills (laughter).

Christopher Canning: Look at your bill.

Dr. Rosenblatt: The Bank of Canada. Okay. Yeah, the Governor of the Bank of Canada, so, anyway, I was in this combined course and my uncle said to me "Look you really should work with this Dr. Scriver, this hot shot who just came back to you know, to Canada, he was in England at the time, I'll try to get you a summer position with him." So in the summer of 1967 I worked as a medical summer student in Dr. Scriver's lab. I spent some of my time grinding out statistics for Richard Goldbloom. He ended up being the Chancellor at Dalhousie and Chairman of Pediatrics at Dalhousie. At least I think he was Chancellor, so Chairman of Pediatrics at Dalhousie. I was doing statistics on these old adding machines, you know, manual stats on a project he was doing on Cystic Fibrosis. I worked with Dr. Scriver on a project where they were looking at different patients with phenylketonuria (PKU), using an amino acid analyzer to look at phenylalanne to tyrosine ratios to see if they could be distinguished into different groups. I was involved with gathering the data for a paper to see if there weren't other types of

hyperphenylalaninemia. The first publication I had that was published in Nature as a result of that work with Dr. Scriver.

Christopher Canning: I was going to say, you're 22 years old, so…

Dr. Rosenblatt: That was because of the summer work with Dr. Scriver.

Christopher Canning: Right. So this would have been the late '60s then.

Dr. Rosenblatt: 1967.

Christopher Canning: 1968 was this publication.

Dr. Rosenblatt: Right. But the work was done in the summer of '67 I believe.

Christopher Canning: Okay.

Dr. Rosenblatt: I can check. I think I worked with him in the summer of '67.

Christopher Canning: Okay.

Dr. Rosenblatt: And so I got to know him and at that time…

Christopher Canning: It must have been quite the honour, not only to do research with Scriver but also to have your first publication with this very respected scientist?

Dr. Rosenblatt: I probably didn't realize the implications of the publication.

Christopher Canning: How could you, I suppose?

Dr. Rosenblatt: I would think more in terms of the interaction and you know, the fun of working in the lab, the people who were there. Then what happened was I was then back in medical school and I came back, I believe, the following summer and did a project on histidinemia which also resulted in a publication.

Christopher Canning: Okay.

Dr. Rosenblatt: And at the time, Dr. Scriver says to me, "Look", the up and coming technology for the study of metabolic disease is the cell culture of human fibroblasts. I don't know if you've ever seen them; I should take you down so you can see what they look like under a microscope. But essentially the procedure is very simple. You take an instrument, I don't know if you've ever had a skin biopsy; it looks like this [indicating the tip of a ballpoint pen] except the edges are sharp and you just go like that, you snip off a piece and you put it in a Petrie dish and you grow the cells along the surface of the dish and this was a technique that had been worked out in the '50s, early

'60s by Eagle, not the bird but the man, Harry Eagle.

Christopher Canning: Is this the only tissue that you're working with then?

Dr. Rosenblatt: Culture fibroblasts but it wasn't routine in those days and Dr. Scriver said I would like you to go down to Boston to work with John Littlefield.

Christopher Canning: That was my next question, is why would you go to Boston…?

Dr. Rosenblatt: Well, I ended up at Mass General Hospital with John Littlefield because John Littlefield was one of the pioneers in development of the use of cultured skin fibroblasts and Dr. Scriver's idea was for me to go for a couple of years, learn that technology and bring it back to McGill so that we could do it. In the meantime, I ended up staying there for four years; we can talk about that in a minute.

Dr. Scriver wasn't very happy about that, and Dr. Hy Goldman who was not part of the group but is still practicing at the Children's and also a very interesting guy set up the tissue culture facility at the Children's Hospital with Inez Wong. All the cell lines at the Children's are now labeled WG, which is Wong Goldman, the initials of the technician and the staff person who set it up. I started working with John Littlefield in Boston and he assigned me to be the first fellow of a young faculty member by the name of Richard Erbe – E R B E, who had his training at the NIH (National Institutes of Health). That's how I got into early studies on folate metabolism in cultured cells. I spent two years at the Massachusetts General Hospital. Dr. Scriver, who never was really much of an advocate of doing things through the traditional routes, said, "Well, you don't really need to get your specialization in pediatrics or write any exams or do anything like that".

Christopher Canning: Weren't there regulations guiding what you needed to do?

Dr. Rosenblatt: No, well, he felt he would hire people, you'll notice he often hires people without a formal education. He is more interested in what they can do.

Christopher Canning: Yes, I noticed this was the case with Carol Clow.

Dr. Rosenblatt: Yes, and you'll notice a lot of the people whom he hired came from different backgrounds. Angie who worked for me as a technician for years was a dialysis nurse, who was co-opted into the lab. This was sort of his style; a bit of a kind of maverick. He wanted me to come back to Montreal after two years but my wife, Linda, said "No David, you've got to finish your pediatric training and get your credentials" so I ended up spending…

Christopher Canning: Was that at Harvard or MIT?

Dr. Rosenblatt: First of all I felt I needed another lab experience. I was trying to get into

David Baltimore's another lab at MIT, but Dick Erbe got me into the lab of Malcolm Gefter, an immunologist who was also working on RNA-mediated DNA synthesis. I was working on very basic stuff in the lab at MIT. It was a very strange environment where the bridge games started at midnight but only the Lab Director could have his column on the table [laughter]. I spent a year there and then I spent a final year at the Boston Children's Hospital to be able to get enough training to have certification in Pediatrics. I have American certification in Pediatrics as well as Quebec certification. I was never able to pass my Royal College Exam in Pediatrics, because I didn't really have as much clinical training as most Canadian candidates. The Canadian exams are always harder than the American exams. I am a Fellow of the Royal College but as a career medical scientist, not as a pediatrician. I finally came back in '75 and…

Christopher Canning: Sorry to interrupt, but one more question just to come back a bit. Did you have any idea before you went down to Massachusetts that you were going to get into research on folate metabolism, or…?

Dr. Rosenblatt: No. Part of it was serendipitous. I mentioned John Littlefield. Littlefield was famous for the development of the, what's called the HAT – H A T selection system and the HAT selection system was something that he adapted to mammalian cells. HAT had been originally worked out for bacteria and essentially, I'll give you some biochemistry, whether you want it or not…

Christopher Canning: Please. And for the transcriber, if you do say anything foreign, please clarify your terms.

Dr. Rosenblatt: Yes. And do you have any knowledge in biochemistry?

Christopher Canning: Well, very little, and it's all self taught. I've read through some of your work, but no formal training in science.

Dr. Rosenblatt: No formal science. It will just come out as gibberish…but so basically what happens is in DNA Synthesis, to make DNA, there are two ways you can go – you can recycle nucleotides, which are part of the structure of DNA, the molecules that have been broken down and used before or you can make the nucleotides de novo, constructing the actual ring of the nucleotides. These two pathways exist in human cells. The "A" in HAT comes from "Aminopterin", which is similar to Methotrexate and blocks folate metabolism. When you block folate metabolism, you can't do the endogenous synthesis of the nucleotides. You can rescue the cells by giving "H"-Hypoxanthine, which is a purine precursor, and T-Thymidine, which is a pyrimidine precursor. Littlefield adapted that system for mammalian cells. When I arrived in Boston, by chance a patient appeared on the wards at Massachusetts General Hospital who had elevated homocysteine and was also being worked up by Harvey Mudd at the NIH. He suspected that this patient had a block and folate metabolism and said, "Let's study folate

metabolism in culture fibroblasts" and that's how I got into folate metabolism.

Christopher Canning: And you were doing the lab work, looking at…

Dr. Rosenblatt: Well, I had no real lab experience other than the two summers I had with Dr. Scriver. I learned how to do tissue culture, how to grow the cells, you know. I learned how to do the enzyme analyses for folate enzymes. I produced two papers with Dr. Erbe, and at the same time I had some clinical exposure in clinical genetics, sufficient that I could get credit for those years for clinical training in pediatrics. At that time genetics was a division in Pediatrics at the Massachusetts General Hospital.

Christopher Canning: Got you… Okay.

Dr. Rosenblatt: So that's how I got into the area of research of metabolic disease in tissue culture systems. When I got back in 1975, Dr. Scriver had already written me into the 1972 application as a staff person.

Christopher Canning: Great. Can you give me a more detailed overview of how you became involved in the Group?

Dr. Rosenblatt: So I knew when I was going away that he was writing this application and I left in '71 and he wrote it in '72. He said, "When you come back you'll be part of the group" and he asked me to prepare an application to go into the group, but he wanted me to come back, I think, two years earlier than when I came back.

Christopher Canning: And, so, how was that relationship?

Dr. Rosenblatt: The relationship was okay. I don't think that he was particularly happy that I was staying on because he didn't see the need to go through these things, to end up in formal certification or stuff.

Christopher Canning: Right.

Dr. Rosenblatt: My wife being a pragmatist said it will serve you well in the long run, and I think in the long run it did serve me well. My year at MIT was interesting.

Christopher Canning: What do you mean by that?

Dr. Rosenblatt: Just because I was in a lab that was doing very basic biochemistry, so I guess I learned some stuff; no publications came out that year.

Christopher Canning: You were trained as a biochemist throughout?

Dr. Rosenblatt: I did some biochemistry the two years I was at Mass General and the stuff I

was doing at MIT was also biochemistry, RNA-mediated DNA synthesis with Okazaki fragments before they were really known as such. Malcolm Gefter had worked in the area of DNA synthesis before coming to MIT but he was moving for himself towards immunology. So as a supervisor, he was moving away from the area of my project but it didn't matter to me. For me, it was more a matter of seeing how different labs do research, a post-doctoral experience. Both Dick Erbe and I thought just to have one exposure out of medical school in one lab wasn't sufficient for someone interested in a research career. After my year at MIT, I did a final year at the Children's Hospital in Boston, which let me get my clinical credentials. I made good contacts; I was a resident with of Paul Goodyer who was head, subsequently, of Pediatrics Nephrology here at the Montreal Children's.

Christopher Canning: Did you know you would always come back to Canada one day?

Dr. Rosenblatt: Well, there were two aspects of that. I was on a J-1 Visa at the time, so one of the…

Christopher Canning: What was that?

Dr. Rosenblatt: A J-1 was a student Visa. It was before free trade and professional exchanges, so the stipulation was at the end of the time you had to go back to your country of origin. I think that had I really wanted to stay I could have. People got job offers and are able to stay in the States, but my intention was always to come back. The issue was that I came back a little bit later than I had planned.

Christopher Canning: I see one of your daughters was born when you were there.

Dr. Rosenblatt: That's correct. Jacalyn was born in Boston in 1972 and so she has American citizenship. She is on staff now at the Beth Israel Deaconess Hospital in Boston, doing hematology, bone marrow transplants. She did her medical school at McGill, and her initial training here and then went on and finished her hematology training in Boston.

Christopher Canning: And now she lives in Boston full time?

Dr. Rosenblatt: And now she lives there full time, and her husband was able to get American citizenship. My second daughter Dana was born in 1976 after we moved back to Montreal. We moved back in '75.

Christopher Canning: Great. This might seem clear to you, maybe not so much to me, but when did your interest in genetics in medicine actually come about and where is this dialogue happening? In what fields of biology was this happening and how did medicine and genetics merge during your early work?

Dr. Rosenblatt: No, it's not entirely clear and I really think that part of it relates to my

orientation of things. My entry into the area was not driven primarily by an interest in medicine or genetics, but by exposure to a mentor who would discuss with you a career path; that in itself seemed to be very interesting. One of the nice things about going into medicine is that you can pick from a very wide variety of areas of interest. When I'm giving advice to students, people you know, who are very concerned, they have their heart set on doing this and this but I say "Look, there are many, many things potentially that you can do and once you choose to do any of them can be interesting" so I just saw the enthusiasm of the work, the enthusiasm of Dr. Scriver that was going on. It was the time when all the amino acid disorders were being discovered, people were adapting cell culture to be able to work on these cells and not have the patients present to work out the disease mechanisms. The whole area was burgeoning and so it was not pre-designed that genetics was what I was going to do. Rather, I was exposed to someone who was doing state of the art genetics and was riding on his experience, and his mentorship.

Christopher Canning: Did you have any hesitation about joining this field that was still, in a sense, carving out its place in the field of medicine?

Dr. Rosenblatt: Not at all because I think back at why I went into medicine; remember I went to medicine out of high school, which a that time was Grade 11.

Christopher Canning: Wow, okay.

Dr. Rosenblatt: I didn't pick the seven year program necessarily because it was medicine; I picked it because it was an academically challenging program that was hard to get into and gave you a lot of options. I'm a nice Jewish boy whose mother wants him to go into medicine.

Christopher Canning: I was actually going to ask you that question at the beginning of the interview: what sort of expectations did parents have as you were growing up, and as you entered your formal training out of high school?

Dr. Rosenblatt: I don't know. Neither of my siblings were academically driven. My sister certainly was not and my brother not very much either. My brother ended up in the family business. I was always more conservative and bookish and not very outside the box and so I think they were pleased when I did medicine. I had an uncle who was a doctor but I don't remember any pressure to do anything other than to do well in school. I saw it as like studying and I like academics and maybe this is an entrée to the academic world. But I don't think I had any clear vision. I mean, my high school parliament, I was head of the New Democratic Party. I have heard the saying that if you're not a socialist when you're young, you have no heart and if you're not a Conservative when you're old you have no head. Is that right?

Christopher Canning: That's the phrase, yes.

Dr. Rosenblatt: That's the phrase. But I don't know if that's entirely true. I think what sort of impressed me was that while it's important to make a living, the nature of the work seems an inherent value in itself. That's sort of what I was driven by, you know, you were advancing knowledge or advancing things and I didn't mind the fact that it had a practical tone to it. I wasn't probably as suited to philosophy as that.

Christopher Canning: And Scriver obviously played a role in your development?

Dr. Rosenblatt: Scriver was definitely a role model, who allowed me to see that there was a career path in this area. He also always talked about the team, the group, in terms of the successes. As a young person, you get caught up in your project and you want to do well; if you do well in what you are doing you just go on. My experience in Boston was extremely good; I enjoyed it very much both living there and the work. I had a good relationship with Richard Erbe and the other people in the unit I was on; it was a really good unit. The year at MIT was a bit weird because of it worked out to be a 24 hour work day and most people were single and not really sure what they wanted.

Christopher Canning: What was your relationship with Dr. Fraser at the time? Or was Scriver more of a mentor?

Dr. Rosenblatt: I came in under Scriver; Fraser and Scriver have very contrasting styles, but their units were all pretty much physically together. I may have also had some undergraduate teaching exposure to Fraser one way or another, not full classes; I took a course by Boothroyd and I took a course by Don Southern, both of whom were in the Biology Department. I don't know if Clarke ever formally taught me, but Clarke was always there, you know. Rounds were always together and more when I came back as a young staff person; I really loved Clarke. In many ways it was much easier to talk to Clarke than to Charles. Both Fraser and Scriver have egos but Clarke has less of an ego, I think, than Charles. It wasn't always Clarke centered on every discussion and Clarke always had very interesting ways of looking at things. He wasn't the kind to say, "That's a stupid, idiotic idea". He said, "I wonder why people were thinking about that; I wonder if there could be any element of truth. I wonder why…could neural tube defects be because of the potato blight on the potato in Ireland?" So I got that openness to ideas that were unconventional from Clarke.

Christopher Canning: And did you recognize this as soon as you came back, the different types of leadership styles between Fraser and Scriver?

Dr. Rosenblatt: I think so but I was certainly very much under…so the group at that time was me and Charles and Clarke and Peter Hechtman. We had little cubbyholes down at the Children's…

Christopher Canning: And Dr. Gold, briefly?

Dr. Rosenblatt: Rennie Gold briefly was overlapping at that time. And Rennie, you should get a chance…did you get a chance to speak with him?

Christopher Canning: He's away right now, but we're meeting as soon as he gets back.

Dr. Rosenblatt: So he's completely different.

Christopher Canning: I got that impression, yes.

Dr. Rosenblatt: So he was a general practitioner in the UK; very, very smart, classical pianist and he came from the United Kingdom to Saskatchewan to break the doctor's strike in 1962.

Christopher Canning: I did hear about that. We actually spoke about that at the dinner a few weeks ago.

Dr. Rosenblatt: So a very interesting guy and very smart. The other guy that was in the unit when I got back was Frances Glorieux. So Frances Glorieux was working with childhood bone disease. He and Charles had some sort of an outing when Frances moved to head a unit at the Shriner's. Charles doesn't really like when people break out and become independent on their own.

Christopher Canning: Interesting. Can you elaborate on that for me?

Dr. Rosenblatt: He likes when they're part of his empire. He lobbied hard to get Frances to be head of the research unit that they were developing at the Shriner's and Frances became independent, created his own research programme, and became very visible. Charles was never very comfortable with that. Francis is a wonderful person, a Belgium physician who got his PH.D with Charles, so I think he's very indebted to Charles, but that had a bit of tension to it. He's still around. He's off getting some honorary degrees.

Christopher Canning: Just for the record, can you state his name again?

Dr. Rosenblatt: Frances Glorieux.

Christopher Canning: Okay. I'll look him up for sure.

Dr. Rosenblatt: My first ten years back here were highly, highly sheltered. I was living in this cocoon of the group; Dr. Scriver would protect me from clinical responsibilities.

Christopher Canning: So you were all lab, so to speak?

Dr. Rosenblatt: I was all lab based for ten years.

Christopher Canning: Wow. Which obviously helped your publication record.

Dr. Rosenblatt: Well, it's not about a publication record – it helped me gain depth of expertise in an area.

Christopher Canning: Okay. What were you doing in the mid '70s?

Dr. Rosenblatt: Mostly my research. I was doing really two tasks; one was doing biochemical work. If I can look at the CV so I can put it in context because it's hard to know from the timing of the publications when exactly the work was done. So the publication that came out in '77 was work that I had done in my fellowship in Boston before '75, pediatric research was just me and Dick Erbre. These publications were actually before Publication 6 and 7. [1]

Christopher Canning: Got you. Okay.

Dr. Rosenblatt: As of course was Publication 3,[2] but then there was overlaps and you start seeing that around '78 I got hooked in something external in McGill that was very interesting. So when I came back here, it was extraordinary because I got a different sort of mentorship, which was mentorship outside the group. So it just so happens, that the two vitamins, Folic and Vitamin B_{12} share branch points in metabolism where they interact and the end manifestation, in this case, elevated homocysteine and various findings in blood cells, such as anemia, are shared by both folate deficiency and Vitamin B_{12} deficiency. The head of Hematology at the Royal Victoria Hospital was Bernie Cooper, who had trained in Boston with classic people who had worked out, not genetics, but the physiology of Vitamin B_{12} absorption. In the last century there were two Nobel prizes for Vitamin B_{12} given out; one for discovering that it was the anti-pernicious anemia factor and one for figuring out the chemical structure. So Bernie was very much involved with the leaders in vitamin B_{12}. He was at the Royal Victoria Hospital and in the Biochemistry Department at McGill was a professor named Robert MacKenzie, who was later in the group but at that time was not in the group. Bernie had a trainee by the name of Michael Whitehead who then later on went off to be a

[1] **Publication 6**: Rosenblatt DS, and Erbe RW,: Methylenetetrahydrofolate reductase in cultured human cells. I. Growth and metabolic studies. *Pediatr Res* 11:1137-1141, 1977.

Publication 7: Rosenblatt DS, and Erbe RW,: Methylenetetrahydrofolate reductase in cultured human cells. II. Genetic and biochemical studies of methylenetetrahydrofolate reductase deficiency. *Pediatr Res* 11:1141-1143, 1977.

[2] **Publication 3:** Rosenblatt DS, and Erbe RW,: Reciprocal changes in the levels of functionally related folate enzymes during the culture cycle in human fibroblasts. Biochem Biophys Res Commun 54:1627-1633, 1973.

hematologist at the Montreal General and then came down to be Head of Hematology at the Montreal Children's Hospital. He also was interested in folates and anti-folates. Anti-folates were the first chemotherapeutic agents in cancer. Methotrexate and amethopterin, the first anti-leukemic drugs, were anti-folates. That is part of the reason the two hemalotogists were interested in folate and vitamin B_{12}. We started having a monthly "folate club" attended by two hematologists, a geneticist and a professor of biochemistry.

Christopher Canning: MacKenzie was the biochemist?

Dr. Rosenblatt: MacKenzie was the Professor of biochemistry, I was the geneticist, and Cooper and Whitehead were the hematologists. We had monthly folate clubs where we'd bring out a case of beer and some French bread and cheese and just sit and discuss folate and B_{12} metabolism. MacKenzie was a physical chemist. Cooper had flights of consciousness and I'd understand about 2% of what was going on in the conversation before them, but after about three or four years, some of it stuck. Cooper was and is brilliant; he's now retired in Palo Alto. I think he's got a clinical appointment at Stanford but he's essentially retired. There were many ideas floated and I'd say to Bernie, "Let's do that one." I'm much more the grinder and focused, on putting walls around the project. I would ask what's the beginning, what's the end. I also started working closely with Michael Whitehead. There were some early reports that methotrexate could be metabolized by adding on glutamates. We said let's start studying this in human cells. Michael and I had a number of publications in the early years back that were really not genetic publications that were cellular publications on cancer and chemotherapy and how the anti-folate methotrexate was metabolized in human cells. Then Whitehead himself took it on later and published on folate polyglutamates in the bone marrow of patients with leukemia.

Christopher Canning: That's publication number?

Dr. Rosenblatt: Number 12.[3] At this time, great work was coming out of this folate club collaboration. Eventually Rima Rozen came into the area in the early '80s. She did her Ph.D with Scriver in the area of methylmalonic aciduria and then she went off to work with Leon Rosenberg at Yale and then when she came back, she got into the folate area.

Christopher Canning: I'm just going to step back one point before we move into the '80s here. You mentioned just before that Scriver didn't necessarily like you leaving the group to do your own individual thing. Can you please elaborate on that

[3] **Publication 12:** Witte A, Whitehead VM, Rosenblatt DS, and Vuchich M-J,: Synthesis of methotrexate polyglutamates by bone marrow cells from patients with leukemia and lymphoma. *Dev Pharmacol Ther* 1:40-46, 1980.

point for me?

Dr. Rosenblatt: No, no, he didn't like when people become independent of the group. Working on scientific questions was not a problem. As long as you were under the structural umbrella of the group that he directed…that was never a problem. If your expectation was to become an independent researcher, the standards were to do good work and he left you alone and he protected you against the Chairman of Pediatrics who wants to sign you for other things. Here is an example that comes completely out of left field. When I came back to Montreal, part of my salary was paid by a fund that was generated by clinicians to allow researchers to do research. However, a technicality of this arrangement meant that I could not work at the Montreal Children's Hospital and generate revenue for the fund. To supplement my income and maintain experience in Pediatrics, I started working in a clinic in the Jewish General Hospital that covered the off hours for 17 pediatricians. I started that activity in '75, and I've been doing it until now every Saturday with Linda; the Chairman of Pediatrics at the time didn't want me doing that work. Dr. Scriver said that since I could not work and bill inside the Children's hospital, he supported me. He has always been professionally supportive. The only time that I had conflict with him, you'll see, is when I moved to set up my own unit up the hill at the adult hospitals in '86. So back to the research – a lot of the interesting research in the late '70s, early '80s were around this whole aspect of methotrexate polyglutamates and I did a lot of very basic type work around folate and how it's handled in cells. Then there was an interesting theory, if you go to publication 21,[4] about folate and Fragile X. Fragile X Syndrome is a very common cause of mental retardation, very common cause in males, but the mechanism of it wasn't known in the early '80s. What they knew is when you grew the cells, cultured fibroblasts from the patients with the Fragile X Syndrome from patients in a medium that had low levels of folate, the fragile sites became more apparent. There were some people who said maybe we could treat some of these patients with folate and cure them; I got involved with a very small trial because we had twins with Fragile X who were older and we had placebos made that looked like folate tablets and we did a clinical trial. We did behavioural measurements. This was a sideline of a project of Brad Popovich.

Christopher Canning: Did both of them have the disorder?

Dr. Rosenblatt: Yes. They were twins. We treated one with placebo and one with folate and then did a cross over after two weeks and did the psychological assessments that didn't show any difference…

[4] **Publication 21:** Popovich BW, Rosenblatt DS, Cooper BA, and Vekemans M,: Intracellular folate distribution in cultured fibroblasts from patients with the Fragile X syndrome. *Am J Hum Gen* 35:869-878, 1983.

Christopher Canning: There was no change?

Dr. Rosenblatt: There was no difference and in fact we were skeptical that it should have an effect. We now know more about the mechanism behind the disease and it's a very different mechanism. So then comes to Publication 23.[5] So all this time when I'm here, I'm still getting cell lines from around the world from people who have suspected inherited disorders of folate metabolism.

Christopher Canning: Folate is Vitamin B_9, is that correct?

Dr. Rosenblatt: Yes, but I use the term folate. It does have the B_9 designation but most people do not use B_9. We'll come back to that a little bit later too. So publication 23 was a pivotal article for me. I'm not first author on that article but all the laboratory work was done in Montreal. Susan Chiu was the clinician in Winnipeg, a resident, and we were contacted by the team in Winnipeg. They thought that the patient had an inherited disorder of folate metabolism and asked if we would study the patient. We studied it and the patient turned out to have a new disorder of vitamin B_{12}metabolism, and we published that in the New England Journal.

Christopher Canning: I see there was a switch from folate to B_{12}.

Dr. Rosenblatt: That is because of the interface between folate and B_{12}. We set up very highly specialized group of tests that delved into a pathway in detail and then we set up a collaborate network. When people send you atypical clinical samples with time, unusual things turn up. So in the old grant and group structure it was very good. We were developing an expertise that became recognized around the world. If I wrote a grant saying "I'm going to wait around, develop expertise, wait for unusual patients on the base of this, find new pathways," they won't fund you, but this group mechanism allowed for time for me to accumulate the patients that allowed discovery to happen. For me, being able to work in what I call a "research cocoon", in a group that was committed to high quality science and was interdependent, you know, was a real blessing for me and I really treasured it. I don't think it necessarily has to be a group structure that can do that. In France they have INSERM units; I think there is some benefit to a hierarchical unit. People like the peer review system because every project is dissected and evaluated on its merit, but in the old days it was more of how was a person trained, are they serious about what they're doing and then let's judge them on their productivity. And I still really have this view of people. I don't care what they propose to do. Give them some space, give them some time and judge them after a period of time on their productivity.

[5] **Publication 23:** Schuh S, Rosenblatt DS, Cooper BA, Schroeder M-L, Bishop AJ, Seargeant LE, and Haworth, J.C.: Homocystinuria and megaloblastic anemia responsive to vitamin B12 therapy: an inborn error of metabolism due to a defect in cobalamin metabolism. *N Engl J Med* 310:686-690, 1984.

Christopher Canning: Like you say funding agencies don't necessarily work that way.

Dr. Rosenblatt: And they don't work in that way at all. More and more, you almost have to propose projects for funding on work that you've already done.

Christopher Canning: Right.

Dr. Rosenblatt: Because they want to see all the preliminary data, they want to see that you've collected all of the families.

Christopher Canning: Was this always the case?

Dr. Rosenblatt: No. Dr. Fraser if you speak to him, if you talk about his first grant it's probably a page.

Christopher Canning: He actually joked about this, too, saying that he would never be funded in this day and age.

Dr. Rosenblatt: I would love to be able to pull up the first grant he ever wrote for something, or to reconstruct the first grant he ever wrote. It was probably not more than a page. I think you should judge people on what they produce. I think you should be very harsh on them; because people can promise you the world but look at their productivity, look at what they've done. In my case, we got this first patient, which was a novel defect. Then we started accumulating and just over time, more and more patients came out with new and distinct steps and in some cases these steps hadn't been shown at all in mammalian systems at all. So the very early part of the work was based on biochemical characterization and the general technique of somatic cell complementation. The long and short of somatic cell complementation is you have a panel of known cell lines that are different from one another. (Littlefield pioneered this technique and I learned it from him). When you fuse two cell lines that are different you can correct the biochemical defect in both.

Christopher Canning: Different DNA?

Dr. Rosenblatt: No, no, no, no…different disorders.

Christopher Canning: Interesting.

Dr. Rosenblatt: Okay? So you have a cell line from a patient with an unknown defect and a panel of cell lines with known defects. You also have a functional assay. You fuse two lines together at a time, a known and an unknown. If you fuse them together, and they correct each other, you say they have different defects. If you fuse them together and they don't correct each other, you say they have the same defect.

Christopher Canning: Okay.

Dr. Rosenblatt: This cell has a defect, this cell has a defect; they come from different patients. If you fuse them together and make one big cell, and it corrects each other, you say they both have different defects, because one defect is able to correct the defect of the other. If you fuse them together and they don't correct the defect, you say they must have the same defect because they're not able to correct each other.

Christopher Canning: And what corrects these defects?

Dr. Rosenblatt: The gene product. We often did not know what the underlying gene product was. During the whole first part of my career, all we did was classify patients into different groups. The whole second half of the career was mostly collaborations with Rozen and Gravel, and was finding the genes that were responsible for the different complementation groups. All the new DNA technology didn't come until the late '80s.

Christopher Canning: But you knew already…

Dr. Rosenblatt: But we knew the genetics, that we had the same defect or different defect.

Christopher Canning: Just by the fusion of the cells.

Dr. Rosenblatt: By the fusion of the cells, but also we have to have a functional assay. We had to show that folate or B_{12} metabolism was perturbed and we had to have something that we could measure that showed that that was…

Christopher Canning: Do you remember which cells they were or is B_{12} present in every cell in the body?

Dr. Rosenblatt: Well, it does in fact matter for different disorders. As it turned out the disorders that we were doing with the pathways were expressed in fibroblasts. We were looking at how the vitamin is handled within the cell, how it metabolizes. For other types of problems where B_{12} can't be absorbed through the gastro-intestinal track, the defects cannot be worked out biochemically in fibroblasts. There are other types of disorders where the defects are only found in the brain; patients do not have anemia. Also, we weren't working in a vacuum. A lot of work was being done at Yale by Leon Rosenberg, who found some of the other early steps in the pathway. He discovered the cobalamin (cbl) A group, the cb;lB group, as well as the cblC, cblD and mut and we went on to find the cblE,cbl F, and cblG groups.

Christopher Canning: And this was with whom Rozen worked. So when she came back obviously she…

Dr. Rosenblatt: But she wasn't doing the same when she came back. We were working independently, but she had developed some molecular techniques, so when the molecular biology revolution came…

Christopher Canning: So this is where biochemistry and molecular biology merged together?

Dr. Rosenblatt: That came together, yes. I had all these well-characterized groups of patients that we then set out to find the genes. For some of these, we didn't know what the functions were so we didn't have a real test for the function. Finding mutations in genes from patients with discrete disorders allowed us to prove that we were looking at the right genes. We were able to go back and forth from the patients to the cells. I worked at the time very closely with Roy Gravel and Rima Rozen. They were the molecular biologists at the time and I was more cell biologist and physician who had both the clinical characterization and the cellular characterization. We published a large number of excellent papers. The relationship was good for all sides. I think that my interest in the inborn errors of folate got Rima interested in the MTHFR and she then just flew on her own to very big heights. She has been mostly working on the relationship of polymorphisms in folate genes to more common problems and not on the rare inborn errors.

Christopher Canning: Such as cancer?

Dr. Rosenblatt: Cancer and birth defects.

Christopher Canning: Okay.

Dr. Rosenblatt: And I've spent most of my time working on the rare disorders where you can get clearer answers.

Christopher Canning: What genes have you been focusing on specifically?

Dr. Rosenblatt: So working together with the others, we found the *MTHFR* gene together. We also found the *MTR* and the *MTRR* genes. Then working with other people outside the group, we found the *MMADHC* gene and then we found the *MMACHC* gene. We also described and found the gene for the cblF disorder, which was one of my most important scientific discoveries.

Christopher Canning: Can you point out on your CV where it is?

Dr. Rosenblatt: Yeah, so that should be '85, so it's publication 27.[6]

[6] **Publication 27:** Rosenblatt DS, Hosack A, Matiaszuk NV, Cooper BA, and Laframboise R,: Defect in vitamin B12 release from lysosomes: newly described inborn error of vitamin B12 metabolism. *Science* 228:1319-1321, 1985.

Christopher Canning: Okay, thanks.

Dr. Rosenblatt: So that's a defect in the transport of vitamin B_{12} across the membrane of the lysosome. So we found the disease and published it in Science in 1985 and we only found the gene in 2009.

Christopher Canning: So you just found it?

Dr. Rosenblatt: Yeah, and that was published in Nature Genetics in 2009.

Christopher Canning: Indeed.

Dr. Rosenblatt: That's publication 157.[7]

Christopher Canning: Wow. So this is a long time coming for you?

Dr. Rosenblatt: I'm very narrow and persistent in focus.

Christopher Canning: I see that.

Dr. Rosenblatt: The thing that gives me a huge deal of pleasure is that my work has been linked been linked to diagnosis. We are doing the diagnosis for the world along with a second laboratory run by Brian Fowler in Switzerland. I also have this habit about competing and collaborating with the same people. We join together at times, we go separately, we publish separately, and we publish together.

Christopher Canning: Is this in Canada or is this around the world?

Dr. Rosenblatt: These are people in Switzerland and Germany; so, yes, around the world.

Christopher Canning: Is it a small group working with vitamin metabolism or B_{12}?

Dr. Rosenblatt: It's not that large. The research community in vitamin B_{12} has in the past been called a fraternity. It is a very prestigious one at that. I can show you some of the books that have come out of it just on B_{12}, not only Scriver's book (MMBID – The Metabolic and Molecular Bases of Inherited Metabolic Disease) but also books only on Vitamin B_{12}. Ruma Bannerjee, with whom both Rima and I have collaborated, was a trainee of Rowena Matthews at the University of Michigan. Ruma then went off to Nebraska and is now back at Michigan. Ruma Banerjee has edited a book on vitamin B_{12} and on the cover of the book is a picture of Nobel Prize winner Dorothy Hodgkins.

[7] **Publication 157**: Rutsch F, Gailus S, Miousse IR, Suormala T, Sagné, Toliat MR, Nurnberg G, Wittkampf T, Buers I, Shariffi A, Stucki M, Becker C, Baumgartner M, Robenek H, Marquardt T, Hohne W, Gasnier B, Rosenblatt DS, Fowler B, Nurnberg P. Identification of a putative lysosomal cobalamin exporter mutated in the cblF inborn error of vitamin B12 metabolism. *Nat Genet*, 41:234-239, 2009.

Dorothy Hodgkins crystallized the Vitamin B_{12} molecule and was awarded the Nobel Prize for solving its structure. She is an example of a woman succeeding in science at the highest level and there is a UK postage stamp in her honor as well; I should show you the book; Rima will also have it. Yeah, because for many reasons it just shows you the perspective. We go to these conferences, and the nice thing about them both for folate and B_{12}, we'd have meetings like Gordon conferences or FACEB conferences; you know what a Gordon conference is? It's a small group of people; FASEB conference is the same thing and there would be about 200 people, in the early days maybe about 150; it's up to 300 now and on folate or one-carbon metabolism or B_{12} and you'd have people who were strict chemists, some of them creating new anti-folates for cancer chemotherapy. You'd have people working in microorganisms and then you'd have clinicians using chemotherapy or people working on birth defects. What I loved about it is I had one foot in both camps. I had one foot in the basic science camp and a foot in the clinician camp. Scriver is a genius at this. He always talked basic science to clinicians and clinical science to basic scientists. So we're translational scientists in that sense, you know.

Christopher Canning: That's great; because one of my questions, actually, was how did the whole group operate under that rubric, the clinical vs. the research?

Dr. Rosenblatt: I was very much in the mould of Dr. Scriver and I saw what he was doing with the RMGA (Quebec Applied Medical Genetics Network- Réseau de Médecine Génétique Appliquée) in Quebec, putting together a newborn screening program. As a physician I have always felt that if a physician were going to do research the same research in a hospital setting that he's doing in a basic science setting on campus, why did he get his MD degree?

Christopher Canning: Right.

Dr. Rosenblatt: My job is not to compete with the basic sciences who do the most fundamental research; I can find collaborators, I can bring perspective, I can bring knowledge of a pathway, I can talk to the clinicians about the appropriateness of a referral and screen things and that's what my job is and to build a very narrow expertise.

Christopher Canning: Which is clearly where you are now.

Dr. Rosenblatt: That is my particular perspective but clearly, if I had not spent that summer with Dr. Scriver, I would not be doing this. God knows I could very well be doing the history of medicine or something else, which I like equally well. I never have made the case that what I'm doing is more important than what anybody else is doing; I'll make the case that what I'm doing is important and because I have been cast in this role, my job is to defend that particular piece of scientific thought and territory, but I will never make an argument that this is more important than another area. I will make an argument that

I'm trying to do this at the highest level that I am capable of doing it and that ultimately all these little bricks will create a totality that will move things forward.

Christopher Canning: Okay. Interestingly, you saw every member of the group from 1975-2009.

Dr. Rosenblatt: I did. I did.

Christopher Canning: And so was there always this discussion in the group that we must maintain some sort of healthy balance between the clinical and basic research?

Dr. Rosenblatt: Never. I think it was more leading by example. It's actually quite interesting to see the evolution. We think of Scriver and Fraser as people who set up clinical services in addition to being researchers, but they were never primarily driven by patient care. They were driven by finding out new things, but they also wanted to give good care to the patients they were seeing. But their goal was not to give care and genetic services to the largest group of patients. Maybe if you were talking about newborn screening, but they didn't want to see more patients than are seen at St. Justine or in having the largest clinic. They wanted to be in an academic centre to have targeted genetic services going on. We got into real trouble because the Quebec provincial government thought that we could do all genetic services and research within a fixed budget. The members of the RMGA said that they wanted a global budget from the province and that they would be able to do patient care and research and epidemiology all within this budget. What happened was the patient care demands grew, the budget stayed more or less fixed, and there was huge frustration within that. Here I am not talking about the Group but the RMGA, the Quebec Network of Genetic Medicine, which was another envelope. That's another history that has to be written as well.

Christopher Canning: That's the first I've heard of it.

Dr. Rosenblatt: The directors were Scriver and Claude Laberge.

Christopher Canning: Okay.

Dr. Rosenblatt: So this was going on also at the same time.

Christopher Canning: Right.

Dr. Rosenblatt: Scriver was good at creating structures as well, which is a sign of a leader. These were frameworks under which he could accomplish different tasks. He realized by getting things done within the Quebec framework, he had to have a strong Francophone intelligent ally; so he hooked up with Claude Laberge. They went to the government and they got this envelope that they said would take care of all the genetic services and they worked very well

while the genetic services were small. But then everything grew, prenatal diagnosis came up, everything became routine and they were always under pressure, "Why aren't you seeing new patients? Why aren't you expanding the clinical service?" and I don't think they saw this as the primary role. It's still a battle even today…what should we be doing, what should we be selecting?

Christopher Canning: Clinicians or…?

Dr. Rosenblatt: No, I'm talking about medical genetics patient care and research in Quebec. It's an ongoing battle and I'm fighting this battle as an academic head. There is still a lot of knowledge to be learned and in a tertiary centre we are supposed to be advancing knowledge, but we have to provide patient care and also teach. I think that is t is reasonable to say that we are only going to provide expert patient care in specific areas and let other people do other things. We are not going to be able to experts in all areas of genetics and therefore in some areas, we should do what is necessary in order to cover those areas. So, these are always areas of tension, but I don't think we ever had a discussion of how much time one should spend on research, how much on teaching and how much on patient care. I think the idea was: how many MDs were there? At the time of the beginning of the group, there was me, there was Charles, and there was Clarke. Later on there was Pinsky and of course there were the PhDs. In general, PhDs were there only for research and teaching, although some, like Rozen, had responsibilities for the clinical laboratory as well.

Christopher Canning: How are you doing for time here?

Dr. Rosenblatt: I don't know because I haven't looked at my clock.

Christopher Canning: Is it 2?

Dr. Rosenblatt: It's 2:10.

Christopher Canning: Well, let's shoot for another 15-20 minutes.

Dr. Rosenblatt: Sure.

Christopher Canning: In my conversation with both Scriver and Fraser and now you, there was talk about how space was important to the Group. What space did you have when you were a young group and what was the concept of say the group needed to be together in this space. I noticed in the application of the mid-'80s, which I'd like to come back to as well, there was talk from Scriver in particular saying that the Group can't, or shouldn't, branch out, that it needed to be in the same physical location. So I'd just like to ask, from your point of view, from starting early on, where did you work, how did the space of the group evolve physically?

Dr. Rosenblatt: Well, there are two different areas. I think at the beginning when the group structure was first posited, the criteria for having a group was that it was in one physical space. You may want to check the MRC regulations but I'm pretty sure that people had to be in one institution and in one physical space at the beginning.

Christopher Canning: By the looks of things, that's the way it was.

Dr. Rosenblatt: The regulations changed later. When I started, I did not know much about space. I was assigned an office of, I don't know, maybe 60 sq. feet or 50 sq. feet and I had enough space to do my work. When I started at the Children's Hospital as a medical student, Scriver's office was over the boiler room. It was very tight, but people got along. With the advent of the Group, Dr. Scriver was able to negotiate for a new floor, so when I came back from Boston, I had excellent space to do my work. It was not a big floor, but everyone on the floor was working with Charles. Clarke had a unit one floor downstairs, but because he was doing mostly "dry research stuff;" he didn't have a lot of "wet" laboratory space. He had his clinical research at the Children's hospital, but also a laboratory at McGill for his mouse work; Clarke would go away to McGill and do his experiments that require mice. I was never an administrative leader of the group. In my first ten years, I just worked at my corner and I was able to do my work. I got along with the people around me. I felt protected and that's why I really felt very comfortable. I think part of my reason for wanting to branch out in '87 was that I was becoming too comfortable. I realized that there's an expectation of rising through the ranks and I didn't want to leave McGill, so the question was what one could do within the McGill framework that would be seen as benefit, and to be able to take advantage of the existing situations.

Christopher Canning: Do you want to go into this detail, then, of 1987?

Dr. Rosenblatt: Over the years, I had had a number of job offers outside McGill. I had an offer to go to Toronto to establish a Division of Medical Genetics in the Department of Medicine at the Toronto General Hospital. I also had offers in Dallas and Calgary. I had always promised my wife, Linda, who comes from Atlantic Canada, that I would not stay much more than five years in Montreal. She never was comfortable with the politics in Quebec. So now it is going on 36 years, and I am still at McGill. So, in the mid '80s, I was looking at positions outside of Montreal. At the same time, Leonard Pinsky had been doing a lot of work behind the scenes, because he felt there should be a genetic presence outside of the pediatric world. He had worked with Phil Gold at the Montreal General Hospital and Peter Macklem at the Royal Victoria hospital to carve out a pool of money to create this division of medical genetics in medicine.

Christopher Canning: Right, in '79 I guess when this should have...

Dr. Rosenblatt: Well, no in '79 they were talking about the Centre for Genetics. That's a whole different discussion. This was more should there be a Division of Medical Genetics in the Department of Medicine because medical genetics has always been in Pediatrics. There was a feeling that new technologies would be applied more and more in general medicine and that McGill should lead the way. Somehow, my retention at McGill was around the time that a group grant was being renewed and we wrote into the grant funds to set up my unit at the Royal Victoria Hospital (RVH)**.** Dean Cruess agreed to front the money with co-operation with the hospitals. In fact, I think that the hospitals funded the project and the Dean never gave it back, but that's a different issue altogether. You should actually meet with Richard Cruess about that, but I doubt that he would remember the details. You should meet with him; anyway, he's a colourful guy.

Christopher Canning: Okay.

Dr. Rosenblatt: Wonderful. Wonderful stories I could tell you, mostly positive, but good fun anyway. So the idea was how do you keep me at McGill and how do we develop this new area of adult genetics. Charles was really quite upset about the fact that someone was leaving the base of the Children's.

Christopher Canning: Yeah, I got that sense. I have one of the letters here that was written to the group by Dr. Scriver; he was concerned about the changing structures and physicality of the Group and how this was going to look on future applications, or how the Group was going to be successful down the road.

Dr. Rosenblatt: That's correct. I think as it turned out just fine, but there were some pressures at the time. I think, you know, that funding was the major concern. I don't know how easy it was to transfer them back to the faculty. Also Charles has uncertainly about the group renewal. He was worried that the application was not fresh enough, and whether the group members were using the latest technology-since we were not strong in DNA work at that time.

Christopher Canning: He wanted a molecular biologist?

Dr. Rosenblatt: Well, we all wanted to have a transition but none of us at that time were really trained.

Christopher Canning: Right.

Dr. Rosenblatt: And it was around the same time Lou Siminovitch had changed everything in Toronto, had made everybody drop what they were doing and drop their projects. I don't think that Charles wanted to do that but he was concerned about our competitiveness. DNA was not really his area of either comfort or interest at that time.

Christopher Canning: So you, as a group, felt the pressure that the tides were turning?

Dr. Rosenblatt: Technology was changing in genetics and we were trying to keep up with that area, and we did change. Also, the rules about groups changed. I am not sure for which application; people could be on different sites.

Christopher Canning: And this was I guess the '80s?

Dr. Rosenblatt: I'm just trying to see what's the last publication that could be called…so we're down around I think…

Christopher Canning: It would have been the late '80s, I guess.

Dr. Rosenblatt: Yeah, but certainly the JCI publication which was…

Christopher Canning: Can you give me the number?

Dr. Rosenblatt: Yes, I'm looking for the number of the publication. I don't remember if the work for publication 32[8] was done at the Children's; I think so. Once we get to '88, '89, the work was done at the Royal Victoria Hospital, but the nature of my work did not change. I just have developed more, and had formal administrative responsibilities because of the mandate to set up a clinical service in adult genetics.

Christopher Canning: So this is where you went from pediatrics to a broader scope in medicine?

Dr. Rosenblatt: Yes, and then I became Director of Medical Genetics in the adult sites. We set up a diagnostic lab for Huntington disease and adult polycystic kidney disease. We started seeing breast cancer patients; I recruited in a cancer geneticist, Steven Narod. This Division was the first Division of Medical Genetics in a Department of Medicine in Canada.

Christopher Canning: It just seemed to be at a point in your career that you were able to do this and…

Dr. Rosenblatt: Well, first of all there was the natural history of an academic. You reach a certain level and then you look for opportunities for growth. I also felt that no matter what I do, the any work done at the Children's would be seen as just derivative of Scriver's work.

Christopher Canning: Right. So this is you in a sense…

[8] **Publication 32:** Watkins D, and Rosenblatt DS,: Failure of lysosomal release of vitamin B12: A new complementation group causing methylmalonic aciduria (cbl F). *Am J Hum Gen* 39:404-408, 1986.

Dr. Rosenblatt: But all this was done while still staying within the framework of the group.

Christopher Canning: Right, because, by the look of things, it didn't affect funding.

Dr. Rosenblatt: It didn't affect anything. No.

Christopher Canning: No.

Dr. Rosenblatt: It didn't affect anything and…

Christopher Canning: Besides maybe a year or two of some animosity.

Dr. Rosenblatt: Well, tension, but also we still continued to publish together, as you can see by publication 46.[9] I think that Dr. Scriver feels very much like the Patron; these are his people and you know; he controls the chessboard.

Christopher Canning: It's interesting because I asked him about this time and he couldn't recall what we might call this conflict, or these changes in the structure of the group.

Dr. Rosenblatt: Very recently things have become extraordinarily cordial again and I've always been in my position as Chair supportive of him for many reasons. He has done great things but my concerns are one of the weaknesses of Dr. Scriver was because of his orientation, the transition of the service was very poor after he left. A lot of successful people are like that and we end up with very poor transitions because "no one can do it if I can't do it." And, in fact, seeing it fail after I leave is a sign of how it was dependent on me when I was there.

Christopher Canning: Interesting. Okay.

Dr. Rosenblatt: One element of success is to see whether you leave the place stronger than when you left, and how many people do well after you have left. We've seen many things at McGill set up by very strong people and when they leave, the whole program falls apart.

Christopher Canning: It's interesting; he sort of alluded to that. He said well, now it's kind of done after he left.

Dr. Rosenblatt: I was very much a strong advocate for the creation of the University Department because I think that what you do is you create a structure that has longevity.

Christopher Canning: This Department in which you sit right now?

[9] **Publication 46:** McGill JJ, Mettler G, Rosenblatt DS, and Scriver CR,: Detection of heterozygotes for recessive alleles. Homocyst(e)inemia: paradigm of pitfalls in phenotypes. Amer J Med Genet 36:45-52, 1990.

Dr. Rosenblatt: Yes, the Department of Human Genetics. I'm at the Chair now, but there was a lot of discussion as to why do we really needed a department, what we were going to gain by having the department. I would answer that it allows you to create the structure that gives you stability and is not individual dependent.

Christopher Canning: And will carry on.

Dr. Rosenblatt: At least there is the potential for clear, orderly transitions, but as I told you from the beginning, I'm very much you know, working within my own framework.

Christopher Canning: You do your own thing.

Dr. Rosenblatt: My own preference is to work within a structure. Pinsky was quite like that, I think, as well.

Christopher Canning: Okay.

Dr. Rosenblatt: It's good to have a mix of people who are both within a structure.

Christopher Canning: Absolutely. I'm going to jump a bit to the mid-'90s. We've talked before about this and it was actually really interesting to see it pointed out for us, but there was a time during the funding in the mid-'90s where some individuals were funded, but not as part of the group, and some individuals were not funded at all. So for instance, Skamene won funding in 1995 but wasn't involved in the group any more.

Dr. Rosenblatt: So there are two aspects. In the early days of the group, it was judged as a whole, although the reviewers would look at and comment on the activities of each of the members. For example, you can look at some of the early reviews of Peter Hechtman. Each individual had to be judged independently and then if they succeeded, they were allowed to join the group.

Christopher Canning: Interesting.

Dr. Rosenblatt: So he was judged and essentially not renewed within the group structure when the group is judged as a whole, so he was the first one out.

Christopher Canning: It was '88?

Dr. Rosenblatt: Okay, and basically there were reviews saying he wasn't pulling his weight within the group. This was before the time each investigator in the group had to submit an independent grant that had been reviewed by a peer panel; this was all within the group-judging panel. Then the MRC moved on I think in that next transition to that period where you had to judge each

group member independently and then look at their fit with the group. They could say, "Look, this is a good guy, but his work is not fitting in the theme of what the other people in the group are doing; we can't structure our imagination to figure that. Fund him but don't put him as part of the group."

Christopher Canning: Right.

Dr. Rosenblatt: So that's a different type of decision. They judged the science as meritorious but he wasn't really a fit for what was going on with other people in the group.

Christopher Canning: Right. Because there was one application where Shoubridge was not accepted at all.

Dr. Rosenblatt: Yeah, which made no sense.

Christopher Canning: And then Skamene was offered funding but not with the group.

Dr. Rosenblatt: Yeah, and also I don't know why Shoubridge was not accepted at all. I guess they didn't read his application correctly.

Christopher Canning: His mitochondrial studies were maybe not as big?

Dr. Rosenblatt: Shoubridge is wonderful; he's sort of a Renaissance man. When he started, his interest was in imaging. He drifted and taught himself molecular biology, and is one of the best in the world at what he does, so it makes no sense that he was excluded at that time.

Christopher Canning: His publications are really fascinating.

Dr. Rosenblatt: Never mind the publications; he's a fascinating guy. I guess that the reviewers were not as turned on by the work, but they judged it wrong.

Christopher Canning: Interesting. Well he seemed to do well after that.

Dr. Rosenblatt: Exactly, and we were able to bring him back in when we were scrambling, quite frankly, to find people of high enough quality to allow the group to keep going.

Christopher Canning: Right. May I ask why you never directed the group?

Dr. Rosenblatt: Uh, probably politics.

Christopher Canning: Okay. What sort of politics?

Dr. Rosenblatt: I think they very much wanted that group to be directed by someone at the

Children's Hospital.

Christopher Canning: Interesting.

Dr. Rosenblatt: Pinsky was for a while the Co-Director of the group but I think that there was a feeling that the Director should be at the Children's. The research community at the Children's was getting other types of support from the Foundation of the Children's, and for historical reasons, the Children's is very invested in the group. I don't think that Charles in particular wanted to see the leadership of the group leave the Montreal Children's site.

Christopher Canning: How was that leadership decided, do you remember?

Dr. Rosenblatt: How was the leadership decided?

Christopher Canning: Yes, you went from Scriver to Pinsky to Gravel to Rozen.

Dr. Rosenblatt: I think it was decided more or less by consensus. I was never advocated to be head of the group. Roy Gravel was recruited from Toronto to be Head of the Research Institute of the Children's. He was doing high profile science, and he was a molecular biologist. It was felt that it would be viewed as a favourable shift, and I think it was. I think those were the strategic decisions that had to be made. By the time Roy left, Rima had an established reputation, was strong and was at the Children's, and had a role there. I didn't fight with Rima and say no, I think I should be head of the group. You don't recall saying hey, I need to direct this or?

Christopher Canning: You don't really recall saying or thinking that you would like to direct the Group?

Dr. Rosenblatt: I probably said something to myself and my wife certainly was not happy that I was not asked to direct the group. But I also probably said to myself that it was not a battle worth fighting because it was not going to make that huge a difference. Also, there was a very brief time when I was out of the Group, if you noticed.

Christopher Canning: I was going to say; you disappeared for about half a year.

Dr. Rosenblatt: I went in for a September competition because that was the usual time when you had to get renewed independently. I was just on the cusp of funding. If you didn't get funding, you couldn't go into the group, so when I was again funded in March, the group petitioned to get me back in.

Christopher Canning: They petitioned to get you back in?

Dr. Rosenblatt: Well, you had to. There is a letter stated from Gravel to the MRC asking to reinstate me into the group.

Christopher Canning: I have it here, yes.

Dr. Rosenblatt: It was interesting, because during that period of time I could not partake in the core funds.

Christopher Canning: Okay.

Dr. Rosenblatt: During that cycle, that cycle of the group, but it didn't really matter because the core funds I was using were being supported anyway. My major use of core facilities was for the cell bank because I would get cell lines from all over and they were kept down at the Children's. I was never was denied access to the cell bank, but if they had extra funds in the core budget at the end of the year, I wasn't part of the distribution of funds.

Christopher Canning: At the symposium, Scriver mentioned – I only have a few more questions here. We can always come back…

Dr. Rosenblatt: Whatever you want.

Christopher Canning: Scriver mentioned at the symposium that the Group always operated from a bottom of approach, and from a sociological perspective I find that really interesting. Can I just ask what do you think he meant by that? What does that mean for this group that was obviously successful for so many years? What does it mean to have operated from the bottom up?

Dr. Rosenblatt: I think Dr. Scriver never intervened directly in the scientific thinking of what the people were doing at the bench and with their research program. The investigators built alliances with people in the group, and also with those outside the group according to their research plan. We developed natural alliances and then we'd go apart, and then we'd develop natural alliances again or we'd recognize people with particular expertise and use them for that. So it wasn't like someone came in and said, "Okay you guys, we're going to solve cystic fibrosis tomorrow and you're going to do this and you're going to do that." It was, you know, do your thing and interact, and this is the facility and structure that lets you do your work. Then you have sales people and diplomats and politicians who will weave it together. It worked. It clearly worked and it worked through various leaders. It spawned the Centre for Human Genetics; it spawned the Department of Human Genetics at McGill. It wouldn't have happened without it.

Christopher Canning: Fantastic. Okay, so where is your research heading now?

Dr. Rosenblatt: I am now 63 and I just put in my grant last year and was ranked number one in the Canadian Institutes of Health Research Genetics panel. The CIHR asked me if they could use the application as a model for grant writing for other investigators. I was very proud of that. My research focuses on two

areas. Having found new genes, the question is one, what is the importance of these genes and could they be related to more common problems like birth defects. The second question is seeing how these gene products interact with one another in the cell. Both of these are long-term projects. On my last grant, I added a young recruit as a co-applicant on the grant. Loydie Majewska is a developmental biologist who works at the Children's Hospital. She is a mouse geneticist so my idea is to transition what I see as at least a ten year project over to her so in the next five years. She should be the PI on the next grant. I am also working with someone in the Microbiology Department, James Colton, who does enzyme purification and structural biology. For that part of the project, I have put a postdoctoral fellow in his laboratory and I hope to transition that work to him.

Christopher Canning: Is this functional genomics biology work – are you still interested in that?

Dr. Rosenblatt: Yes, but it is more mechanisms of actions, gene products and relations. Everything is given terms now so you can solve what you're doing, but it is functional genomics, yeah. It's to see what these genes actually do, how they interact with one another. For the mouse work, when the mutations are put in, the mice don't come to term and they may also have birth defects before term. We are trying to develop our system in the same way that Dr. Rozen has done for the MTHFR mouse, but with new genes that we found.

Christopher Canning: Okay. You have a very recent publication on the epigenetic modification of the gene responsible for B_{12}.

Dr. Rosenblatt: That's from my lab.

Christopher Canning: It is from your lab, yes. The only reason I ask, and this is purely a selfish question because I have an interest in epigenetics. Are you noticing in your work that epigenetics is creeping in more and more?

Dr. Rosenblatt: Well, epigenetics is creeping in there for a number of reasons. I have an interesting example. A number of years ago, an investigator at the University of Ottawa by the name of Robert Liteplo approached me and said he had a melanoma cell line that looked in culture to mimic cell lines fro one of our Vitamin B_{12} disorders. Working with David Watkins, he found that in cell culture, these cells didn't correct the cells from one of our inborn errors. We thought that the cells would have a primary defect in the gene responsible for this disease. When we cloned the gene (Lerner-Ellis publication 141[10]), we took out the cell line to see whether we could find

[10] **Publication 141:** Lerner-Ellis JP, Tirone JC, Pawelek PD, Dore C, Atkinson JL, Watkins D, Morel CF, Fujiwara TM, Moras E, Hossack AR, Dunbar GV, Antonicka H, Forgetta V, Fobson CM, Leclerc D, Gravel RA, Shoubridge EA, Coulton JW, Lepage P, Rommens JM, Morgan K, Rosenblatt DS: Identification of the gene responsible for methylmalonic aciduria and homocystinuria, *cblC* type. *Nat Genet* 38(1): 93-100, 2006. Erratum. *Nat Genet*

mutations in the gene. There were no mutations-but then we looked at the expression of the gene-and it wasn't expressed. We postulated and demonstrated that the problem was methylation of the promoter for the gene-thus the link to epigenetics.

Christopher Canning: But you've been interested in methylation for quite some time.

Dr. Rosenblatt: That is because of the involvement of our genes in transmethylation, the conversion of homocysteine to methionine and then to SAM. That is why I have an interest in the area of epigenetics.

Christopher Canning: And especially now how epigenetics is being understood in terms of inheritance.

Dr. Rosenblatt: Absolutely. You know all the work with Agouti mice?

Christopher Canning: Indeed.

Dr. Rosenblatt: So first of all it's inherently interesting. Also, it is a very easy way to say why the work you're doing on these obscure diseases is relevant, pointing out the mechanisms that lead to the recycling of single carbon relate to methylation. While we always write "pro forma" in our grants that our work is relevant for cancer and heart disease, it is indeed the case that we are working in this area because it is advancing knowledge in an area that does have medical relevance.

Christopher Canning: How much longer are you Chairman of Human Genetics?

Dr. Rosenblatt: My term is supposed to end in the spring of 2010. I think they will extend it for one year for various reasons; there was a year gap when I was appointed so my initial term was only four years and in 2011 I'll be 65, so I think we'll go an extra year. I do not intend to stay on beyond August 2011.

Christopher Canning: And you just mentioned that you are building a ten-year project out of your current application or something thereabouts. Is that when you hope to retire?

Dr. Rosenblatt: I don't know. I probably will never retire as such, not as long as I'm healthy and still have ideas. There are other types of things. I'm disappointed that in the rare Mendelian diseases, advanced diagnostics haven't really taken off as much as I'd have liked. I would like to work on more applied projects to see whether we can mobilize the facilities across campus. Rather than everyone having their own little competing small units, I would like to see an internationally competitive diagnostic unit that can tackle all comers.

38(8): 957, 2006.

Christopher Canning: Specifically for Mendelian diseases?

Dr. Rosenblatt: For specifically Mendelian diseases. The problem that I worry about is that molecular diagnostic laboratories will be taken over by people who are diagnosing H1N1 and somatic changes in breast cancer. The problem with most of the Mendelian disorders is that they are usually rare, but there are thousands of different diseases and it is important to be able to offer diagnosis to patients with these diseases. There will be a lot of political fighting for resources. One of the problems is that our health care system is provincially based, so although there is a national laboratory in Winnipeg for infectious disease, I think the politics of trying to create a national lab in Canada may be insurmountable. However, perhaps, at least in Quebec, we may be able to achieve some centralization. I'd like to see diagnostics run out of a university consortium that involves all the players at McGill. Other places that have done it well include Baylor and Emory. That is why I am willing to spend some energy on this kind of project.

Christopher Canning: That's great. I'm available any time you want. Thank you very kindly for your time.

END OF INTERVIEW

Dr. Rima Rozen, February 16, 2010

Andrew Hoffman: My name is Andrew Hoffman, and I am here with Dr. Rima Rozen in the Department of Human Genetics. Again, here we say Department?

Dr. Rima Rozen: That's correct. I am a Professor in Department of Human Genetics and Pediatrics.

Andrew Hoffman: And Pediatrics. It's February 16, 2010. It is my great honour and privilege to be here with you, Dr. Rozen, to discuss broadly two main themes regarding human genetics. First, I would like to discuss your academic background, which of course significantly contributed to the growth of medical genetics in Canada and beyond.

And secondly, and perhaps more importantly for this particular study, I am interested in your involvement with the MRC and CIHR Medical Genetics Group, not Department, of which you have been a significant member, and which has operated until this past September as I understand it, under the leadership of others such as Dr. F. Clarke Fraser and Charles Scriver.

Dr. Rima Rozen: Well, not correct, which has operated under many different leaderships, including --

Andrew Hoffman: Such as. So as sort of an introduction, I think, that this might be where you will be repeating yourself a little bit, hopefully not, again, but to give an overview maybe of where you are from, where were you born, where you grew up, where you did your schooling, etcetera.

So I see from your CV that you were born in the Soviet Union. That you attended University here at McGill. So I guess it's helpful to go back a little bit to trace where it is that you are from and how your personal history influenced your academic work.

So let's start at the very beginning and we will move through.

Dr. Rima Rozen: I wouldn't say that my personal history influenced my area of research, simply that education was important to families that are immigrants to Canada and the U.S. obviously, so it was important for me to continue my education and become qualified for something important. But beyond that, there was no real specification or encouragement to do biology or genetics or anything else, particularly since my parents were not very well educated, having survived a Holocaust, and so beyond their level of education, which was high school, they were not familiar with genetics or biochemistry or metabolism or anything else. So my upbringing is irrelevant other than what I initially said.

Andrew Hoffman: But they were encouraging with regards to --

Dr. Rima Rozen: To education, absolutely. And of course whether I chose medicine or law or research or physics; my father always wanted physics, but that was just simply looking from the Soviet Union point of view, and I guess in those years mathematics and physics and the Cold War and the space program, maybe that influenced his thinking, but there was never any push to go to particular areas, as long as my sister and I had an education.

Andrew Hoffman: So you had sort of an amateur attachment perhaps to the sciences?

Dr. Rima Rozen: Yes.

Andrew Hoffman: And is your sister also --

Dr. Rima Rozen: My sister has a PhD in biochemistry and is now in the private sector, or actually working for -- she is a science analyst for private sector funding of science. So we are both in the science area, I am on the academic side, she is on the investment side, so there is a discrepancy there, but that could be a timeline issue.

Andrew Hoffman: A timeline issue?

Dr. Rima Rozen: Because she is my younger sister by eight years, and I think the academic route for PhDs was pretty much the only route when I was training. When she finished, there were other options and so on.

Andrew Hoffman: And do you think you had an influence on her career also?

Dr. Rima Rozen: Not really. She started in the academic sector, but then chose to -- just because of opportunities or whatever, went into the private sector.

Andrew Hoffman: So your family immigrated from the USSR to --

Dr. Rima Rozen: Through Poland to Canada.

Andrew Hoffman: Okay. And about what year was that?

Dr. Rima Rozen: We came here in 1960. I did all my schooling in Montreal, so I didn't start school elsewhere.

Andrew Hoffman: So you were about eight when you --

Dr. Rima Rozen: I was six, which is why I speak English without an accent, other than you might say I have a Canadian accent, but other than that --
Because I learned English here at school, so I don't have a trace of an accent, but that was my fourth language. So I appreciate language, I appreciate different cultures and immigrants, communities, and so on. Maybe that drew me to genetics, but never really thought of it in that light.

Andrew Hoffman: Were the sciences something that you were interested even in elementary, in high school as well?

Dr. Rima Rozen: Yes, yes, the mathematics, biological sciences, yes.

Andrew Hoffman: And so you chose to do your Bachelor of Science in Biology?

Dr. Rima Rozen: Which was the only sort of -- yes, biology, and then it sort of became a genetics program; genetics is not independent at the undergraduate level. The only way we learned genetics at McGill is through the Biology department, the graduate program in Genetics became available later, but we still don't have an Undergraduate program in Genetics.

Andrew Hoffman: So while you were doing your Bachelor of Science, was genetics something that was --

Dr. Rima Rozen: It was taught, yes, it was a concentration or a major, I can't remember what it was called in those days, but there were certainly excellent courses and leadership in Human Genetics at McGill. And in fact, Charles Scriver and Clarke Fraser, and others, Peter Hechtman, were my teachers, and so it was their influence that made genetics seem so attractive, and that was essentially why I sort of went into the area.

Andrew Hoffman: So did you notice while you were, or even in retrospect, that while you were doing your Bachelors, genetics was something that was maybe changing at the time, or it was becoming more important within the curriculum?

Dr. Rima Rozen: Yes, yes, and it was clear that genetics was evolving into a different kind of discipline. Genetics started as, just looking at patients, and then it became more about chemical, and then it became more molecular, and it was clear that it was evolving and was going to be a fascinating area.

Andrew Hoffman: And you remember thinking that at the time that you were doing it as well?

Dr. Rima Rozen: Do I remember thinking that way when I was whatever? Probably not. But now if you are asking me retrospectively, so I can sound very intelligent now and tell you that yes, I appreciate --

Andrew Hoffman: You knew it was going to happen.

Dr. Rima Rozen: I appreciated all those things as an undergraduate and could clearly see that there was future in genetics.

Andrew Hoffman: Well, we will get to the details of the changes soon enough. So you said you worked, or that you were taught by Dr. Fraser and Dr. Scriver and --

Dr. Rima Rozen: Peter Hechtman, I remember, was an excellent teacher in those days too, and so these people were the leaders, the gurus.

Andrew Hoffman: And how would you say that they influenced you from going from a simple Bachelors of Science in Biology, to moving on with your career?

Dr. Rima Rozen: Well, because I became a PhD student of Charles, but I did sort of an independent -- I think I was an Honor student, yeah, I was an Honors student. So we had to do an undergraduate research project at the time and I chose to do it in genetics, but for some reason I ended up with Dr. Gold, who was in fact a member of the Group, but not quite sure how I selected him as opposed to Charles; maybe Charles was out of town or couldn't be reached, it's hard to say with undergraduates.

But the point is, I was actually physically placed in that Genetics Group area on the 7th floor of the A Wing, and so I became friendly and interested, and in more than just Dr. Gold's research, in fact, his I found a little bit dry.

Andrew Hoffman: The 7th floor A Wing in --

Dr. Rima Rozen: In the hospital, that's where -- that's where they have always been, and that's where the Group started. It didn't start in the 7th floor, I think it started somewhere else.

Andrew Hoffman: I think it was on the 6th floor actually.

Dr. Rima Rozen: Possibly, but when I started it was on the 7th floor, and Charles was, I guess, he was Director of the Group at the time. So I initially gained entry into the Group through Dr. Gold; it was Charles' research that actually interested me and so I spoke to him about graduate school.

Andrew Hoffman: So my question here was, you actually took a course specifically in human genetics?

Dr. Rima Rozen: Several courses, I can't remember details in those days but --

Andrew Hoffman: So in the other interviews I noted that they were actually taught by Scriver, Fraser, Hechtman and Gold, so I was going to ask, which of those you had, and how that --

Dr. Rima Rozen: I probably had all of them, I can't remember, or some of them, or whatever. But yes, they were the ones who taught the undergraduate level, they were excellent teachers.

Andrew Hoffman: Each one at a time, or was it taught as a group, or do you remember?

Dr. Rima Rozen: I can't remember.

Andrew Hoffman: So you said you had an undergraduate Honors project in Genetics.

Dr. Rima Rozen: An Honors project, right, so that's my final year, undergraduate.

Andrew Hoffman: And do you remember what you did for that project?

Dr. Rima Rozen: Yes. It was measuring -- looking at hair, and measuring sulfur compounds or sulfur proteins in hair, because it was related to a genetic disorder that was being investigated at the time, and I don't really remember the name of it at this point. So that's what I was doing. It was developing a technique which was not working well, and it was frustrating, but I think I got some data at the end. It was very dry shall we say.

Andrew Hoffman: Okay. So was it then that you sort of decided, I guess that --

Dr. Rima Rozen: That I enjoyed doing the research, but that particular project or area was not one that I wanted to pursue, and so --

Andrew Hoffman: But genetics was?

Dr. Rima Rozen: Yes.

Andrew Hoffman: Okay. And so you began your doctoral work at McGill, with Dr. Scriver?

Dr. Rima Rozen: Yes.

Andrew Hoffman: As your primary supervisor?

Dr. Rima Rozen: Yes.

Andrew Hoffman: And your first project?

Dr. Rima Rozen: That was an interesting story. My first project that he gave me -- and I was always interested in metabolic disease and inborn errors of metabolism. So he gave me a project to work on, which was to identify a particular defect in an inborn error of metabolism. He thought it was going to be a novel defect in the pathway. It was a patient who appeared to have this kind of defect, and so the patient cells and so on.

I spent two years on that project. It was very exciting, because I got to go to Toronto and learn some new techniques there and brought them back to McGill.

In fact, that's relevant because I learned these techniques with Roy Gravel in Toronto. But I came back and then worked on this project and showed at the end of two years that it was not in fact a novel defect as Scriver had hoped. The work I did, if I say so myself, was quite clear and there was no discrepancies, but

it was not a new defect. I was able to show that it was in fact a defect that had been described, and therefore it was not appropriate for a PhD thesis.

Andrew Hoffman: Was it a variant of a defect or was it simply --

Dr. Rima Rozen: Not really, it was essentially the same problem that had been described in the literature. So after two years I had to start a new project, a brand new project.

Andrew Hoffman: Okay. So hold on one second before we go on.

Dr. Rima Rozen: And I have even forgiven Charles for that.

Andrew Hoffman: I think it happens all the time, I have a feeling, not with me yet but --

Dr. Rima Rozen: It was a very different area that I had started.

Andrew Hoffman: Yeah. So can you tell me at all about the defect or --

Dr. Rima Rozen: I am not sure it's really relevant for the history of the Group.

Andrew Hoffman: Now, you said that you went to Toronto and brought techniques back that hadn't actually been practiced at McGill.

Dr. Rima Rozen: It was a technique that Roy Gravel was an expert in.

Andrew Hoffman: And what was it?

Dr. Rima Rozen: His complementation. And I came back and set it up to do it on my patient to see if it was in fact a new defect and it turned out not to be the case.

Andrew Hoffman: And so can you describe the process of complementation sort of in a --

Dr. Rima Rozen: I think you are getting more assertive. I mean, I am not sure that you want this level of detail in this.

Andrew Hoffman: Well, just a basic understanding of what it was that you brought back and what --

Dr. Rima Rozen: I mean, it was only relevant for that particular patient, that project, I didn't continue shall we say. So it wasn't something that I left McGill, and in fact, David Rosenblatt does a lot of complementation work. So I would never be recognized as the complementation expert, shall we say. It was something I learned, I did it for my patient, and then that was it; I never touched it again.

Andrew Hoffman: But you were doing it at McGill before Rosenblatt was?

Dr. Rima Rozen: That I can't remember.

Andrew Hoffman: Okay. The bottom line is that you simply brought it back with you, and you used it for what you needed to do, and it helped you figure out that what you were actually working on was totally not novel.

So moving on from there, what was the next step?

Dr. Rima Rozen: Right. So then he gave me -- I mean, I had to do something that was ongoing at the time or something that was likely to get me a PhD, I didn't want to develop something for another six years. So I worked on amino acid transport in mice, defining a transport system for amino acid called taurine. And there were supposedly some mice that had different levels of taurine in the urine because of differences in amino acid transport. So I had to learn a whole new set of technologies in the transport field, very different from what I had done before, it was mice not in people. It was transported, not metabolism.

So I really was -- I mean, I did the work, got my thesis, good publications, but it was clear to me that it was not an area I wanted to continue.

And in fact, I think I should mention that for most of that project, Susie Tenenhouse was actually the expert. I don't remember if she was a Group member at the time or a research associate. She was a research associate with Charles before she became a professor and a member of the Group. But she was the one who really sort of supervised me on a regular basis; that was her area of expertise when Charles was off giving lectures, what he normally does.

So it was actually Susie Tenenhouse who trained me in the scientific method, shall we say.

Andrew Hoffman: So it was Charles who gave you the project to work on?

Dr. Rima Rozen: Yes, and we met every, whatever, so often to discuss things, but it was Susie who showed me how to do the experiments and guided me on a regular basis.

Andrew Hoffman: So given that sort of dynamic working with two different people, how would you characterize your relationship with Dr. Scriver?

Dr. Rima Rozen: Oh! He was wonderful to talk to and he always had ideas and he was articulate. He was unusual in the sense that he could do the science and he could write equally well, if not better than most scientists.

If you handed in a draft of a manuscript to Charles, it came back with lots of red marks. So it was a different kind of mentorship from the mentorship I got from Susie, but both were important.

Andrew Hoffman: Was Susie eventually involved with supervising the project officially more or less?

Dr. Rima Rozen: I don't think so because you -- I think she was still a research associate at the time, you cannot supervise, you have to be a professor to be able to supervise officially. So she was my day-to-day supervisor. And that was sort of a standard way of doing things in those days. There was lot more money for research. People sort of developed little empires, large groups could be built up with a lot of funds, and so they tended to have a fair number of research associates, the big sort of directors of projects and so on. It was fairly typical for the successful researchers to have sort of research associates who would train a student.

Andrew Hoffman: So you notice a change from then to now with regard to funding, which is something that I think we will get to. But do you think that it was that structure that really helped you flourish in your own thing? I guess what I am getting at is that, you were basically -- you had a topic that you were working on technically under one person, and then really working with it on a day-to-day basis under another person.

Dr. Rima Rozen: It wasn't a problem; it worked very well. I see a lot of that in my own lab now, that I am not here as often as I should be, and so the research associates or postdocs or whatever, help train the younger students, which seems to be common method of training students and large groups.

Andrew Hoffman: Did Dr. Tenenhouse help you sort of refine what your project was?

Dr. Rima Rozen: Yeah, maybe the details of it, but the general direction was Charles. Here, this is the project I should work on. Obviously we would meet to refine. I mean, they were both involved in the refinement, but it was certainly something that Charles had identified as a potential area of research.

Andrew Hoffman: And what kind of autonomy did you have in being able to refine it or not?

Dr. Rima Rozen: Well, I certainly would have had the potential, whether I was clever enough to do it myself or how much day-to-day hand holding I needed, I can't remember that far back. They must have thought I was capable or they wouldn't let me keep going or bring me back or whatever they did.

Andrew Hoffman: So you said that it was the project working -- this was the project with the mice.

Dr. Rima Rozen: And it was amino acid transport, amino acid physiology and transport.

Andrew Hoffman: And is this homocysteine/folate metabolism?

Dr. Rima Rozen: No, that's what I work on now, that was amino acid called taurine.

Andrew Hoffman: But that was sort of where your interest in amino acids --

Dr. Rima Rozen: No, it was actually the first project. I really enjoyed the patient, inborn errors of

metabolism in amino acid, two conversions. It was the first project that really interested me, and in fact, the work I do now is more closely related to my first project than to the amino acid transport in mice.

Andrew Hoffman: Which is, I guess, why you said it got you some nice publications, but --

Dr. Rima Rozen: But it didn't really interest me as an area that I wanted to pursue.

Andrew Hoffman: Yeah. So how was it that -- how do you remember or recall experiencing the shift from working with people to working with mice?

Dr. Rima Rozen: Well, I didn't work directly with people, it was cells.

Andrew Hoffman: Human.

Dr. Rima Rozen: Right. It was human cells as opposed to mice. It's not so much the techniques you use or the nature of the materials, it's really the nature of the science that influences you. And this was transport, which is -- in my mind transport is not -- or at least the way we study transport, it's not really something that allows you to investigate the entire picture shall we say. Transport is very isolated. So that you isolate fragments of the kidney, membranes of the kidney, and it's very in vitro.

And so -- I mean, there is some big picture involved in there, but not to the same extent as when you study a patient with a disease, because then you are not only looking in one tissue, in one membrane, you are trying to understand what is going on throughout the body.

So it was -- and I think that's probably because at some point I had debated whether I should go to medical school or do research. And I thought about both when I was an undergrad. Why did I end up going into research? I think in those days there weren't enough mentors. It was always a concern that I would not have the time to do what other women do or women like to do.

In other words, I wanted to do everything. I wanted to be a professional, but I also wanted a family and children and so on, and it wasn't clear at that time that you really could do both without seriously sacrificing the one or the other. So I thought research might be a better avenue. Whether that's correct or not, I mean, yes, I have my family and my kids and so on, so it certainly allowed me to do that.

Would I have been able to do it as an MD? I am not convinced. I don't know. But having now, with so many medical colleagues, I see how much time they -- how little time they have to do research. And so maybe I -- and I am better trained than the average MD, not that they couldn't be. I am not suggesting PhDs are cleverer than MDs, but certainly we have had much more formal training. And so competitively we often do better in terms of the way we think about things.

Maybe more rigid.

So in the end, maybe I did make the right decision, because I can do research the way I like to do research and still have home life and so on. And maybe I would not have been able to do research at the same level or quality or type of research with an MD degree.

But I have always been attracted to medically related projects is my point.

Andrew Hoffman: Yeah. And I think that it sort of shows in your career, in the things that you have --

Dr. Rima Rozen: Right. So when I started with a patient and metabolic disease, it was medically oriented and it was very exciting. And when I switched to just sort of looking at radioactive amino acids and crossing membranes, it wasn't as interesting. And then when I moved back, I have always done more sort of metabolic disease focused research.

Andrew Hoffman: Yeah, that was, kind of, what I was getting at when I said people, I maybe didn't mean the whole human body.

Dr. Rima Rozen: Yes, the whole human body as opposed to one sort of organized way.

Andrew Hoffman: Yes. And so from McGill, sort of moving on with -- or moving away from what it was that you had then devoted for your --

Dr. Rima Rozen: Six.

Andrew Hoffman: Six years of your life.

Dr. Rima Rozen: Two years for the first project, four years --

Andrew Hoffman: Yeah, so four years doing something that wasn't

Dr. Rima Rozen: So it was a six year PhD.

Andrew Hoffman: Well, that's a lot quicker than sociologists have to take. Hopefully not me. And then, so you went from your PhD at McGill to a postdoc at McGill as well.

Dr. Rima Rozen: At McGill and at Yale.

Andrew Hoffman: Yes. So McGill first, you worked with Dr. Shore.

Dr. Rima Rozen: Yes.

Andrew Hoffman: And that was on Morris Hepatoma?

Dr. Rima Rozen: Well, it was metabolic enzymes again; it was related to metabolic disorders in the liver, but the angle was more sort of gene regulation.

So this was at a time now when -- so this was in 1981, I guess. This was at a time that molecular genetics was starting to become more routine, whereas my whole training had been in amino acid and sort of protein type work. So it was obvious that I had to learn some molecular genetics in order to succeed as a geneticist.

And so I chose to work in a lab that was much molecular, as opposed to looking at how often mice peed into a cup and measuring acids. In fact, they laughed at me because it was -- when I came into Gordon's lab, it was the first time I had ever run a gel. They couldn't believe that anybody had not run a gel before.

Andrew Hoffman: And what is a gel in basic terms?

Dr. Rima Rozen: A gel is one way of separating proteins in an apparatus that -- it's an apparatus and a gel like structure in which the proteins run into the gel and you separate them on the basis of molecular weight. It's a very standard technique in our chemistry, but if you hadn't done biochemistry and then moved to molecular genetics, it was something new. So that was actually protein biochemistry, which I really hadn't done, and then I moved to studying RNA in Gordon's lab, and so at least I was starting to get a handle on molecular genetics.

Andrew Hoffman: And this was a two year postdoc?

Dr. Rima Rozen: It was two years because I recognized -- well, I was married already and so I recognized at the time that -- I mean, McGill has this policy, shall we say, informal or formal, of you really don't want to do all your training internally. Even though I had switched areas that were so different that it really didn't matter whether I was at McGill or elsewhere, but just there is this mindset that you shouldn't do all your training in one place because you might learn that same techniques or biases, which was ridiculous.

But nonetheless, I recognized that I should probably try and get some training elsewhere, and by then molecular genetics and human disease was really quite prominent. So I looked for a year, because I had my own salary, so I could really go wherever I wanted to. So I looked around for a few labs in the U.S. that were doing something that I wanted to do in terms of molecular genetics and disease.

I went to Yale for a year; my husband stayed in Montreal. So that was why it was only one year, and that's probably why I didn't do it right away, because the conditions had to be worked out, and they were not straightforward. So I spent a year at Yale.

Andrew Hoffman: And that was working with Dr. Leon Rosenberg?

Dr. Rima Rozen: Again, not directly with Dr. Leon Rosenberg; he was the same level as Charles, with a huge lab, and in fact, he might have been Dean of Medicine at the time, I can't remember, but he certainly wasn't in the lab on a regular basis. He had research associates; in fact, much more senior than research associates even at McGill, because it's hard to get positions in Yale and some of these other universities. Fairly senior people could stay at the research associate level for quite some time.

So I was in fact supervised by a couple of -- one or two research associates in the Rosenberg lab, but it was a wonderful experience because that was the basis essentially of what I continued to do.

So from my perspective, that one year defined my career, and it was an opportunity, because Gordon Shore's lab was more about chemistry, it wasn't human genetics per se, it was an opportunity to learn a few techniques, but they didn't think like geneticists or clinicians, they worked out the biochemistry.

So here, now, diagnostics were becoming prominent, and so that's what I did at Yale; I learned sort of molecular genetics with DNA and --

Andrew Hoffman: Still with metabolic disease?

Dr. Rima Rozen: Yes, but genetic diagnosis essentially at that point, to a large extent.

Andrew Hoffman: Yeah, I saw that he had a written or edited a textbook on metabolic disease, and also that he was a molecular biologist by training also.

Dr. Rima Rozen: Who, Leon Rosenberg?

Andrew Hoffman: Yeah.

Dr. Rima Rozen: No, no, he is Charles [Scriver's] vintage in age, so molecular biology didn't exist when he trained. I mean, it was his postdocs and research associates who were doing molecular genetics; he was way beyond that. He was DNA medicine when they were doing molecular genetics.

Andrew Hoffman: So maybe that --

Dr. Rima Rozen: So yes, he wrote all those papers because they were his research associates, but he clearly wasn't trained in that. He was trained in amino acid metabolism and transport. Very analogous to Charles, they are coauthors on papers or books or whatever, they are very good friends. It was a coincidence, shall we say, that I went [to Yale], not because Charles recommended it; it was simply that I was interested in metabolism.

Andrew Hoffman: But that might explain sort of the way that labs were operating with, or tend to operate maybe even today, with this sort of head guy or head woman.

Dr. Rima Rozen: Absolutely, absolutely, yes.

Andrew Hoffman: And so this is something that you had mentioned earlier that maybe I would like to explore a little bit further in depth. You said that you noted a transition by the time that you were really even starting your postdoc here at McGill, from more maybe a traditional human genetic approach, so I guess Mendelian Genetics.

Dr. Rima Rozen: Right, and classification of patients and trying to understand --

Andrew Hoffman: Pedigrees and --

Dr. Rima Rozen: The basis of a disease, but without necessarily having the tools to investigate the kinds of technology that we have now. And then it moved from those sort of clinical and descriptive and some biochemical approaches into protein based studies and cellular studies. And then from there it moved into the DNA, genome studies. And that was in the late 70s, early 80s that molecular genetics really started to move.

Andrew Hoffman: So how would you maybe characterize the transition. Was it something that you were able to see while you were --

Dr. Rima Rozen: Yes, yes. I mean, and that -- the reason I mention it to you is because, I had literally been -- I mean, I won't tell you, I was gouging eyes at some point to get blood from mice, and then looking at amino acid patterns or whatever in Charles' lab, as well as examining their urine for whatever. That's all the people -- fluids, I mean, that was an easily accessible tool and that's what we did.

When I moved into Gordon's lab, it was protein biochemistry, and starting to run gels and looking at RNA. But then when I moved into Yale, it was DNA, and DNA is here to stay.

Andrew Hoffman: Already at the same time, so McGill was maybe a little bit behind --

Dr. Rima Rozen: Yes, exactly, exactly.

Andrew Hoffman: Not to put words in your mouth.

Dr. Rima Rozen: No, but McGill was not yet -- at least certainly not all areas of McGill were working in molecular genetics. And in fact, that was more or less my mandate when I came back from Yale to McGill and started on staff here in 1984; I was supposed to bring molecular genetics to this hospital.

Andrew Hoffman: Okay. So you arrived in 1984.

Dr. Rima Rozen: Back here at McGill.

Andrew Hoffman: Back here at McGill, where you came from Yale and you set up your research laboratory at The Montreal Children's Hospital.

Dr. Rima Rozen: In fact, I worked at the Stewart Biology Building for a year, because when I was coming back, there was nobody here doing any molecular genetics, and starting out as a brand new -- every time I moved from one lab to another it was a different project, and when I left Yale, I didn't take anything with me, and in fact, that's a long story, I am not going to go into that, but --

Andrew Hoffman: Like physical things.

Dr. Rima Rozen: I didn't bring any physical things. I didn't even bring anything. I mean, yes, you learn the technology, but very often when a postdoc trains and does proper training in a lab, they usually work on a project that they can actually take with them, that becomes their work and their project as an independent investigator, and in fact, that's part of our mandate. If we have postdocs that are ready to start on their own, they should have a little project that they could take with. And that didn't happen for -- I don't want to get into that.

So I didn't have anything to start on when I got here, I had to start from scratch, with a brand new area and a brand new project, and write up grants on something that I had not worked on before.

Andrew Hoffman: Which is --

Dr. Rima Rozen: So it was challenging.

Andrew Hoffman: So when you first arrived, what kinds of things did you --

Dr. Rima Rozen: Well, I had to sort of figure out what I was going to do. I actually ended up starting to work on an enzyme in folate metabolism with Bob MacKenzie, who was not a Group member for many, many years. He only became a Group member in the very recent past. But simply because I was interested in genes and metabolic disease and whatever, and I sort of went to Bob and started talking to him and writing out this project. But it was brand new, and in fact, quite frustrating to have to come here and start from scratch.

So anyways, I did that. In 1985 I got my first grant. I mean, I got another salary award at the start of grant, when I first arrived, but in 1985 I picked up my first CIHR grant, I believe.

Andrew Hoffman: So your startup grant was basically to help open the lab that you --

Dr. Rima Rozen: My own lab, right. I got a salary award from the FRSQ, and those salary awards come with 25,000 to start your lab or whatever, and in that interim, I don't remember what I did. But then I figured out what I -- another grant to work on, and I put an application. I got my first independent grant in -- I mean, first MRC

grant in 1985.

Andrew Hoffman: With the money that you got though for the startup grant, what kinds of things did you get for your laboratory? Presumably you had to buy --

Dr. Rima Rozen: Some minor equipment.

Andrew Hoffman: What kind of equipment, was it more of the traditional equipment?

Dr. Rima Rozen: No, it was more molecular equipment. But not a lot, and I didn't want to work here, at least to get going, because there was nobody here that could give me any guidance in the molecular genetics area. So the deal was that I would work for a year in the Stewart Biology Building, where presumably they were more molecular genetics programs to get me started, and then I could come back here.

Andrew Hoffman: So that was 1985 that you came back here?

Dr. Rima Rozen: Right, but I became a professor in 1984 of this department, it was just physically I was in the Stewart for a year and then came back physically to this place in 1985.

Andrew Hoffman: So you showed up in 1984 as an independent investigator.

Dr. Rima Rozen: No project.

Andrew Hoffman: No project.

Dr. Rima Rozen: I would figure something out.

Andrew Hoffman: But you did two things, you had your own lab, but you also established the Molecular Genetics Diagnostics Service as well.

Dr. Rima Rozen: Right, right, and that was largely R&D at the time; it was in fact a research activity, because this was not something that was done routinely. It was really related to the work I had done at Yale, so it gave me the credibility to do that. It was an interest that I had as well, and so I set up this service. We started in 1985, and I worked on it until 2003.

Andrew Hoffman: And you also had to populate that service with new technologies.

Dr. Rima Rozen: Right, get money for the service. So it was all R&D money. I had an FRSQ grant, and then whatever bits and pieces. And then some hospital money, because diagnostics was not routinely funded. But nonetheless, there was credibility, and we were offering a service, and we did actually get money from the provincial government one way or another, I can't remember how it was, but we were one of the first labs to actually get some established funding for the service.

Andrew Hoffman: And that's FRSQ?

Dr. Rima Rozen: FRSQ is a research agency, so FRSQ gave us money for R&D. So we used FRSQ money for some work, then eventually, after we established the credibility and it was clear that the research was no longer research, it was really more service-oriented that we --

Andrew Hoffman: Clinical or --

Dr. Rima Rozen: Exactly, so that we went through the hospital, to some ministry rather to get funds for service.

Andrew Hoffman: So is that then maybe the $8,400 you got from the Faculty of Graduates?

Dr. Rima Rozen: No, no, that was a piece of equipment or something, it was not --

Andrew Hoffman: And I was looking at the amount and saying, well, you got 12,500 from --

Dr. Rima Rozen: No, it was 50, 60, I can't remember what it was; it was enough to get a technician to run this. I mean, I stopped working in the lab essentially, so I had to have money to hire technician for the service. So I did have one starting in 1985 or 1986, whatever it was.

Andrew Hoffman: So I guess the funding was basically coming from different places for these two different --

Dr. Rima Rozen: Right, exactly. So my research, my own real research was funded by the MRC, but then the Diagnostic Service was funded, either through FRSQ R&D grants or small amounts here and there, or hospital based, whatever, fund, support, various ways.

Andrew Hoffman: And how did the tools that you had in these different places, both in your lab and in the Diagnostic Service, relate to the kinds of questions that you were asking at the time in your research I guess?

Dr. Rima Rozen: I wouldn't say there was a lot of overlap. I mean, it was all under the umbrella of molecular genetics, but that's a big umbrella. Diagnostic service is all DNA based. So you isolate DNA from blood or cells or whatever, and then you test a patient for a particular mutation or a deletion or polymorphism or whatever.

Research, at least my research, was never limited just to DNA, so particularly in the basic sciences, it was always, you did RNA, you did proteins, you looked at RNA, you did sort of the realm of the molecules. And you used mice or you used cell culture, whatever, to address specific questions. So diagnostic work is uniquely focused on DNA, because that's really all you have access to with patients. RNA is a tissue specific. I don't know how much molecular biology you

yourself know, but --

Andrew Hoffman: I know about cytogenetics and that's it.

Dr. Rima Rozen: Well, okay. But DNA we have in all cells, and your DNA is essentially identical in all cells and tissues. DNA then gets -- is the blueprint for synthesizing RNA, but that's specific to a particular tissue. In other words, you don't have the same RNA in all your tissues. So you have RNA for genes that are expressed in liver, you would find the RNA in the liver, you won't find them in the kidney. You have a brain RNA that's not expressed and whatever.

So we use DNA, because you can then get blood, and it reflects the DNA in the rest of your body, whereas if you get RNA from blood, it's not necessarily going to reflect the RNA composition in the tissue where you have the disease.

Andrew Hoffman: So if you are looking at liver cancer --

Dr. Rima Rozen: Exactly, if you are looking at Cystic Fibrosis, which is what we worked on for many years, which is a pulmonary disease, I mean looking at the RNA and blood is not going to tell you anything. So for genetic diagnosis of disease we use DNA.

Andrew Hoffman: And was there a relationship between the work that you were doing in the diagnostics lab and the work that you were doing in --

Dr. Rima Rozen: At the beginning maybe --

Andrew Hoffman: Maybe helping you identify interesting cases or something like that.

Dr. Rima Rozen: Well, we did some population studies, because in order to -- I mean, I always had a basic science focus, so my grants were very often in terms of identifying mutations or cell studies or mice studies or whatever.

But we also often had additional funding to do population genetics, for example, because some of the things that we identified when we first started doing diagnostics was the kinds of mutations that we were more likely to find in our population, meaning the Quebec population, which is obviously unique genetically. So that we identified the proper spectrum of mutations that we would want to screen for in French-Canadians, shall we say, or mixed population, whatever, which might not be the same spectrum of mutations that you would test for elsewhere in the world.

So we had a handle on that. We did a lot of research in Cystic Fibrosis. We did a lot of PKU studies. Obviously, Charles was interested in PKU, but we did the molecular genetics. In other words, we defined the mutations that were present in the French-Canadian population, so that it would be more amenable to diagnose the treatment that was more specific to the individual genotype.

Andrew Hoffman: So you said Charles did -- you guys did the molecular genetics for the PKU studies and Charles was doing more of sort of --

Dr. Rima Rozen: Well, it was always just patient oriented treatment, and he was also more interested in the history of populations, which we obviously collaborated on, because in order to do the history of the population, you need to look at mutations, but he wasn't a molecular geneticist; he couldn't supervise any of the molecular genetic work. So we actually had a student, who was at our Group thing, who actually worked in my lab and did all the mutations and identified mutations, but then he would discuss sort of the history of populations or demographics with Charles.

Andrew Hoffman: So to kind of recap a little bit, beginning in 1984, you had a research grant to work on a project doing these genetic analysis of multi-functional protein and folate metabolism?

Dr. Rima Rozen: That was where I started, yeah.

Andrew Hoffman: And that theme sort of continues for the next many years of your career.

Dr. Rima Rozen: A little while. And then I moved into PKU and CF population genetics, and then from this early --

Andrew Hoffman: So these are kind of more applied, would you say?

Dr. Rima Rozen: Exactly. The CF and the PKU is much more applied. And then, by around 1990, because of our work that we had done on this other gene and folate metabolism, we actually set off to clone this other gene, and that's been our focus since then. Since the early 90s we have been largely limited to this one very interesting gene, because it has an effect on so many different disorders. And we are also looking at dietary interactions with genetics and other mutations in the pathway, but we are looking at common disorders now, quite extensible.

Andrew Hoffman: So correct me if I am wrong, but there seems to be a kind of dichotomy in your work, where some of the things that you have done are very specific to the laboratory and other things have a more distinct clinical application.

Dr. Rima Rozen: Yes, right.

Andrew Hoffman: This is something that came up earlier, but I am trying to --

Dr. Rima Rozen: No, I have always enjoyed both, absolutely. And then at some point, unfortunately, I had to, because of all the administrative responsibilities and other things, I had to give up something, and I ended up giving up the diagnostic service in 2003. And do I regret it? Of course.

Andrew Hoffman: But that still exists, just under someone else's --

Dr. Rima Rozen: It still exists, under someone else's directorship and so on, but I don't have a role in it any longer. But yes, I am thrilled that I was able to start it and get it going. And do I miss it? Sometimes, yes. But it was time to give it to somebody who could really -- the service had grown to a large extent, I could no longer do it in my spare time, shall we say, because McGill doesn't pay you to do -- doesn't pay PhDs -- nobody pays PhDs to run services, you pay PhDs to teach and do research for bringing the grants. The Diagnostic Service wasn't going to be grants' revenue generator, so it became -- I had a focus, and once I -- certainly in 1999, when I became Research Director here, I just couldn't do it anymore, so I had to give up something, and it was that.

Andrew Hoffman: And in 1987, that was the year that you first became a principal investigator on what was then the MRC?

Dr. Rima Rozen: Right, it was still called the MRC Group at the time.

Andrew Hoffman: So it was the Medical Research Council Group on Medical Genetics. And despite your obvious interest, can you tell me maybe a little bit about how you ultimately became involved in the Group?

For example, were you recruited, or was it something that you yourself pushed for, did having your own lab at The Children's Hospital factor into that?

Dr. Rima Rozen: Oh, of course, and the fact that -- I mean, Charles was very instrumental in bringing me back to McGill. There had been this hiatus between the time I graduated from his lab and I went elsewhere, but I think in the back of his mind he always saw me as sort of potential recruit back to McGill and was very active in it and that's how I ended up at this hospital, to some extent.

So once I had come back and I had that history, as an undergraduate with the Group, and now I had my own area of research, plus the diagnostics, which was relevant, and again, nobody will remember this, but I was recruited back to develop molecular genetics, because nobody was doing it. And so here was this new skill, shall we say, or skill set that I was developing, that other members in the Group didn't necessarily have, maybe nobody did at the time, I can't remember. But at least I was bringing in an area of expertise that didn't exist, that was clearly going to be important and had to be incorporated into the Group for the Group to have credibility as a modern evolving area of research.

And was I interested? Of course. I mean, these were my mentors. It was very exciting for me to work with them as colleagues. I mean, here Charles was my collaborator as opposed to my mentor, and Peter Hechtman was a member of the Group, he had been my teacher.

So from my perspective, it was very exciting, and presumably I had a role to play

in this molecular genetics area that was developing.

Andrew Hoffman: And maybe they even relied on you a little bit for --

Dr. Rima Rozen: Well, certainly in terms of the molecular genetics that we did with Charles, that was a direct influence and something that he needed to get done in order to pursue this history of PKU or population history.

Andrew Hoffman: And about the time that you came with molecular genetics, did other people follow pretty quickly after?

Dr. Rima Rozen: Here? Yes. I can't name names, and I don't remember when Roy joined. Do you have the year that Roy became Institute Director here, was it 1994, 1995?

Andrew Hoffman: 1995 sounds right.

Dr. Rima Rozen: Okay. So with him coming, and that was his area of expertise. I mean he really developed the institute at that level, in terms of the resources that he had and the equipment that he was able to purchase and so on, so it certainly developed even more at that time.

Andrew Hoffman: But if that was in 1995, then there is still seven years really that you were --

Dr. Rima Rozen: Right. So what did I do? Well, we had a genetic service and I was involved. Yes, we were actually doing all kinds of little bits and pieces here and there.

Can I remember who we recruited in molecular genetics in those days? No, I can't remember, but of course I was a new recruit, I wasn't bringing people in; it was something that the Director of the institute had to do.

Andrew Hoffman: I mean, I guess the question was more of, if it was one person and then a flood or --

Dr. Rima Rozen: It wasn't the flood, the floodgates weren't opened, that's for sure. PhDs in the Department of Pediatrics are a rare commodity still, and in fact, I don't mind giving you a few sort of fodder here, a little bit of fodder here. But when I came back and Charles tried to bring me back, the Chair of the Department of Pediatrics at that time was not particularly excited about bringing a PhD into the department. Pediatrics, traditionally, is obviously a medical department, and certainly in those days PhDs were not as welcomed as MDs were, limited recruitments everywhere of course.

And so I am not sure that the Chair of Pediatrics at that time would have opened the door, shall we say, to 20 molecular biologists. I don't remember when he left, but certainly when Dick Hamilton became Chair of Pediatrics, we were more progressive, shall we say. Human genetics didn't exist as a department, so we didn't have recruiting power. So the only official recruitment was [in] pediatrics;

there was only a center for human genetics at that time.

Andrew Hoffman: So then there must have been some jostling in order to --

Dr. Rima Rozen: There was a little jostling, a little politics to get a PhD here in pediatrics and whatever. Fortunately, I managed to get my own salary award, so he didn't have to -- that was probably part of the deal, but I can't remember. If she gets her own salary award, would you take her into the department, and I did, so it was not an issue.

But would he have paid me voluntarily? Maybe, depends on how influential Charles was. But certainly the Chair at the time was not particularly hospitable to PhDs and molecular geneticists.

Andrew Hoffman: So once you were there though, did you feel welcomed, I mean obviously --

Dr. Rima Rozen: No, I must admit that in pediatrics in those days PhDs, particularly here, were somewhat removed. We don't have a lot of contact with the clinical staff. I did have contacts because of my service, so that was useful, but again, we were focusing on certain diseases, so I would only become familiar with the physicians that were involved with those diseases. In fact, because of our work at CF, I actually became quite friendly with the CF physicians in the province, because we were doing the service for everybody. Well, that's sort of the way genetics is going, and when we set up CF, we provided for the entire province.

Andrew Hoffman: So you basically acted as a central laboratory.

Dr. Rima Rozen: Absolutely! We were a central laboratory for the diseases that we were testing.

Andrew Hoffman: And that was CF?

Dr. Rima Rozen: CF. We started with the Thalassemias, and then later on we moved into Tay-Sachs, and a little bit of PKU, and MTHFR, that we now work on from the research lab, became a test, but just a test, but it was mostly CF for quite sometime. CF is a very high volume disease, with 1,000 and 2,000 or whatever --

Andrew Hoffman: There are so many different variants of it too, right?

Dr. Rima Rozen: So many different variants, and it's also particularly high in frequency in the Saguenay, about 1 in 900 in the Saguenay. So we were getting lots of samples, and just continued to grow at whatever. I am saying, at least I did enjoy my clinical connections, because again, probably some -- I was an inspiring medic obviously, but --

Andrew Hoffman: How long did the diagnostic lab sort of act as the central lab for the province?

Dr. Rima Rozen: Oh, it still is. No, for certain diseases, it still is the central diagnostic lab for CF,

for Tay-Sachs, for PKU. Now, maybe some people are providing little bits and pieces, you get these little research area, sometimes a particular physician wants to develop something. But in terms of centralized routine service, no, we were doing the province, still do so.

Andrew Hoffman: I didn't know that, not that I am an expert on the history.

Dr. Rima Rozen: In terms of genetic diagnosis, it makes sense to have a centralized laboratory, there is no point having three labs doing CF with different quality controls and different techniques and whatever.

Andrew Hoffman: Did you, kind of, develop your own standards within the lab though for --

Dr. Rima Rozen: Oh yeah, absolutely, yeah. I mean, it didn't exist when we started. When we started the gene hadn't been cloned yet, so we were doing CF diagnosis by linkage analysis, which, I am not going to go into it, but the point is, the gene hadn't yet been cloned, so we were doing sort of markers.

And then the gene became cloned in about 1989, and then we could test for mutations directly, so we switched our procedures to direct testing, and then we enforced carriers, prenatal diagnosis, and we were running a routine service, even though I wasn't -- I had not been specifically trained in laboratory management or anything, but at that point, I don't know if you are familiar with the Canadian College of Medical Geneticists.

Andrew Hoffman: Are you a member of that?

Dr. Rima Rozen: Yes.

Andrew Hoffman: That's about the extent of --

Dr. Rima Rozen: Yeah. Okay. It's an organization that grew up to train and foster the medical side of genetics. It wasn't an official specialty for many years. It wasn't a real college specialty at the time. So it was a Canadian college that was founded by people like Clarke Fraser. I know Clarke Fraser was quite instrumental, I don't know about Charles.

So they created this college for people with different genetic backgrounds to work together to develop procedures to support the use of genetics tools, spread the discipline around, and so on.

Andrew Hoffman: And about what year was that initiated?

Dr. Rima Rozen: Well, the college -- but they have a website, probably in the 70s.

Andrew Hoffman: So it was pretty much there by the time you had shown up?

Dr. Rima Rozen: Right, but it hadn't been doing a lot of molecular yet, because molecular was quite new, and that was the only area that I was really familiar with. But they had started developing the difference subspecialties. And by that time they had developed a subspecialty in molecular genetics. They have actually four subspecialties in the CCMG: Clinical, Biochemical, Cytogenetic, and Molecular. And it reflects sort of the history of genetics, that first it was only clinical, then more about -- molecular genetics being the last one that was developed as a subspecialty.

And there were some individuals who were trained and were certified at molecular genetics at the time. So there was this subspecialty, and so that's when I wrote the exam to become certified in molecular genetics and be able to offer the service with some sort of credibility.

Andrew Hoffman: Was that the year that you showed up or that was --

Dr. Rima Rozen: No, it was later. In 1990, I actually wrote the exam. I am not sure they had developed molecular genetics enough, I don't know. It's a formal training program. You are supposed to now spend a year-and-a-half or two years in a certified laboratory to learn the technique, but because it was just developing and I had already done a fair bit of it at Yale and then with the service here, they gave --

Andrew Hoffman: You were grandfathered in.

Dr. Rima Rozen: No, not grandfathered. I had to write the exam. Grandfathered means -- Charles was grandfathered, he didn't have to write an exam, they just developed the college. But I didn't have to take the training because they accepted my sort of on the job and my director qualifications as having done enough training, but I had to write the exam just like everybody else. And that's what I did and got my certification in 1990.

So we were the first accredited -- I mean, I was the first accredited director in Quebec in molecular genetics. So I was really the only one who could really offer the service.

Andrew Hoffman: So not only did you bring molecular genetics to McGill as an institution more or less --

Dr. Rima Rozen: Well, I won't say McGill, I would say the hospital. A lot of people doing molecular genetics, biochemistry or wherever, but not in the hospital, certainly not The Children's, so I am going to say Children's.

Andrew Hoffman: Okay, Children's Hospital, but you also basically brought it to the college itself, sort of, you were the first --

Dr. Rima Rozen: Yes, the subspecialty, and I stayed as the only accredited molecular geneticist for

many years in Quebec. I think finally in the late 90s or maybe 2000 or whatever, there were one or two more people becoming certified in that area.

Andrew Hoffman: The Diagnostics Service benefited though from your membership in that.

Dr. Rima Rozen: Yes, absolutely, because we have the credibility to offer the service. A lot of people were offering services on a research level, shall we say. And I am not saying they were not equally qualified. A lot of good people offering services. I am not saying we were better, but we passed the test by sort of the national standard.

Andrew Hoffman: And do you feel like the work that you did there has sort of helped bring molecular genetics elsewhere in the province and to different kinds of practices?

Dr. Rima Rozen: Yes, it has become routinely accepted as the service. Molecular genetics was -- nobody thinks about molecular genetic testing for their favorite disease. This was the first lab that was sort of routinely offering it as an accredited service, but it might have only been familiar to those that were doing CF or Thalassemia or Tay-Sachs or whatever, but certainly we were recognized as a provincial lab, and that brought molecular genetics, and I might add, some funding to the hospital here to do molecular genetics. We were one of the first, maybe the first, I don't remember, to get an actual hospital based budget, because we had been doing it for so many years.

Andrew Hoffman: And this is in the clinical realm.

Dr. Rima Rozen: Right.

Andrew Hoffman: So there's only a couple of more questions.

Dr. Rima Rozen: Boy, you are really going into history. We haven't touched anything in the last 20 years at all.

Andrew Hoffman: I know, it is an oral history. We want to make sure that --

Dr. Rima Rozen: It is history, I suppose, yeah, and now you are stretching my poor brain cells. Okay.

Andrew Hoffman: We know what's been going on in the past few years. You did the interview in 2008 with the British journal, Pharmacogenomics, I believe.

Dr. Rima Rozen: Oh! Okay. Well, are you talking about in terms of molecular genetics or my research or --

Andrew Hoffman: Well, this next question is actually about you as an individual coming to work with the Group. So as far as I can tell, maybe aside from Dr. Tenenhouse, you are really the only woman who was involved with the Group.

Dr. Rima Rozen: That's right, she and I were the only female members.

Andrew Hoffman: Were you a member before her, technically speaking?

Dr. Rima Rozen: Good question. I had all this --

Andrew Hoffman: I probably have the dates and --

Dr. Rima Rozen: Yeah, I have the dates somewhere too, I swear, I don't remember.

Andrew Hoffman: Because I guess I would just ask you to --

Dr. Rima Rozen: No, she must have been a member before me. She was a member before me, absolutely. I now remember the pictures. Yes, she was a member before me.

Andrew Hoffman: So given what seems to be a minority status within the Group, if not within the hospital at large, was the issue of gender ever something that was obvious to you?

Dr. Rima Rozen: I must admit, I have never really encountered any -- at least not any overt bias. What people say behind close doors, I have no idea.

Andrew Hoffman: And clearly it doesn’t seem to have impeded your --

Dr. Rima Rozen: No, it has never influenced me one way or the other. I don't really think about it frankly. It never occurred to me that I should be treated differently. I just did what I had to do and I never worried about it.

Andrew Hoffman: I guess it seems that, more so, dealt with your life decisions and the things that you wanted to do, like you said, to give up something in order to have a family and that kind of thing.

Dr. Rima Rozen: I am not going to say I haven't given anything up but -- well, I suppose yeah.

Andrew Hoffman: Or make certain decisions.

Dr. Rima Rozen: Right.

Andrew Hoffman: Sorry.

Dr. Rima Rozen: It's a compromise, certainly I will say that, that there's clearly a difference in being a female in research and medicine, no question. I have often said to myself, gee, I wish I had a wife at home. That when I came home would sort of make my supper and take care of the kids and whatever. I don't have that luxury. So I have had to be the wife at home as well as researcher or professional or whatever.

There's no question that women do not have the same -- they have intellectual potential, but they don't necessarily have the same potential, given that many of us have a fulfilling home life and a fulfilling professional career. So there's no question in my mind that women have to work harder.

So the women that do make it are a different breed to some extent. Not so much nowadays, it's very different, but certainly before. You have to have certain skills that men don't necessarily have to have.

Andrew Hoffman: Such as?

Dr. Rima Rozen: Time management, compromise, be willing to adapt. I think just the time factor is really the issue, and organizing your time is really a critical issue.

Andrew Hoffman: Now, this is kind of going back a bit, but since we have been talking about the Group now, and I guess for you maybe historically, but in general, in more recent time, there are these two approaches and various people in the department have been around for varying levels. You brought molecular genetics, for example, to the Group. But there were people who are your seniors, who you have worked with, in the earlier parts of your career as well, such as Dr. Fraser and Dr. Scriver.

Dr. Rima Rozen: I never actually worked with Fraser, that was --

Andrew Hoffman: You did not?

Dr. Rima Rozen: No, never directly.

Andrew Hoffman: But here you did? No? Not during your degree, but in the Group presumably?

Dr. Rima Rozen: Well, I am trying to think, it's possible that he was a co-Director for one of our Group grants in which I was a junior member. But did I actually ever really work with him? No.

Andrew Hoffman: Okay.

Dr. Rima Rozen: I am not -- overlap for them, if at all. So he was there, but I am not sure he was necessarily a Group Director at the time that I was in.

Andrew Hoffman: So then the question that I am about to ask might not necessarily apply to him, but was it the case that those older members of the Group who didn't necessarily work with molecular genetics before you showed up continue working with more traditional methods, for lack of a better term, while new recruits, such as yourself, and maybe those who came after you would work within the more recent paradigm? Could you possibly characterize like the groups or subgroups within the MRC group?

Dr. Rima Rozen: Well, it has been such a long history that certainly the more recent history has all aspects of genetics within the group, but it certainly became more and more molecular over the years. So that if you look at the last ten years, shall we say, all investigators were doing molecular.

Now, Charles wasn't -- I don't think a member -- wasn't a member in the last one round or two rounds or whatever, so I think everybody was literally doing molecular genetics, because nowadays science covers all areas. In other words, is not exclusively molecular.

Those of us that were in the Group, let's say in the last round, we did at every level. We worked with proteins. We worked with DNA. We worked with mice. We worked with people. We were supposed to sort of do it all. But in the earlier days, I would say that people were more specialized in the sense that they tend to certainly -- Charles' expertise has always been metabolic genetics and biochemical genetics and so on; he has never done cytogenetics, of course neither have I.

But as the field progressed; he may have taken on some individuals in his group that could do the work, he himself was not necessarily an expert in it.

But that's the same thing even now. There are people in my lab doing things, even with molecular genetics, that I have never done in my life. So we all evolve. We don't necessarily do it hands-on, but we learn the literature and we learn from our students, and that's why it's nice to have a group, it's nice to have trainees, because they essentially teach you, not how to do it, but at least to understand and interpret it and so on. Which is why a group program or a large group, if you can afford to have eight or ten people in your lab, is very nice, because you learn from the younger people in the lab.

So I am not sure I answered your answer but -- to avoid it. I think everybody evolves one way or another to learn what they need to do to get the job done, shall we say.

Andrew Hoffman: But given the structure that scientific education, especially at the doctoral level, how it happens, it seems that your answer indicates that inevitably that's going to be -- that has been the case for a long time, and that it might always be the case, that so along as there is more junior colleagues working with the newest technologies --

Dr. Rima Rozen: Exactly, exactly, exactly, that we have to evolve with them, that they help us evolve into better scientists.

Andrew Hoffman: Even while people were working on different kinds of things, did that affect the way that the Group's material was published, for example? So was certain research published mainly in journals devoted to molecular biology, and others

just the basic sciences, or clinically oriented journals, for example?

Dr. Rima Rozen: I think certainly everybody's expertise was reflected in the nature of the journals that they published their papers in, yes, of course. But the Group structure that was interesting for us was not necessarily that we all had to collaborate or we all had to do the same things, the success of our Group was in fact based on the fact that we had our own projects, we had our own diseases, we had our own technologies.

So why were we a Group? Well, because we all took a clinical problem and tried to dissect it in the best way that we could do it, and some of us used one approach, others used different approaches, but that was our goal. We started with a disease and we tried to understand it. And that's what was so good about the Group's program, at least in those days, we didn't have to work on the same theme, whereas nowadays, when you have team grants and platforms -- well, I won't say platforms, but team grants and so on, you take a theme and you beat it to death, which is fine, it's a different approach.

So now you may have a team grant on diabetes, so you have ten people working on diabetes and they all approach different aspects of the same disease. There is nothing wrong with it, but I am saying the group's approach, we all worked on seven different diseases, each of the seven -- sometimes we overlapped a bit, but we worked on different diseases. But that's what was the interesting thing that we learned from each other in terms of the different diseases.

I mean, I became -- I learned more about bone than I ever would have learned otherwise. I learned more about mitochondrial disorders from Eric Shoubridge and whatever. So we didn't work on the same projects at all; we worked on very different diseases, but sometimes the approaches were similar and we learned from each other.

Andrew Hoffman: But when you say that there was a clinical problem at the heart of the Group, for me that was --

Dr. Rima Rozen: Yes, everybody had their own clinical problem, that's my point, that's my point. Everybody had their own clinical problem, clinical disease.

Andrew Hoffman: Okay. So not a central unifying clinical problem, which as you say is actually --

Dr. Rima Rozen: Exactly, I was contrasting with the way team grants are structured nowadays. We want to put money into diabetes, the government decides. So everybody works on diabetes, everybody works on cancer, whatever. We had our own diseases, but we were all interested in the same questions and answers. How does this person get the disease? Which gene is it? Which nutrient is it? Which metabolic pathway is involved? Is it treatable? What can we identify in terms of targets to make it treatable? What are the issues at the level of the protein, at the level of the cell, at the level of the in vivo, mouse as the substitute for

human? We all had the same questions but we applied it to different diseases, so that's what was very interesting.

Andrew Hoffman: But you also had different ways of doing it, no?

Dr. Rima Rozen: Sometimes, yes, but we all sort of evolved to do it in the best way that we could. And if you were a young scientist and developing, then you basically picked up the tools of molecular genetics. That doesn't mean you gave up your protein studies or your patient studies, but you explored things at newer, newer levels depending on the technology.

But obviously, depending on the time when you came into the Group, I mean, if you look at the phases and so on, certainly those that started early on, I mean, Charles wasn't going to be a molecular genetics expert, he may have picked up some of the techniques, people that came in sort of in here may have started in protein chemistry or whatever and they retained their protein chemistry skills, but then they sort of also adopted the newer technologies.

Andrew Hoffman: That was actually my next question which you preemptively answered. So it wasn't that the basic science folks were only working amongst themselves and that the clinical folks were only working amongst themselves.

Dr. Rima Rozen: No.

Andrew Hoffman: Do you think that, that was kind of the way that it worked in a different area than it works now is maybe an artifact of -- I mean, it seems to me that it wouldn't, but an artifact of the way that the knowledge base was structured. So now molecular biology, as you said, within the past ten years, everybody comes in doing molecular biology. When you started, not everybody was doing molecular biology, in fact, you were pretty much one of the few. So that applying maybe for grants with that kind of less developed -- I mean, I don't know, you know more about it than I do, but the level of development of the field itself and the way that it could be applied was still maybe a bit more vague than it is today, and that's why funding might be more generous across a larger spectrum.

Dr. Rima Rozen: No, I think funding models have changed. We just don't have as much funding as we used to, on a per capita basis. I mean, yes, there is all kinds of new initiatives and so on, but I think we are focusing more on big science, big platforms, big technologies.

Andrew Hoffman: Platforms in what sense?

Dr. Rima Rozen: Platform meaning a big technological platforms, shall we say, core facility. There is a lot more focus on that, and on big science, and big groups, and big teams, all focusing in one area, whether it's cancer, diabetes, and so on. We were essentially individual investigators, because we didn't work on the same theme and that --

Andrew Hoffman: Contradistinction to platforms or --

Dr. Rima Rozen: Or grew large targeted -- there is a lot more targeted science now. There is also a lot less in terms of fundamental questions. So much of what we get now is targeted, and there is this constant battle now between, how much do you give -- in CHR, for example, how much do you give in terms of the basic science and fundamental discovery questions, compared to the translation or platforms or big science priorities, the government, and so on, as opposed to just letting people do their thing, knowing they are going to come up with something interesting at the end of it. Obviously you have to fund the right people, but sometimes you fund the right people and you get all kinds of surprises, good surprises.

Andrew Hoffman: So while you were all kind of working on your own things, the Group was all pretty much in the same geographical location. Now, I guess this is --

Dr. Rima Rozen: Early on, yes, when we started to spread out more, because we weren't necessarily recruiting into genetics as much as we would have liked at The Children's. Plus, genetics was becoming important in many different areas on campus and so we obviously wanted to make sure that we had the best individuals in our Group, and weren't limited to those at The Children's necessarily.

Andrew Hoffman: But you and Scriver were still at The Children's.

Dr. Rima Rozen: Well, I have been at The Children's the entire time, so has Charles. And then Roy came of course to The Children's as well. So the directorship was always based here at The Children's, but we picked investigators who were interested in the same kinds of questions as we were, and they didn't necessarily have to be in the same physically at The Children's.

Andrew Hoffman: Were there concerns that it would impact your ability as a Group to get funding, for example, by sort of being more diffusely --

Dr. Rima Rozen: There were some concerns, it wasn't so much more the physical location that was an issue, it was more -- I guess we were feeling the pressure to identify people who were similar in terms of the kinds of disorders that we were studying, to make sure that there was a sort of a nucleus of activity that would be attractive to the agencies.

In other words, we had a little focus on a few people. We had some focus on folate, there were several of us, folate and Vitamin B_{12}, there was sort of a little focus on metabolic disease or whatever. So we tried to develop little foci just so that we could present ourselves as having a cohesive structure, shall we say. So there was some selection on that basis as well.

But it was always the science that drove our choices of investigators and that drove the application in the end, and I still see that a lot. I am pleased to say that many of the reviews and programs that I have been involved with as an administrator and so on, very often the science still does win out. The excellence wins out. It's not the politics or it works on who their friends are; it's still the excellence that is often a criteria in that, that is rewarded.

Andrew Hoffman: Which I guess is good. Finally, the last question, given the shift then that we have sort of been talking about, from traditional Mendelian genetics -- the shift from Mendelian to being more focused on molecular biology, and considering the Group's relationship to Fraser and Scriver, how it played out with regard to their more clinical interest, so they still continued on working --

Dr. Rima Rozen: On clinical problems, as did the rest of the group. As I said, what tied us together is that we were all interested in a clinical problem. We just performed our experiment in different ways, shall we say. More and more of the experiments were largely molecular as the Group was younger and brand new for people. But it always had a clinical bend. That was the success of the group, it was always medial or clinical.

We kept that word medical -- it was the CIHR Group in Medical Genetics, to stress that, that we all started with some disease, we just approached it in different ways, more and more as the technology became driven by molecular genetic strategies. We all used those strategies, but it didn't really matter, because it was always a clinical question, and we were answering it as was relevant to the topic.

I mean, some topics are more amenable to non-molecular approaches, other topics are more amenable. So that's where the excellence comes in, that a scientist will use the right approaches and will learn new ones as required to test a hypothesis related to a particular disease.

Andrew Hoffman: So it wasn't then the individual scientists who were getting the grants to work in the laboratory?

Dr. Rima Rozen: It actually changed over the years. I think in the early days it was a group grant and we only applied for a group grant. I don't remember when that ended. Probably in the early 1990s, once I started, I started in 1997, whatever. But at some point, in order to receive funding as a group, we also had to be successful at the individual grant level.

Andrew Hoffman: So the second phase maybe was applying for group, but in order to get the group you would also have to be applying and getting funding as an individual.

Dr. Rima Rozen: Right, and that took away this notion that somehow we were getting preferential treatment, or we weren't being reviewed by the same criteria as the regular panels. So now we had to undergo both. We had to be reviewed by the

regular panels, just like the rest of the world, and then on top of that, we would go through a second round for group funding. So we were actually reviewed twice in a sense.

I would undergo review in my own individual grant, my own individual topic, in a particular committee, and then every five years or whenever the group grant expired, we would apply as a group, and we had to show that each one of those members within the group had their own operating grant.

Andrew Hoffman: But you never really drew the distinction between basic science and medical/clinical concerns?

Dr. Rima Rozen: No, basic science was always to address medical questions. Basic science is a tool. Basic to me means -- some people use the word basic working as a molecule.

Andrew Hoffman: I mean, more strictly laboratory, where as like you said, Dr. Scriver was more of a clinician?

Dr. Rima Rozen: Right, but he also had -- he used a lot of laboratory work to answer questions, he wasn't strictly looking at patients at Charleston.

Andrew Hoffman: Okay. One more, this one is really quick. With regard to your publishing, there seems to be sort of -- or was there kind of a divergence between what you were working on and what Dr. Scriver and others were working on? Because if you look at sort of a map of the publishing records, there seems to be a cluster where you are and then a cluster where Scriver --

Dr. Rima Rozen: Because they were different topics completely. Charles never worked on folate ever, and all our work since 1987, different enzymes, different whatever, pathways, but always with -- I have worked on folate for many years; Charles has never worked in that area.

In addition to my folate work, I occasionally did other subjects, where I collaborated with Charles, whether it was the PKU or whatever story, but the particular focus on folate did not have anything to do with Charles. In fact, I must admit that, that was -- certainly that was a motivation that when you train with someone, you really should be working in an independent area. And even though I started doing some PKU stuff with Charles and whatever, it was clear that I had to develop my own area, so that I would not be considered part of his group, shall we say, or part of his influence. So I started working in this folate area, which was totally unrelated to Charles.

Andrew Hoffman: So it was kind of a move of professional sovereignty and things.

Dr. Rima Rozen: Yes. You have to do that, everybody has to do that. Sometimes it's more difficult, because as I said before, some people come from their postdoctoral training and

they develop their own area of expertise in that same area, and then sometimes there is a question, if you continue to collaborate with your former supervisor or you publish together, there is always this question of independence.

So this particular area, in folate, fortunately or unfortunately, had nothing to do with any of the training that I had ever had. So yes, it clearly demonstrated independence, on the other hand, I didn't come with any tools or materials so that I could start quickly, I had to develop it on my own. But nonetheless, it's now my own. There is no question of Charles having contributed to it, or any of my other supervisors, they had nothing to do with folate, so in that sense I am gratified. But it was hard in the beginning, no question.

Andrew Hoffman: Okay. Well, those were all the questions that I had for you today.

Dr. Rima Rozen: Today?

Andrew Hoffman: But maybe a follow up to clarify once --

Dr. Rima Rozen: Fine. And they were clearly different questions and there were issues that I discussed with Chris, so you are okay, okay in my books.

Andrew Hoffman: I am glad. Okay. Good!

END OF INTERVIEW

Dr. Charles Scriver, March 2, 2011

Andrew Hoffman: My name is Andrew Hoffman and I am here with Dr. Charles Scriver in the Department of Human Genetics, March 2nd, 2010. It is my great honour and privilege to be with you today, Dr. Scriver, to discuss broadly, well, less broadly I guess, more the first part of your career as well as your more family background and that kind of thing, since we have already covered in the past, it's on-record and things are good there.

So beginning basically with where you were born, where you are from, where you grew up, and the kind of schooling that you did, to basically draw the focus in a bit to see how your personal history for example has influenced your academic work. And hopefully without interruption.

Dr. Charles Scriver: I was born on November 7th, 1930. I was born into a three-generation family, with my father's parents living with us, as a result of economic difficulties at the time. It was an interesting family to grow into with hindsight, because both my parents were professionals, in medicine and on faculty at McGill. And I will come back to those details later if necessary.

I went to school in Montreal, first in the local grade school in the street that I lived. But later at a rather special school called Lower Canada College which had a high academic profile and aspiration. And I would say that my education at that school didn't do me any harm, it certainly allowed one to excel.

When I graduated from high school, I went to McGill, and I registered as a Humanities and Arts faculty student, and I majored in Geography and Comparative literature. I certainly loved the experience while it was happening and with hindsight. I do not edit or change that opinion, and I did think when I graduated from my Baccalaureate degree that I would be a geographer, because McGill had one of the great geography departments of the day.

And as it happened, there was no pressure put on me by my parents; that's a true fact, but I observed them and noticed that they were extremely happy in what they did. They loved medicine, they served the patient, the family, the community. They thought that was the right thing to do in the world we lived in and so they were interesting role models, and I guess honoring them maybe, I don't know what the conscious motivation was, I applied to study medicine, and in those days, you didn't do all 16 medical schools. I applied to one school, McGill, and sort of waited to see what would happen, and they accepted me to be a student of medicine at McGill.

So I joined the group. It was an extremely interesting time. We are talking about 1951. I graduated in Arts, as I said, and the class that I joined was so

different from the class that I had been in, in the Humanities and Geography stream. I was a fellow student with a stream of Americans who were using up their last year's opportunity for the GI Bill of Rights. These were experienced students.

These were people who had seen the best and the worst of human behavior, and conflict, and combat, and I think their values must have had some impact on me. But anyway, I really enjoyed the study of medicine. I saw it as a degree in Human Biology, and I was good at it. I was endowed with brain power through my Biology, but I was also given the opportunity by circumstance to pursue medicine and enjoy it.

So now I brought you up to the fact that I got my medical degree, so called M.D.C.M., which is a McGill nomenclature, and I graduated in 1955. I graduated in Arts. Now I was doing it in medicine cum laude, which there was some evidence of brainpower there.

Andrew Hoffman: If we can pause for a minute, you said that the people who were in your medical school class, in large part you said, Americans coming from the states who were taking advantage of the final years of the GI Bill, and that their values had impacted you. What do you mean or can you explain? I guess a bit about what kind of values those were?

Dr. Charles Scriver: Well, I think one of our concerns, again, spoken with the hindsight, because I can't say I recognized this when I was around at the time, but I think that the values of people like of my age and cohort, in the 1950s, would have been that going to college was almost a right for some people, and you could afford to be relatively trivial about it, and these guys who joined our medical class had been in combat in Europe and the East. They had seen death and hardship. They had been fighting for values that were made clear and apparent to them. And people like myself, [did] not [have] that experience, and therefore had not the perspectives that they had. They were serious people, most of them, which consciously or unconsciously, well, it had an influence on people like me.

Andrew Hoffman: And now I guess backtracking even further, before we go into the rest of your medical education, I have a note here that says that you are from a musical family.

Dr. Charles Scriver: I don't know where you got that note from, but my mother was the musician. I think in her young adulthood there was a choice of her being a performing musician as an accompanist; she was good and she showed piano facilities until her late 90s really. My father was not a musician. He was not formally trained, but he was the one who loved music and collected shellac discs of Mahler Symphonies and people even thought that was a sign of a insanity, and I think he communicated to me, a fundamental love of music. I had two friends at Lower Canada, We formed a trio. I played the bass, not well, but I

enjoyed doing it, and I developed in my young adult and late teen years, a great admiration for musicians such Duke Ellington. I would collect Ellington wherever I was, and I think I went on to appreciate some of the great figures, one of the cultural gifts of the 20th century, which was Jazz and after Ellington, I ended up collecting in my late middle life everything I could about Bill Evans, the pianist, and I listen to Bill Evans and Ellington still with great pleasure.

Andrew Hoffman: And so was this something that you were involved within school as well growing up?

Dr. Charles Scriver: Only in the last year when we formed this trio, and did gigs around the city.

Andrew Hoffman: So you took lessons or taught yourself?

Dr. Charles Scriver: Taught myself, not well, but it was pleasurable to me, and --

Andrew Hoffman: I guess at the end is this something that you still take interest in, are you still a fan of Jazz music?

Dr. Charles Scriver: Absolutely. I still listen to Jazz with intent, with some insight. The family musical interests, my wife was also very competent in music.

She could read it, and she was in the Choral Groups here at McGill. Of our children, one is a musician and has his name on a Grammy award disk as an engineer, sound engineer. Our first born daughter graduated in music and math from Mount Allison University. Our second daughter was a dancer, and was in Les Grande Ballet Canadiens de Montreal, so she got an injury, and changed the direction of her life after that. And our son who is, our first son, he is an architect on the faculty in Adelaide Australia. He loves music the way I do.

Andrew Hoffman: So, I guess it's something that's been passed down through the generations?

Dr. Charles Scriver: It seems to be yes. Either nature or nurture, but both obviously.

Andrew Hoffman: And so, I guess we are still backtracking a bit, but Lower Canada College was not a college per se, it was a high school?

Dr. Charles Scriver: It was a Grade School High school. You had to pass the exam to get in. It was, I would say it was not an equal opportunity school, because you had to pay fees, and they were not the lowest of fees in the Montreal region.

My parents believed in education, and so they were willing to spend the money to send me to the school. They believed it was better than others that I might go to because of proximity. And I've never regretted that.

I got exposed to literature, history, geography, science in ways that I suspect would not have been as available in the other schools in the neighborhood.

Andrew Hoffman: And were you a good student?

Dr. Charles Scriver: Yes, I was. And one of the great things about being a good student in that school was they had a prize giving ceremony at the end of each year, and the prize was a book, and you could pick the book you wanted, and I still have a lot of those books. But for me that was an interesting incentive, and for the rest of my life I've loved books.

Andrew Hoffman: And so this is maybe where your interest in geography first began?

Dr. Charles Scriver: Oh, yes. The Headmaster of the school, Stephen Penton, was one of the great educators in Canada; he taught geography, and he taught it brilliantly, and it certainly imprinted me.

Andrew Hoffman: Okay, skipping ahead again to the future, I am sorry that the --

Dr. Charles Scriver: That's okay, interesting questions.

Andrew Hoffman: I mean, Dr. Scriver, we are really trying to get -- it's an oral history of the group, but it's also an oral history of the group members themselves. So, if we can kill two birds with one stone, and you know, we never know who is going to come along doing research on geneticists, who like Jazz music for example.

So, you came to McGill, and actually studied arts, geography, it was something that you had intended to do, and then --

Dr. Charles Scriver: It was literature which influenced me forever after, I enjoyed Russian literature, not in Russian, but in translation.

Andrew Hoffman: And then eventually, like you said, coming, whether in tribute to your parents or whatever making the decision to ultimately study medicine instead, at which point you've gotten into McGill and you've done your education here.

Now you said, both your parents were physicians?

Dr. Charles Scriver: Yes. A little background on that. They were both bright, they had no difficulty with academic studies. My mother I think was being encouraged by her mother to do the traditional thing of become a missionary or something like that. And my mother also thought that the other thing she might have been encouraged to do was to be a teacher. She did not want to be a kindergarten or a Grade school teacher, and she discovered she did not want to be a missionary.

Her father who was the Chief Miller or became the Chief Miller of the flour

mills here in Montreal, said, you can do anything you want, just choose. And with that she said, I could study the Ogilvy courses that are necessary to give me qualifications to study medicine. And he said, go for it.

And she went down to Harvard and took both make up courses that were needed for enrollment, and she was enrolled, and as it happens; in the first class of McGill Medicine, to accept women students, because up to that point only men could study. She was one of five women, and guess what, they all ended up in the top ten positions of a class of 100. The selection pressure was considerable on these people.

When she graduated, she said, I had been given an opportunity to study, therefore, I have a responsibility to honor it. And she did. She did her, as it were, post graduate studies here in Montreal, she did some interesting basic work on sickle cell anemia. She looked at the nutritional factors in infants, and by 1930 she had a couple of papers in the literature. But people were saying, Jesse, these are not exactly frontline things in medicine, why don't you go and do something useful? I mean, that's how she summarized it to me once.

So she became interested in the immature, premature baby. She created one of the first premature nurseries in the country. And she became a great physician, she made house calls at any time of the day and night. She was a great role model for the women who came to study medicine thereafter. And she also was a good mother, the nice thing to record here is that she realized that she had been given this opportunity, and she had to honor it.

So, how could she be wife, mother and physician? And the way she did it, was she interviewed an extremely interesting group of women who had come out of Britain after the World War I. Their fiancée's dead or whatever, and she interviewed one of them, Effie Salter and my wife and I have subsequently said, we wonder who did the interviewing. Did Effie interview my mother or did my mother interview Effie? Because they were both professionals in their own way.

Andrew Hoffman: Yeah, and what did Effie do?

Dr. Charles Scriver: She was a governess I guess in that way. So, she came into our house in 1930 and that meant that my mother could after my delivery, could go back to being a doctor. And so I had a working mother, and Effie was the other part of the partnership in our family. Effie stayed with us for 16 years. She looked after my grandparents, she saw them both die in our house, she looked after my growing up with my mother, and she literally became part of the family.

My father was in the World War I, got typhoid, which saved him from being killed in the trenches, and he was demobilized, they lost his records. He reenlisted and he joined the Q-Boats, which were supposed to deal with the submarine problem. And he survived that, because that was the most

dangerous part of the Navy outside of the direct combat.

And he came back, and he took a double degree, an Arts degree and a Medical degree simultaneously. He loved the science side of medicine. He used to tell me his thoughts about the kidney as an organ of adaptation and evolution, and he became, in his career, he became Physician-in-Chief at the Royal Victoria Hospital, which was an admired achievement, and he was also a super physician. He and my mother were both great at listening to patients, and then working through what the problem might be, and giving them advice, and they both cared about all sorts of dimensions, the social conditions, the medical conditions and so on.

So eventually -- maybe we can come back to that later, but my father gave me the best advice, single piece of advice in my whole career, I'll tell you about that later.

Andrew Hoffman: Okay. I'll note it so we don't forget. So you finished med school in?

Dr. Charles Scriver: I'm now an intern, yes, 1955.

Andrew Hoffman: Okay.

Dr. Charles Scriver: I became an intern, the rotating internship in those days in the McGill system at the Royal Victoria Hospital largely. In `56, `57 -- `57, we had an innovation in the McGill Training System, and I was allowed to study medicine for six months and pediatrics for six months. So I got exposed to the pediatric side of the medical curriculum in some detail, and I liked that. I found myself even more comfortable in the pediatric stream than in the internal medicine stream.

I also got exposed to the Physician-in-Chief of Pediatrics, who was Dr. Alan Ross. Alan spelled, A-L-A-N, and Alan Ross was one of these extraordinary people whose ego never got in the way of him helping other people, and he created a community for those of us who were interested in pursuing the question, why does this person have this problem now, so that we can understand the origin and cause of the disease condition. And he put together a department which in its own way was probably one of the best in the country, and we were the beneficiaries of his wise and profound support.

He never claimed that he knew what we were doing in detail, but he knew how to look after us so we could deal with the details of our careers.

Andrew Hoffman: And this was a pediatrics' department?

Dr. Charles Scriver: At the [Montreal] Children's Hospital. There was a pediatric service at the Royal Victoria Hospital, which was also the big general teaching hospital. My mother was Pediatrician-in-Chief for that pediatric limb in the McGill System.

Andrew Hoffman: Okay. Now there were certain conditions around when you first entered or started working at the Royal Vic, as I understand it, a certain meeting with Ronald Christie?

Dr. Charles Scriver: Yes. That was one of the important meetings in my career. My father as Physician-in-Chief, in the `50s, had witnessed some challenges to the function of the department of experimental medicine. There was a famous person in-charge of that department, his name was JSL Brown, John Brown. But he was not a great administrator, although he was a great thinker, and he had been in on the early days of the development and discovery of cortisone in medicine.

My father organized a committee that was looking for a new Physician-in-Chief. My father wanted to retire from that, and the search committee identified Ronald Christie in England as the person to bring to Canada to McGill to recreate and restart what became the Premier Academic Medicine Department in the country for a while, that was its reputation.

Ronald Christie had a colleague, a second in command, or whatever you'd like to call him. His name was John Beck, and these two guys were of towering strength in Canadian Medicine and McGill Medicine, and they were always on the look out for smart people who could be recruited into the McGill System. This was a great time in being a clinician scientist in this country, where the medical degree contributed to the way people thought about things and did things.

So I was brought into the Physician-in-Chief's office. He was sitting in his chair, John Beck was sitting or standing at his. And the question more or less put to me was, Scriver, what do you want to do when you grow up? I said, I don't know. I would like to be -- I think I would like to be an academic physician like my parents. And they said, but what special facility or insight do you bring, because we don't need another generalist. So I said, I don't know, and they said, well, maybe you should go to the library and find out what that might be.

So I went to the library at the Royal Victoria Hospital. It was a good hospital library, and this is a real story. They put the journals out with the cover showing, so when you walk down the library you could see all the journals and their covers, and my eye was caught by a journal that had a red-white-red banding.

The red was the title of the journal and the year, the white was the table of contents. I picked up a copy of the journal because my attention had been captured, and it was an issue of the British Medical Bulletin describing chromatography, and chromatography had just become a major sort of physical chemistry area of interest, and it also achieved a Nobel Prize.

Andrew Hoffman: Of Will, you said?

Dr. Charles Scriver: Yeah. At the back of that particular issue was an article by Charles Dent and Walsh describing the use of chromatography to examine the chemical composition of people with different diseases. And because I was trained in the arts, and I'd been brought up in a family that liked art and so forth, I also liked the pictures of the chromatograms with their colored spots. So the aesthetic part of it appealed, intellectual part kind of intimidated me. But I thought, hey! This is really interesting stuff.

So I went back to my next meeting with Christie and Beck, and I said, I'd like to do chromatography, and I have discovered that there is no expertise for it here in McGill.

Andrew Hoffman: Would you remember thinking that that was a good way to put yourself to them, or did it just so happened that?

Dr. Charles Scriver: It's just so happened that they'd ask me, go and find something that you want to do, and I said, I think this is what I'd like to do. So their next question being astute guys, Christie and Beck said, so where would you like to go? We suggest there are two places to go. One is to the Rockefeller Institute in New York, and the other would be to London where Dent works in the University College Hospital Medical School.

So I asked the question, if I went to the Rockefeller, would I be able to see patients, because I was thinking in terms of the clinician side, and then they said, no, but you'd probably be able to work in Standford Moore's Laboratory, and learn a lot about chromatography. The absence of patient connection deterred me, but I got to know Stan Moore later on, and he was good to me and gave me advice, but he also won the Nobel Prize for his development of quantitative chromatography and instrumentation to do that.

So it would have been an interesting time to be in his lab, but I went to London instead, and I was exposed to Dent, and I was there for two years. At the end of the first six months I was totally depressed, because I knew I didn't know enough, and I wasn't accomplishing anything. And Dent says, nobody accomplishes very much at the beginning of their training in this area in six months, hang in there, and I did, and I came up with a couple of interesting discoveries, and they launched my career. But the base of it was begun by Christie and Dent saying, “what do you want to do when you grow up?” By the chance discovery of chromatography and by the advice [of] go to London. How did I get to London? Christie and Beck put my name up for [the] McLaughlin Traveling Scholarship. I got it, and that took me to London, and I was allowed to renew it after the first year. So I spent two years in London getting things under my feet.

Andrew Hoffman: So you were still somewhat affiliated with McGill although you were working in London?

Dr. Charles Scriver: Yes, I was a McGill post-doc doing my post doctoral studies in a lab that had a reputation, Charles Dent's, and getting exposed to the concept of inborn errors of metabolism. And the person who helped me with that was Harry Harris, who was initially across the street at the Galton Laboratory, but also at this point had moved to Kings.

And Harry was very kind to me. He recognized my interest in trying to answer that question: why does this person have this disease now? He recognized that I was interested in chromatography and wanted to use it. And intellectually and socially, he was a great support for this formative stage of my career.

Andrew Hoffman: So what was your biggest accomplishment working there, or under – were you working under his supervision?

Dr. Charles Scriver: I was working – the Dent Lab belonged to the "sink or swim" school. If you could swim, they were very able and willing to support you. If you were sinking, they would examine why you were having trouble. And if you were likely to not have a strong career later on, they would I think probably advise you not to continue with that stream.

Andrew Hoffman: So it seems like that lab did not work in a bottom-up kind of capacity.

Dr. Charles Scriver: Well, the bottom-up approach was, there were other people in the lab, Mary Efron, who was interested in chromatography and went back to Harvard and has an important figure in the development of chromatographic newborn screening etcetera in the `60s.

And there were other people who -- I mean, they taught me amino acid biochemistry. This was the bottom-up approach we taught each other during the lunch breaks, couple of times a week. Roland Westall was an important figure in that. And I would say that they were very much the bottom-up approach. You help yourself, and we'll help you.

We haven't talked about the intervening period between McGill and internship and junior medical residency and getting to London, and that's the year I spent at in Boston, at the Children's Medical Center.

Andrew Hoffman: So this was again after medical school?

Dr. Charles Scriver: This is right. This would be 1957-1958. Alan Ross liked to send people away to get a broadening of their medical experience. Boston was a good place to go to the Children's Medical Center, because medical experience came from all over the world. They were the hub for expertise.

So I went there, and I joined the house staff; a remarkable group of guys and women. And it was an extraordinary year for me, because I just saw stuff that you never see anywhere else in the way of medical experience, and I've used the casual word like “stuff.” I met great teachers who were great mentors.

I met colleagues who were really the bottom-up approach to life, we help each other. And at the same time there were rigor and discipline in the teaching program, and if you could survive the pace and so forth, you came out a different person at the end of the year. I was on duty at [the Children’s Medical Center] somewhere around the beginning of 1958, I think it was. A child was admitted with convulsions, and the mother from whom I would take the history looked at me and said, “please listen to me.”

And my response 50 years after that experience is, why wouldn't I listen, that's what I am supposed to do. Her comment says that we don't always do it. But what she was telling me was that this was the second time one of her children had been affected.

Now, I did not know enough about heredity or genetics. But I recognized that probably I am looking at something that might be biological, might have an inheritance factor.

Andrew Hoffman: Sorry to interrupt, but to think like that, is that something that was formed while you were in medical school, or – I mean, I guess looking to the very origins of your interest in genetics.

Dr. Charles Scriver: I don't' know where it comes from, because genetics in medicine was a pretty early arrival. So maybe I am just – and maybe I am fabricating that, but in hindsight --

Andrew Hoffman: I think because that would be interesting to maybe pinpoint where in your career that genetics really was the “aha” moment or something like that.

Dr. Charles Scriver: Yeah, I can give you a couple of examples in that line in a moment. Okay, so we'll continue on with the story first. I have taken the case history. This child is having terrible time with convulsions. No medications work, and the mother is scared, because her first child with this set of symptoms died at the age of four months.

I am tired, but I had been advised by the mentors, the Chiefs of Service and so forth, always read the journals, don't give up reading. So I did read the journal that night -- this is another example of chance. I opened the journal Pediatrics, and there is an article by Bessey and others describing seizures responsive to Vitamin B6 in an interesting set of conditions.

Next morning on rounds, I say, maybe we should consider giving this child

Vitamin B6. It has never been done in this child's or in the sibling's experience. So we take a decision to give the child Vitamin B6. Actually, that's not true. We get a consultation, because this is a new intervention.

And Sydney Gellis comes over from the Boston City Hospital, and we give the baby Vitamin B6. I can't remember whether we injected it or gave it by mouth -– I think we injected it. And within 10 minutes the seizure stopped. This is an epiphany of sorts, and it was decided to document this again; one experiment is no experiment. So the next time we do it, we do it with electroencephalogram connected, and we watch the change in the tracing, as well as the change in the behavior of the infant.

And the second event produces the same result; the seizures stopped. So we have discovered a Vitamin B6 responsive form of seizures. And since there were two siblings, maybe there is something metabolic in the brain that may come to light through this.

I write that story up. It gets published in 1960 in Pediatrics --

Andrew Hoffman: Was this a publication exclusively by yourself?

Dr. Charles Scriver: Yes. And it was a peer reviewed journal and so forth. So it represents perhaps the earliest step in my academic career. I think it would be good to finish that line of story now, because there were several ideas about what had been going on in the brain, as it happens; none of them was correct.

Fifty years later Peter Clayton at Great Ormiston Hospital in London discovers what the explanation for pyridoxine responsive or Vitamin B6 dependency epilepsy is? It's an inborn error of lysine metabolism at the alpha-aminoadipic semialdehyde step. There is an enzyme involved called antiquitin, and the antiquitin enzyme is mutant.

As a result, the pathway is blocked, and the stuff coming down the pathway goes through various chemical conversions, and one of the products of the chemical conversions is of such a nature that it binds the Vitamin B6, the entire molecule itself and removes it, so it is an induced form of deficiency, and when that Vitamin B6 molecule is not there, then other enzymes depended on it shut down, and that causes the seizures. It took 50 years to understand what the actual…

Andrew Hoffman: So this is a very recent discovery?

Dr. Charles Scriver: This was published a couple of years ago, and it finishes the mystery of pyridoxine-dependent epilepsy. Anyway, while I am there at the Children's Medical Center in Boston, on another night, I am in the emergency room with my co-fellow resident Irwin Schafer and a little boy comes in and he has got meningitis, and we were dealing with that. It's a viral meningitis as I recall.

However, since we did our own lab work, and did everything and worked up the patient, I looked at the urine, and we looked at the blood and the various things that we could do, and I noticed his urine contained lots of red cells. So he had Hematuria. The mother said, you may have noticed, this is about 1:30 in the morning, you may have noticed that Francis doesn't hear very well. We have a family problem with deafness, and he seems to have inherited his deafness from his -- my line of the family or I don't remember the detail, but anyway, we have a boy who has got coincidental viral meningitis. He has Hematuria. He is deaf. And because we are invited to read the literature and ask questions, we were led, Irwin and I, to recognize that the patient has Alport Syndrome.

So nobody knows much about Alport Syndrome at that stage, except that, yeah, it's inherited, and it's dominantly inherited. So here is my second encounter in a year with conditions that have a basis in heredity, and they're both Mendelian disorders, single gene disorders. We leave Francis at that point. I go off the service. I go to London. I enroll in the teams work in Dent's lab. Schafer sends a letter and he says, I haven't forgotten Francis, can I send some urine and blood to you to use your chromatography on to see whether there is anything there? I mean this is a "screening and searching" exercise.

So the blood arrives, or at least the plasma arrives, and the urine arrives, and I examine it with my little techniques, and I find that in the blood there is a big spot of proline and we know that that's not normal, because Dent has told us in everything that he has looked at, he never saw hyperprolinemia. And I look in the urine, and in the urine there are three spots that are enlarged, proline itself, hydroxyproline and the molecule glycine.

So here is a boy with hyperprolinemia, and we discovered that that is an autosomal recessive condition. And in the urine, there are three spots, and isn't that interesting? We will – to just end this line of the story, there is no connection between the hyperprolinemia and the Alport Syndrome. This is one of those patients who has in fact, manifested two independent genetic disorders.

So I get lots of encouragement to think in this direction, but the question is, why does he have three spots in his urine, and only one in his blood? And this is again a true story. I am walking down the corridor, I am passing the glass cupboard where all beakers and everything are kept. I am turning the corner and I saw it, of course, the proline is sitting on a carrier in the kidney and it's blocking the entry of the other two amino acids while spilling over itself. It's saturating a carrier that recognizes the shape of those three molecules.

Andrew Hoffman: So it comes out in the urine, but not only once in the blood?

Dr. Charles Scriver: That's right. The proline is elevated in the blood because of some metabolic

problem, enzyme deficiency. It produces hyperprolinemia. The proline sits on a carrier in the kidney tubule that's destined to carry the three amino acids and they all come up in the urine.

So this is an observation. This is one of the tools of science. The next tool of science is experiment. What are you going to do Scriver? So I thought of a neat idea: I will infuse myself with proline and look at the urine after I have produced hyperprolinemia in me. That was acceptable in those days. I did it, and I produced the triple aminoaciduria in myself. And this was thought to be really exciting, because this is very early in the Biology of transport systems. You have to recognize that there have to be carriers in lipid membranes that take water soluble molecules and shuttle them across lipid barrier, and the kidney is a very important place to study transport.

By using animals and a couple of other people in the lab, we identified a new aminoaciduria and the evidence for a transporter in the kidney that we did not know about before.

Andrew Hoffman: And this was in London?

Dr. Charles Scriver: We did this in London, but again through the intervention of John Beck and Ronald Christie I was encouraged to write it up as an abstract and submit it to the American Society for Clinical Investigation. I ended up on the plenary session, scared as hell, like me talking about this, but what I was doing was reporting evidence for specific carriers to shuttle water soluble molecules across the lipid barriers.

And so, this is an early, early contribution to the literature that became the literature of transport systems, and it was my entrée into the science side of being a clinical investigator and discovering things. And again, I was by chance given the opportunity to speak to the American Society for Clinical Investigation, which was the Summit of the day. And out of that presentation at Atlantic City on the plenary session came an invitation from Alek Bearn, who was another person in the early days of biochemical genetics to write a review about what was known, and when I look back on it, it wasn't a very good review, but it was the first in my stream of interest. And behind all of these, was Harry Harris back there in London who was saying, Scriver, you are doing okay, keep going.

Andrew Hoffman: That seems interesting that you went to London rather than going to New York, because you wanted to work with patients, and it was through working with patients that you realized that you wanted to focus more on the scientific kind of things it seeks.

Dr. Charles Scriver: You got it.

Andrew Hoffman: This strikes me as an interesting paradox in terms of the grand scope of your

career where you intentionally go somewhere go to do something else, because of what's available there yet, you take away something that --

Dr. Charles Scriver: Well, what was interesting, when I got to London, Dent wanted me to work in the clinic a lot more than I wanted to work, because I wanted to discover how to measure amino acids. Stan Moore by the way from the Rockefeller, he visited Dent quite often, and he was the one who taught me how to wash resin, and he was interested in what I was doing, but I got Stan Moore experience in Dent's lab as it were, and I was able to pursue my interest in amino acid metabolism, and the idea of transporters that would be specific in Dent's lab. I could be the scientist of the clinician scientist side of things by saying to Dent, I don't want to spend a whole lot of time in your clinic.

I would like to continue in the laboratory side of it. So, I submitted my credentials in a way as a clinician scientist, and I think that's what I have been all along.

Andrew Hoffman: Now, we are kind of up to page seven here from the previous transcript, and I know you said there wasn't much past 9, but I thought, since we are at 50 minutes already, if you want to take a break then we can sort of go --

Dr. Charles Scriver: If you want to keep the momentum going?

Andrew Hoffman: Yeah, I mean, it's up to you, I am fine with it. But I just want to make sure that you are happier with the answers that are coming now than the ones before, I mean, I guess you probably won't know, until you sit down and read the transcripts again I assume, which is fine.

Dr. Charles Scriver: We have covered the ground of home, schooling, medicine by chance, introduction to the idea that I needed further rigorous training, if I wanted to be in academic position. Exposure through Christie and Dent, and Beck, and the influence of Alan Ross on me, getting me to go to Boston for the exposure, and then these two extraordinary encounters. One, child with epilepsy, and the other, the child with hematuria and Alport Syndrome. And the introduction to Genetic Thinking, Mendelian experiments of nature, which I am looking at. And some of the mentors who had a profound effect on me, Alan Ross, Harry Harris, Charles Dent.

Andrew Hoffman: Yeah, so that basically, I am just looking here. And I guess there is the discussion of biochemical genetics versus more traditional genetics, but I guess that sort of comes later on a bit.

Dr. Charles Scriver: Yeah, it comes when you ask how did we put together this interesting application through the MRC.

Andrew Hoffman: Which, I think, the transcript is actually quite far in. But again, it's totally up to you, I basically, I mean, I have the transcript and I have the first set of

questions which would have taken us up to page seven.

Dr. Charles Scriver: I think it's fair to say that, with tools like chromatography enzyme analysis and so forth, we have entered an era wherein it's possible to discover what the mutation and whatever gene you are interested in does to perturb metabolism.

Andrew Hoffman: And this is the intersection of genetics in chromatography?

Dr. Charles Scriver: That's right, genetics and biochemistry. And so, Garrod has talked about the Inborn Errors of Metabolism and he gave the Croonian Lectures in 1908, and people's response to Garrod's Croonian Lectures would be, so that's interesting, but what's that got to do with medicine? And it's another 50 years from 1908, before there is enough expertise in enzymology, after all enzymes in medicine didn't appear until the 1930s.

There's enough expertise in enzymology to begin to look at whether there are enzyme deficiencies associated with these inborn errors of metabolism that Garrod described.

So, by 1958, things were poised to launch off. I wrote an article for the British Medical Bulletin in my own time; after coming back to McGill and being able to work here, in which I plotted a graph showing the growth of information about Inborn Errors of Metabolism, probably an appropriate name, and if possible the evidence to the enzyme deficiency, and it's a logarithmic growth curve.

Andrew Hoffman: Like a creation of knowledge basically.

Dr. Charles Scriver: That's right. And so, because of the available tools for investigation and the inquiry, there were, the interest in inquiring or interrogating, you'll end up with a growth of knowledge that becomes human biochemical genetics. And Harry Harris is one.

Andrew Hoffman: Sorry to interrupt but this, you wrote an article charting this growth of --

Dr. Charles Scriver: Yes.

Andrew Hoffman: And that was in what year, do you know?

Dr. Charles Scriver: I don't remember; it was a British Medical Bulletin [and] was probably late 1960s.

Andrew Hoffman: Because it sounds somewhat like the kind of work that we have been doing with regard to this specific oral history project where we are kind of trying the visualization basically of what the field looks like over time.

I don't know if you know about any of the work that's done there. But for example, Alberto is the expert at making maps like this, which basically allow you to visualize clusters at certain points in time, in where certain keywords fit in. So, it seems totally analogous to what we have been doing.

Dr. Charles Scriver: Are we allowed to think forward and just deal with that now?

Andrew Hoffman: Sure, if that's what you want to do.

Dr. Charles Scriver: Well, I just want to respond to your introduction. As you know I was interviewed by Nathaniel C. Comfort, the historian of science. And when he finished with me, which was an interview that went on for one afternoon, one whole day, and one morning, he said, here is your career, and he put up a network diagram.

Andrew Hoffman: Oh yeah, I read about that in the other transcripts.

Dr. Charles Scriver: And what I was unconsciously doing was looking into various aspects of what we were doing in genetics and biochemical genetics, as creating publications which would be like nodes in the network and they were linked to hubs and had something to do with one direction or another direction in our interest. And it made sense to create a diagram like that.

Andrew Hoffman: So, you were doing it in 1960 something.

Dr. Charles Scriver: Well, I didn't do that in 1960, creating the map came quite late, but when you put -- he asked me, now I want you to identify eight to ten key publications. So, I told him I couldn't do that, the key publication would be a hub for a set of nodes that were connected. And that went to the idea of having this diagram.

Andrew Hoffman: But this review that you did in the 'British Medical Bulletin' --

Dr. Charles Scriver: Would be an early one describing the growth of information and awareness knowledge in the area of amino acids metabolism, Inborn Errors of Amino Acid Metabolism.

Andrew Hoffman: So, this is probably more specific than what you were doing, but I think that it's the same idea, exactly. Yeah, I mean, I can show you these later, I warn you that I am not an expert at reading [them]. I had to sit down with Alberto, I mean, he uses them every so often in his own research, so the articles that I have read that he has done, but he can look at about that -- to me it looks like just a series of clusters, and he can just say, okay, there is a cluster, there is a cluster. But we'll get back to that.

So, now we have covered through --

Dr. Charles Scriver: I haven't given you the story of how I got back to McGill.

Andrew Hoffman: Okay, let's do that. So, you are in London --

Dr. Charles Scriver: I am in London and –

Andrew Hoffman: You have made these interesting discoveries and written them up.

Dr. Charles Scriver: And it's been too long after the six months of depressed activity; it's been a wonderfully exciting time. I should say that, I didn't mention my wife in all of this. We met when we were teenagers. My future father-in-law would not allow me to marry his daughter until I finished my medical studies.

When we got married in 1956, a lot of people came to the ceremony because of my academic connections, and so many of them said, we thought you would never get married. Glad you did.

So, she grew up in an academic family. Her father was a Radiologist, Chief at McGill, had been much involved in big things, including the Manhattan project, and my wife had an instinctive understanding of what it is to be an academic.

In 1959, I don't know, in the late winter, early spring months of 1960, it was apparent that if I was going to get the data to show that there was the experiment of infusing proline and a person produced the triple Aminoaciduria in the urine, I would have to do a lot of the analyses to get the data to support the hypothesis.

I worked out that I could run the Moore-Stein column at twice the recommended speed, and Stan Moore's and so then you discovered why we recommended 8 mils an hour instead of 16 mils an hour, because then he wouldn't have to get up at 2 in the morning to change the fraction collector. And I said that's what I discovered, and I brought it up with my wife, if we did that, would that be alright by her? And she says, if that's going to get the data for the hypothesis, that's okay by me.

Andrew Hoffman: So you did it the way that you had to wake up at 2 in the morning?

Dr. Charles Scriver: That's right. I said to her also, and that means, because I worked out how many samples I will need, we won't be able to go on visit your godfather in Norway. She took a deep breath and she said, if that's important for your career, we can always figure out how to get to visit my godfather later on, 20 years later we did. And that was wonderful experience.

Anyway, my career has been supported by that understanding at home, and I think it's terribly important to have that in the record. Anyway, we did all of those things, and so that's one of the influences on me.

Andrew Hoffman: Now how long did that experiment take for you to prove your hypothesis?

Dr. Charles Scriver: I used up the whole six months that were available to me to get the data, and to put it into the abstract to submit to the American Society for Clinical Investigation. Now when I got back to Montréal, I guess somebody had written from England to say, Scriver shows potential.

Alan Ross received me and I had decided I would like to be in the pediatric department rather than the internal medicine department. Culture, behavior, personalities were more like me in pediatrics, than they were in the medical department. I think I disappointed John Beck that I didn't stay in medicine, but I was definitely attuned to pediatric interest.

Also, important here is metabolism presented in early life, so pediatrics is a good place to be. That's why a lot of biochemical genetics seems to have a pediatric access as of the age at onset.

I was registered or signed on to be the Chief Resident in pediatrics, which is a great honor. I did not enjoy it. It was always a conflict of interest. I was very busy as a Chief Resident, but I wanted to be writing out this stuff and so forth. I mean, we did produce a paper describing hyperprolinemia and the transport system that was published in '*Nature,*' which is a pretty interesting way for an early start on your career.

Anyway, Alan Ross was very supportive and would look at me and say, you look miserable. Would you like to have time off so you go down to Boston and finish that paper with Schafer and Efron? I said yes.

Well, that led to an interesting development. In McGill, they realized that one resident was not enough, one Chief Resident was not enough to deal with all the things that they needed to do. So they had -- I was the initiator of twinned Chief Residency etcetera.

Anyway, Alan Ross had this idea that I should be put up as a candidate for a Markle Scholarship, the Markle Foundation, which then went on later on to support Sesame Street, was the acme of academic training or exposure, and I was one of the competitors for 25 physicians in the whole of North America. And with luck and somebody looking after me, I got one of those Markle Scholarships. The Markle's hoped that I would become a Department Chairman or a Dean. That was their goal to populate North America with Markle scholars over deans than department chair. I wasn't interested in that, I wanted to continue to do what I was doing.

Andrew Hoffman: Now was that tied to a specific research project, or it was just kind of based on your academics?

Dr. Charles Scriver: It was based on academics and performance and so forth. I probably disappointed the Markles, because I did not become a dean or a chair, and I did not because I refused the invitation to pursue that stream.

But Alan Ross was absolutely brilliant. He says, you've got a Markle. My job is to protect you that you can use that Markle to do what you need to do. He made some critical moves and decisions in this as head of pediatrics and allowed me to continue to do what I was doing, and at the end of the five years of the Markle, I had a publication list that was very convincing and I was creating a reputation as a human biochemical geneticist. I wouldn't have been able to do that if I hadn't received the Markle, and if I didn't have Alan Ross buffering my colleagues and keeping them away from me. I was told that I had to work in the emergency department, and do whatever everyone else was doing.

I told Alan Ross, I will work in the emergency department if they will come in and work in the lab, because I work in the lab every night, as well as day. And he says, interesting answer, and went to his group and came back and said, nobody seems to want to go into your lab to do your work while you are in the emergency. Problem over.

Andrew Hoffman: So it was no mutual enhancement of one another's skills?

Dr. Charles Scriver: Not in that direction. I must say I was blessed with colleagues who seem to understand what I was trying to do. They did not make life unpleasant.

Andrew Hoffman: Now, Alan Ross was, what was his capacity?

Dr. Charles Scriver: He was Physician-in-Chief of the hospital and the Chairman of Pediatrics in the McGill, Academic stream.

Andrew Hoffman: Okay, so he had a say in, people listened.

Dr. Charles Scriver: That's right. Yes.

Andrew Hoffman: I guess that's good to have someone like that in your side when you are trying to accomplish something.

Dr. Charles Scriver: That's right. He was what one would call a great mentor.

Andrew Hoffman: So you went back to Boston and you wrote up this?

Dr. Charles Scriver: I went down on weekends and we wrote up this paper. We submitted it, one of them to '*Nature*' and the other one was description of this family with alport and hyperprolinemia and the two Mendelian disorders, and that was published in the New England Journal of Medicine.

Andrew Hoffman: So the two articles were based on this one case of Francis?

Dr. Charles Scriver: Yeah.

Andrew Hoffman: So now, basically we are up to the Fraser-Scriver relationship which I don't know if you wanted to continue on with that?

Dr. Charles Scriver: Sure.

Andrew Hoffman: This is up to you. If you were happy with what's on the record as of now, then it can be that.

Dr. Charles Scriver: I think it would improve the join here of the revised beginning and what was there, by saying, when I came back to the Children's Hospital, it was recognized that I had an interest in genetics. Clarke Fraser who you have been interviewing and know had created a genetics clinic in Montréal Children's Hospital, one of the first in the country, and Clarke was being recognized as a medical geneticist of extraordinary insight, intellectual power generating information and publications.

The prediction was that Scriver and Fraser could not work together, because they will be two independent competing fashions, and the predictions were totally wrong. We loved working with each other. It was easy, and we left each other to do what we could do as individuals, but the sum of our joint work was greater than the sum of the parts.

Andrew Hoffman: Why were those predictions made?

Dr. Charles Scriver: For predicating temperaments.

Andrew Hoffman: So you both sort of were very entrenched in your own ways of doing -- or perceived as being entrenched in your very specific ways of doing things?

Dr. Charles Scriver: We were committed to what we would do, that we wouldn't pay attention to what the other person was doing.

Andrew Hoffman: Okay.

Dr. Charles Scriver: So we were creating a laboratory that was developed for human biochemical genetics, and Fraser was running his program, which was medical genetics. And somewhere along the line, we recognized that we had created a momentum. You may have heard that at McGill, they are honoring the Group. The excitements came up and says, Fraser and Scriver ran these courses that we're so exciting. Everybody had to be there; I mean the room was so full that people sat down on the floor to leave room for other people to be there.

Andrew Hoffman: Now this was your course on Human Genetics that you were teaching at the

Medical School?

Dr. Charles Scriver: No, this was in the hospital.

Andrew Hoffman: Okay.

Dr. Charles Scriver: Sort of round, there was an extra round, there was a spontaneous thing that worked and excited a lot of people.

Andrew Hoffman: Okay.

Dr. Charles Scriver: Things like that made us feel what maybe we should try to respond to the invitation from the Medical Research Council of Canada to form, create groups of shared interest. And we put in an application for medical genetics that included biochemical genetics, and there were as I was led to understand, I think five different applications and we won the competition to do that. With hindsight brought to us by reviewers at the MRC, it turned out that one of the reasons we won is because we had strong access of science, Clarke was interested in teratology and what caused malformation, mal-development, and was doing great in work and advice and I was doing the human biochemical genetics side of things and that was considered acceptable and satisfactory.

But one of the things that we had initiated in the 60's, and again, there is this retroactive history report. I had developed with the chromatographic method, several little tasks that led to a 40,000 family study in the newborn. How we could identify inborn errors of metabolism using this new methodology that would capture whole variety of disorders if they were there in the population.

And because we believe that if you found something early, you would want to counsel and treated. We developed a system in Quebec called the Quebec Network of Genetic Medicine, which was supported by Castonguay, the Minister of Health. And we therefore had developed an interest in a clinical access that was almost public health, and the reviewers at the MRC noticed that this was a dimension in our application which was different from the others, and so it was, and the person -- and it's in your transcript already -- the person that made that possible for us to have that access of interest was a colleague of mine by the name of Carol Clow, who came in and did all sorts of interesting things.

So we were half sort of in public health, we were in screening which became major access in modern genetics. I mean that's --

Andrew Hoffman: Is it the test that you developed as a simple test?

Dr. Charles Scriver: Yes.

Andrew Hoffman: I mean what did it entail?

Dr. Charles Scriver: It uses chromatography to identify disturbances of the metabolism of individual amino acids.

Andrew Hoffman: Based on urine samples?

Dr. Charles Scriver: Yes.

Andrew Hoffman: Okay.

Dr. Charles Scriver: And they take a lot of blood samples and they would get sent, actually the urine sample was how one access, the other access a blood sample in the baby before it was discharged from the hospital.

Andrew Hoffman: And so, I mean, it seems that, like you said, the distinguishing feature of your group was that you had this sort of clinical access? That tied into the rest of the work that you were doing. The point of Carol Clow I think is somewhat interesting because it's something that I have noticed in your interview as well as other things that I have read about the group and this might be a digression. So I apologize but it struck me as curious that it seems that she didn't really have any formal scientific training.

Dr. Charles Scriver: That's right.

Andrew Hoffman: But she wasn't the only one who was working within your group in a kind of scientific capacity without formal training as a scientist. I don't know if it's something that you care to elaborate on, but it just seems interesting to think of this group that claims to be the longest continuous refunded group in the mid history of the MRC/CIHR -- it just ended in 2009, but was employing people who presumably were not scientists by training.

Dr. Charles Scriver: Well, I'd say something about us but also I'll also say something about McGill. I think I probably learned this from my parents: don't look at the initials after the name, look at the person who has the name and judge that, and I knew Carol Clow as a girlfriend who was a classmate of mine in Lower Canada College. I also had medical connections with her during my internship and residency, and then she experienced a tragedy and one of her children died of a sudden death in infancy.

My mother happened to be in the room when it was appropriate to counsel Carol about what to do and my mother says, gave her some wonderful advice and a few months later we approached Carol Clow to see if she would like to come in and help us with this problem. And then she said, yes, I'd like to do that, and I didn't care what her training was.

Andrew Hoffman: Does she have a medical or -- I mean as you said, you had a medical connection with her but --

Dr. Charles Scriver: Oh she had another child who had been afflicted with leukemia.

Andrew Hoffman: Oh okay.

Dr. Charles Scriver: And my mother was chief of service when her child was on the ward, and that's how I learned about the dying child. But Carol is innately intelligent and is not afraid of hard work and she and I and one or two other people in the lab did this 40,000 family study, looking at newborn screening as a tool for early diagnosis, prevention of disease through appropriate interventions of treatment and so on.

And so it was clear that she was also very good at talking to mothers whose blood test -- their baby's blood test report comes back and says, you've got this problem and the mother gets scared and wants to talk to somebody and I made a decision that if I did all the talking over-and-over again, I would not be doing so well in biochemical genetics. And so I asked Carol, would you be willing to talk to the mothers and she said, "yes, I would provide back up with the facts; or when I am out of my depth."

So we've suddenly has established a bifurcation and a limb in the Group that says, here is counseling, genetic counseling in a specific area, and we are implementing the public health side of things, etcetera, etcetera.

So Carol Clow becomes -- by those series of events, a founder of a genetic counseling process at McGill and she becomes the model for developing a new program at McGill different from that created by Clarke Fraser. Leonard Pinsky was very good at supporting this as an actual academic activity at McGill. McGill recognized her academic performance and promoted her and her retirement to Associate Professor without any of the formal qualifications.

Andrew Hoffman: Did she have like a bachelor's degree?

Dr. Charles Scriver: No. I don't think she even had a high school leaving certificate because she had to leave her education during the war because of difficult conditions in her family; [she is] a remarkable woman who made a difference.

Andrew Hoffman: And so this was one of the new genetic counseling program related to the genetic screening program in biochemical genetics?

Dr. Charles Scriver: It was in Canada.

Andrew Hoffman: Yeah. And did she -- I mean, I guess I can find her. I don't think that – I don't think Christopher has gotten in touch with her in the last --

Dr. Charles Scriver: I don't think so.

Andrew Hoffman: I'll check.

Dr. Charles Scriver: I'd be nice of you if you could interview her.

Andrew Hoffman: Yeah, it seems like it would be an interesting story to tell about how a woman who didn't even have finished high school came to be a founder of genetic counseling service in Canada. I mean, it strikes me as somewhat remarkable. And of course, it didn't happen without a network around it as well.

But I think I'll get the contact information from you and depending on if it's in the purview of what we have money to do -- I mean, I don't make the executive decisions.

Dr. Charles Scriver: Well, I certainly would strongly recommend that you interview her, because she is one of the reasons why we won the competition.

Andrew Hoffman: Yeah. No, I know. The way that you describe it and correct me if I am wrong but it seems like she was like the public face of the work that you were doing in so far as being able to communicate with the people who were consenting presumably to being tested or having their children tested.

And I guess that it became something that you would -- was it something that you did advertise once it was in place? Like, we have this test and here we have this person or was it only something that came in after the fact once in a regular test.

Dr. Charles Scriver: Well, we made it, I think it's fair to say that we would not have implemented the Quebec Network of Genetic Medicine if we didn't have the capacity to follow up the positive tests to interpret and counsel and, where treatment was available, to provide the treatment. And that required people who were willing to do that side of the story. And she was the role model to illustrate that.

Andrew Hoffman: Yeah. Well, I am definitely going to get her contact info from you and I'll talk to the others involved in the project. So now we are about half-way through where – yeah, I think we are probably to about page 11. I have a couple of other questions that sort of tie in with things that are in this transcript.

One deals with the group and its relationship with Dr. Hechtman and other deals with the issue of space that was written about in 1988, which I think came up briefly here. But it seems like something important.

Dr. Charles Scriver: It was.

Andrew Hoffman: So I figure maybe we could talk a bit further in-depth about that. But chronologically the group was founded in 1972. And it was yourself on the application along with Dr. Fraser.

Dr. Charles Scriver: Yes, and our colleagues were Peter Hechtman and Renny Gold.

Andrew Hoffman: Gold, yeah. And so --

Dr. Charles Scriver: And David also came in later.

Andrew Hoffman: Yeah. But he was written in the beginning.

Dr. Charles Scriver: Because he was away getting expertise.

Andrew Hoffman: Yes, being expected to come back. So that was the foundation and that was a five-year grant that basically lasted until 1977.

Dr. Charles Scriver: Yeah. The five-year grants at that time were gold in themselves because you didn't have to immediately start writing a progress report when you didn't have much experience or had much to report on.

Andrew Hoffman: Yes, of course. So Peter Hechtman was brought in as a member of the original group. And you noted in your first interview with Chirstopher Canning that "he didn't have much, but he was capable of asking good questions and doing interesting things".

And then as we find out, once I was going through the records, I came across the reply from MRC in 1977 where the council seemed concerned about the productivity of Dr. Hechtman in those first five years. And so I was curious about how -- I mean like you said, a five-year grant at that point was gold, and it was something that was obviously very cherished among those of you who were part of the group.

And I don't even know if this is something that you can recall, but it seems like the dynamics of the group probably would have changed once you receive this follow-up and you realize that someone who you have presumably been working with to various extents of closeness is now no longer considered to be part of the group by the people who are giving you money.

Dr. Charles Scriver: Yeah, I don't remember the details well enough to know whether he went with us into the next round. Did he?

Andrew Hoffman: I know that he appeared later. I don't know if it was the immediate next round, but I know he appeared later on.

Dr. Charles Scriver: Yes. Well, I think he wouldn't have appeared later on having gone through that sticky patch. He went on to do some really interesting things.

Andrew Hoffman: Yeah. And that's what struck me as interesting is that he came. He was part of the core group, and then there is this sort of rejection as it seems, and then he came back. Yeah, I just thought that it was an interesting point.

And the last issue is this letter that was written. And I think that Dr. Rosenblatt had given you a copy before you met with Christopher Canning maybe or unless you had a copy of your own that was sent to many of your colleagues about the space issue and concerns about the future of the group. Do you recall that letter?

Dr. Charles Scriver: What I remember was Malcolm Brown coming to McGill to award McGill a Medical Research Council Group in Medical Genetics. The terms of Malcolm Brown I thought was we will not give the money to McGill unless McGill gives you good space [in which] to work.

And that catalyzed a flurry of activity over in the Children's Hospital on the seventh floor, which was the storage space only at that time. And we worked with a firm of architects, and one person in particular, Jim Malling. And again it was a bottom-up approach. Everyday the people who had that space had a chance to declare what they thought would work. And we produced a set of plans that was encumbered into a working space of 5000 feet. And the rest is history as they say, because it worked for another 25 years.

Andrew Hoffman: But there seemed to be a concern about the, I guess incorporation of -- or the existence of the genetics group in the adult hospital as well.

Dr. Charles Scriver: What happened was that we were successful enough that our activities spread beyond the physical space of the Children's Hospital and the academic space of pediatrics and so on. And we wanted to see genetics get into other areas of medical care and medical education and research. And so one of the things that David Rosenblatt did was to initiate a movement to develop a research space in the Royal Victoria Hospital. And after that I think as I recall we also were interested in having space development in the Montreal General Hospital. I think the affiliation with the Jewish General Hospital was dicey at that time. There was a wish by the Jewish (as I would interpret it) to protect their identity and turf. That's changing now with the recruitment back to McGill where one of our winning graduate students Rod McInnes. And I now see a very good axis of interaction between the Jewish General Hospital and McGill in the area of genetics. Does that answer your question?

Andrew Hoffman: Like you said, it seems like things were on the mend but the tone of the letter that you had written seemed pretty stern and pretty concerned about how -- it was almost a double-edged sword. It was good that genetics was in fact growing and that programs were being started in other departments in other places besides the Children's, but at the same time, it had the potential to nip the funding in the bud because of the way that the funding structure was allotted based on how the group itself was geographically --

Dr. Charles Scriver: I don't remember the timing or the details, but was this before we came in Department of Human Genetics?

Andrew Hoffman: Well, the Department?

Dr. Charles Scriver: Well, someone in the last major --

Andrew Hoffman: Because this was in 1988 that the letter was written. So it seems like it would be before.

Dr. Charles Scriver: It certainly would be before, but I think the worry that we might have had was that we needed a focus of authority for the academic responsibilities and the research coherence and yet we don't want to give up the opportunity to colonize other areas of inquiry such as in adult medicine, obstetrics and so on. So there may have been an apparent conflict of interest or of tension between different axes and I think a resolution. I can remember arguing the case and with David Rosenblatt doing it very well himself in his own guise, and arguing the case for having not just the Center of Medical Genetics, which is what Leonard Pinsky was in-charge of, but also going to the idea of the Department of Human Genetics, and I think when we did that, most of the problem dissipated, I think so.

Andrew Hoffman: And I guess the funding probably evolved along with that also in the way that the funding agency construed -- because the department itself was never funded by --

Dr. Charles Scriver: That's right.

Andrew Hoffman: By the group, MRC or CIHR.

Dr. Charles Scriver: No, no, it was funded –

Andrew Hoffman: It was the group itself.

Dr. Charles Scriver: Yeah. And the other thing that I think is worth recognizing is that the MRC was always interested in what else you are doing besides research. And tell us about your teaching, tell us about your interaction with students, how do they view you, and so clever leaders of inquiry, such as Arno Motulsky said, "I don't want to talk to you guys at all. I want to talk to those students. I want to see what your graduate students think about what you are doing and whether it's working."

So we were left to sit outside the door in the empty room. Well, Arno and his interviewers would go and talk to the students, and what they got back was positive news that was compatible with--I don't know that that was before or after the formation of the department--but it was compatible with a coherent phenotype for what we were calling the MRC group that was in fact the sort of epicenter of training and teaching.

Andrew Hoffman: So you were able to build in sort of training grants as well?

Dr. Charles Scriver: Yes, I mean that was another wonderful thing. The MRC gave us the opportunity to recruit very good students by sort of offering trainee issues in advance.

Andrew Hoffman: And that was probably tied in with the positive reviews that your students gave you I would imagine?

Dr. Charles Scriver: Yes, and we didn't pay the students!

Andrew Hoffman: It's good to know that there is no conflict of interest there. So we are at an hour-and-a-half.

Dr. Charles Scriver: I have had enough; you got enough?

Andrew Hoffman: I think I have enough. Thank you.

END OF INTERVIEW

Dr. Reynold Gold, July 13, 2010

Christopher Canning: My name is Christopher Canning and I'm here with Dr. Reynold Gold on July 13, 2010. It is my great honor and privilege to be here with you, Dr. Gold, to discuss broadly two main themes regarding human genetics.

First, I would like to just discuss your academic background, which, of course, contributed significantly to the growth of medical genetics in Canada and beyond. Secondly, and perhaps more importantly for this particular study, I am interested in your involvement in the MRC Medical Genetics Group which you joined in its formation in 1972 and were a member until, as I understand, 1977.

To begin with, can you please give me an overview of where you're from, where you born and where you grew up?

Dr. Gold: Well, I was born in England and I did a degree in natural sciences (it's called the Natural Sciences Tripos) at Trinity College Cambridge. I was an open scholar of Trinity College Cambridge, so I did my degree in natural sciences there, which was called a BA because they have yet to officially acknowledge the existence of science at Cambridge and so even the scientists are given arts degrees, but then I got an advanced degree in biochemistry—part of the Natural Sciences Tripos and then I got my medical degree, which again is not an MD in England, but it licenses me to practice medicine. It's actually Bachelor of Medicine, Bachelor of Surgery.

Finally, I got my PhD in genetics at McGill just before embarking on the MRC group. So that's roughly my education.

Christopher Canning: Where did you spend the early part of your life then? How long were you in the UK?

Dr. Gold: I was in England until I was 30 and then I came over here to Canada at 30 actually as a strikebreaker.

Christopher Canning: Okay. I'd like to go back—I understand that that's why you went to Saskatchewan?

Dr. Gold: Yes.

Christopher Canning: So what about your personal history? Your family and siblings?

Dr. Gold: Well, I'm an only child. My father was a civil servant. He was working in counter intelligence with MI5 in England. My mother was a housewife. She came from Germany. She came from a German-Jewish family, which had a

paper products company—a big paper products company, which was confiscated by Hitler. My mother came over to England and married my father just at the end of the First World War and my father was a member of the occupation troops and then my grandmother came over as a refugee later in 1939 just before the war started.

So my father was English and my mother is German-Jewish. My father was English-Jewish, my mother was German-Jewish.

Christopher Canning: How did your parents influence your academic life starting from, say, your first BA in science?

Dr. Gold: They always told me that—their message to me was always—your first job is to study. They had much influence in my intellectual achievement. Later on, I had a row with my father and he cut me off without a penny, but the Trinity College lent me the money because my father had a fairly good income so the scholarship was restricted because of my father's income. When he cut me off, the college lent me the money to continue my studies and I eventually paid it back, so that row was eventually mended.

But apart from that, both my mother and my father would always stress the importance of intellectual achievement, but that's typical of a lot of middle class Jewish families, I think.

Christopher Canning: I'm going to go back a little bit because we're going to move on to your academic background in a bit here, but how were you as a younger student in, let's say, middle school or high school?

Dr. Gold: Well, I went to one of those awful institutions called a British boarding school and I hated athletics; for eight years, I was compelled to pursue a ball I had no desire to catch, but apart from that, I did well at school work, I mean, I was good at school, on the whole, particularly in the subjects that I enjoyed and eventually I got an open scholarship to Trinity College Cambridge, which is very competitive. I mean, there are about 3000 entrants and 1500—well, 150 scholarships available so 5% of the entrants got scholarship, so I did fairly well.

Christopher Canning: Can you explain what that open scholarship was?

Dr. Gold: Well, I mean, it's partly money. I mean, actually, the open scholarship gave me £60.00 a year, believe it or not. It's mainly an academic honor more than a means of living because the amount of money was sort of largely symbolic. So it's sort of recognized—and everybody in the country can compete for these scholarships and so there was an enormous amount of competition and they're very much prized, I think.

Christopher Canning: And when you received that, did you know that you were already heading to

Cambridge or was Cambridge a choice as a result of the award?

Dr. Gold: It is really a choice as a result of the award. I was pretty certain I'd go to some university or another, but I wanted to go to Cambridge because I was conscious of its tradition and so I wanted to go and got my scholarship and I went.

Christopher Canning: Were you aware of the particular genetics research happening in Cambridge at the time?

Dr. Gold: No, I wasn't, although I was up at Cambridge when the structure of DNA was discovered.

Christopher Canning: When Watson and Crick--

Dr. Gold: I was totally unaware of it at the time. I became aware of it later. But I was aware of Fisher. I had tea with Fisher, the great genetic statistician and I was aware of him, but I wasn't up to date on that recent work [that] just came out when I was up at Cambridge.

Christopher Canning: So did you start your science degree, which was a BA at the time, with an interest in genetics in particular or just science in general?

Dr. Gold: I did have an interest in genetics because I'd been very much influenced by a book I had read earlier in my life by Wells Huxley and Wells called "The Science of Life," which went into great detail in genetics, [such as] Mendel's discoveries and the work of Morgan and so I was very interested in genetics, but curiously enough in spite of my interest, I remained unaware until later of the structure of DNA and how it worked, but of course, I got to know about that later and so I've always been interested in genetics and I had a great friend called Ian Shine; he was a fellow student. He read medicine with me at Cambridge and he became a medical officer at St. Helena's and he did a study and of course that's an in-bred community, an island community. It's the stuff of which genetic studies is made and he started studying the rare diseases that prevailed on St. Helena and I was the ship's surgeon and I visited St. Helena as a ship's surgeon early in my life and he started going over his work with me and I helped him edit his book on the population genetics of St. Helena and that was another entry into my interest in genetics.

Christopher Canning: What particular diseases were being studied at this time, because this is obviously early population genetics, no?

Dr. Gold: Well, they were diseases—well some of them were general, you know, but as one would expect, several diseases which prevailed only in St. Helena, particular kinds of mental retardation and dwarfism. I don't actually remember all the details now because it's a long time since I even looked at

the book that I helped to edit, but I was very fascinated by the studies he was doing. He was untrained in science but he was a very great observer. He was one of these sort of born natural observers and so he made a very, very good genetic study of the island and as I say, I helped him edit the manuscript and I've given some sort of—and I wasn't a co-author of that, but I was given some sort of auxiliary credit on the book.

Christopher Canning: How old were you when you were working on this ship?

Dr. Gold: I was a ship's surgeon. I was on a passenger liner and I did it for a couple of years--

Christopher Canning: Like a cruise line?

Dr. Gold: Yeah, well people didn't cruise in it.

Christopher Canning: They traveled, of course.

Dr. Gold: This was in the days, as you can imagine it, when people got on ships the way they now get on planes not because they wanted to gamble or play bridge or have a holiday but because they actually needed to get somewhere, so it was a passenger liner, really not a cruise liner because that didn't really exist then.

And so I was a ship's surgeon for two years on the Union-Castle Lines, which no longer exists and it was mainly concerned with delivering the mail to South Africa and also taking largely civil servants from England back to their posts in South Africa and various parts of Africa. And it's on one of those trips that I met up with my friend on St. Helena.

So my interest in genetics stemmed from these various disparate sources, not curiously enough from the discovery of the structure of DNA, which happened while I was at Cambridge.

Christopher Canning: And you were so close in proximity to that discovery?

Dr. Gold: Yes, and also, I was interested in it because of its inherent power because I recognized, even though I was unaware of the discovery of the structure of DNA, I was aware that this was really atomic theory of biology.

And if you really wanted to know anything about biology, you were going to have to study genetics. It was like particle physics. It's the particle physics of biology.

Christopher Canning: Well, this was the early emergence of physics with biology?

Dr. Gold: Yes, indeed, with Delbrick, for instance.

Christopher Canning: So, moving on, you finished your MD in 1958?

Dr. Gold: Yes.

Christopher Canning: Which wasn't actually a medical degree in the Canadian sense?

Dr. Gold: Well, it wasn't anything like that. I mean, it licensed you to practice; it's the English equivalent of an MD. In fact, I now call myself an MD because when I first got to Saskatchewan, I wrote down faithfully M.B.B.Chir and everybody thought I was a chiropractor, so I changed it to MD, which is one of those rare cases, I suppose, of fraud committed in the interest of clarity [laughs].

So I call myself an MD even though I'm not one because I have a license to practice. I have the English equivalent of an MD. Actually, there is an English MD, but the English MDs, as it were, were PhDs in medicine. It's a PhD degree.

Christopher Canning: That would license you to practice medicine?

Dr. Gold: No, it doesn't, it's a PhD. So that's my situation.

Christopher Canning: So, when you first got your medical degree, what was your area of medicine? Were you in pediatrics?

Dr. Gold: Actually, I did the usual rotation; it's called an internship [in England]. I was a houseman in ENT medicine and general surgery for a year and then I did a bit of anesthetics actually. And then I went off to be a ship's surgeon, which was great fun, but I never thought of it as a career. It was sort of a year or two of fun for a young man and getting some experience too. I had a lot of medical experience. The idea of a ship's surgeon is a sort of gin-sodden wreck for a physician. I mean—but there is some truth in that, but you really have to practice a lot of medicine because you have a crew of 500 plus 800 passengers. As a matter of fact, they were 1300 and when you're out on the high seas, you're the only physician so it's serious medicine in spite of the reputation of ship's surgeons.

Christopher Canning: You would be the only doctor on a ship of 1300 people?

Dr. Gold: Unless there happened to be a passenger who was a doctor, yes, I was totally responsible; I had a nurse and a hospital assistant, that was all.

Christopher Canning: By the looks of things, you spent about five or six years after that in the UK before you came over to start your work in Canada?

Dr. Gold: No, actually, I graduated in 1958 from Cambridge and I came over to Canada

in 1962 at the time of the strike.

Christopher Canning: Right, we'll move into that. How much, then, before we get into your early academic interest in genetics, was genetics a part of your medical training at the time? Were you interested in genetics and medicine?

Dr. Gold: Oh, as part of my medical training, practically non-existent. There was practically no genetics. And, actually, I gave course in medical genetics, a part of it or all of it, but quite a bit of it to the medical students. I taught more genetics than they really wanted to know and I started off my course by saying, "What I'm supposed to tell you is that a thorough understanding of genetics is essential to the practice in medicine," so I said, "you're far too intelligent to believe that."

I would also say, "so I'm not going to tell you that, but what I will tell you is that in the course of your lifetime, genetics is going to revolutionize the practice of medicine." By the way, it hasn't yet, but it will in the next 20 to 25 years." And then I said, "You know, you're too expensive to fail, so only spectacular ignorance will secure yourselves failure. [Genetics] is very interesting stuff, so why don't you just sit back and enjoy it."

But, long story short, genetics almost never comes up in general practice.

Christopher Canning: In general practice?

Dr. Gold: No, I mean, geneticists will assure you that it's very important because everybody wants to sell what they sell and geneticists want to sell genes and nephrologists want to sell kidneys and so on, but that's going to change, but it hasn't changed yet.

Christopher Canning: Do you still think, then, that the study of DNA as the fundamental unit of heredity will one day revolutionize our understanding of medicine?

Dr. Gold: Absolutely! I would—you know, when people finally sequence the genome, a lot of people thought of that as a sort of race to the finish, but it's really a race to the starting line, right? As I think Collins said, what you have now is—let's say you didn't understand that. I don't know much biology you know.

Christopher Canning: The more I speak to scientists the more I understand; I guess I know the basics for sure.

Dr. Gold: Our situation is like, supposing you didn't know how a car worked, but you just saw them zooming around, apparently going on their own steam and emitting a bit of smoke and making a hoot every now and again, turning and turning and you wanted to find out how it worked; you're not allowed to take the car apart, but what you do have is a pile, not of spare parts, but of

the blue print of every spare part that the car has. From that pile of blue prints, you're only allowed to look at that, you have to figure out how a car works. That's where we are now.

Christopher Canning: At the time when you were doing your early work in genetics and medicine, was there a conflict between geneticists and medical practitioners?

Dr. Gold: Oh I don't think so, I mean, you mean—you mean a personal conflict?

Christopher Canning: No, an academic conflict—I say a turf war or an academic conflict?

Dr. Gold: No, not at all. No, I don't think so. I mean, I think that despite what some clinical researchers say, there's a tremendous gulf between practicing medicine and doing research, but that's a cultural gulf; it's not warfare; it's just a different universe. Now, clinical—so-called clinical researches would tell you that the fusion of the two is very productive and that's to a certain extent it true, but it is rarely true. We will come into that later.

Christopher Canning: Great.

Dr. Gold: So if there is any conflict, I mean, I don't think that physicians despise researchers. I think researchers tend to despise physicians more than physicians despise researchers.

Christopher Canning: Is that perhaps why people choose to do both simultaneously?

Dr. Gold: Well, I think people who do clinical research can be divided into various categories. Some do it out of genuine intellectual curiosity; some do it because it's brownie points on their CV. I think a very high proportion of what's called clinical research is really garbage. It has tremendously high garbage content, but there is some genuinely good interaction between clinicians and researchers.

Christopher Canning: Can you give me an example of an area that you find fruitful, that conversation between the clinician and the researcher?

Dr. Gold: Well, I think in human genetics, the prime example is sickle cell anemia where as a result—there was a single gene and knowing the target protein; it was a rare case when you knew the target protein because we had no proteinomics or genomics, but Ingram did the peptide sequence, found the single amino acid substitution and then deduced the nucleotide substitution from there.

And so that was a good example and Pauling and Ingram were involved in that. But that's pretty rare.

Christopher Canning: They were discoveries of single gene, Mendelian disorders.

Dr. Gold: Right, that was one of the early ones and in fact, I started the course in biochemical genetics. I don't know what is still going on, human biochemical genetics—is that still going on—that course at McGill?

Christopher Canning: It must be; I'm not sure.

Dr. Gold: I started it. It was still going on when I left and half of that was devoted to hemoglobin.

Christopher Canning: Well, eventually I would like to have a more detailed conversation about the science. I'm very interested in the sociology and history of science. But, for now, perhaps a little bit more about you. I'm intrigued about you coming to Canada in 1962 to work on the strike in Saskatchewan, so maybe you can tell me how you were recruited for that?

Dr. Gold: Well, at that time, I had finished my internships, my anesthetics; I had decided I didn't want to be a ship's surgeon as a career, and I never intended it as a career and I wasn't really quite sure what to do. I really always had academic leanings. I say leanings, maybe not at that time ambitions, but leanings and I didn't quite know how to execute or pursue them.

And so I was doing a little bit of locum and general practice and then I got a phone call from this chap at Saskatchewan House in London asking if I wanted to go out to Saskatchewan as a strikebreaker. And this appealed to me very much because I'd always believed in single payer medical care—I believed in the National Health Service; I thought it was the next big thing.

Christopher Canning: Sorry, can you please repeat that?

Dr. Gold: The National Health Service. I was a member of the labor club in Cambridge. I was a member of the labor party in Cambridge; I was a social democrat. And it seemed a great adventure and the pay was very good, so I said, sure and so off I went. I thought it was very exciting and when you are a young man of 30, there's no pleasure more exquisite than working for a cause in which you believe, particularly sort of bearding your elders and veterans, you know, which is very attractive prospect for us.

Christopher Canning: Can you tell me more about this prospect?

Dr. Gold: Well, the introduction of Medicare into Canada. So I went over. It was a very exciting time.

Christopher Canning: Who were you working with on the strikebreaking work?

Dr. Gold: When I came into Canada, I wasn't working with anybody. I was collected

by the government. I was hustled into a seedy motel and then spies from the College of Physicians discovered where we were living and told us to go back. We didn't understand what we were doing or they invited us to come and join the regular guys who were on strike and be their guest, but I refused and then they hustled us to the—this was in Regina—they hustled us to the government building and handed out hundred dollar bills.

Christopher Canning: To silence you?

Dr. Gold: No, the government as initial pay and they said, well, you have to stick around because we're waiting to get your licenses. And the thing was that because—I don't know how much you want to know about this.

Christopher Canning: I want to know as much as you want to tell me.

Dr. Gold: Well, I'll tell you. So okay, we were entitled—I was entitled, well the English doctors were entitled, all of them, to be licensed automatically to Saskatchewan because there was a reciprocal agreement between Saskatchewan and England that we would license each other's doctors. So anybody with an English medical degree, which I had, was entitled to be licensed by the college, who were on the side of the strikers, of course. Because remember the college at that time was a mixture of a disciplinary body and a trade union, so there was a bit of a conflict of interest.

So, they delayed and while they delayed I was hanging around in the hotel being paid by the government. We wanted to get to work, so then the government issued a writ of mandamus. No, they applied for a writ of mandamus, which was granted and then they gave us a license. Then, I don't know—I applied to join the Saskatoon community health clinic, which was being assembled by a certain Dr. Sam Wolfe, a very charismatic chap who was a professor of public health at the University of Saskatchewan and he was very courageous because he gave up his tenured appointment in public health to come out into the battle field. There were two Canadian doctors, he and a psychiatrist, Canadian doctors who were really very courageous in doing this because they were sacrificing the goodwill of all of their colleagues.

I mean, for us it was easy; we didn't know anybody from Adam. The fact that all of the Saskatchewan doctors—well, not all of them—decided to send to Saskatchewan the doctors regardless whether they're called communists, mercenaries didn't affect us at all. He didn't know them anyway, so for the Canadian doctors, it was a great sacrifice.

So Sam Wolfe made a very great sacrifice. He assembled this sort of motley crew of people; there were six of us. Well he got Tulchinski, who was a general practitioner, Mahood was a psychiatrist, and her husband was a sort of fiery red Marxist and who else? Then Dr. Langer, who was a surgeon,

came in later. And he was a big find because surgeons earn big money and he agreed not only to join our group, but he was a Marxist too. He was a real fiery red revolutionary. So some of those—I mean, some of us were—I wasn't a communist, but two of us were communists.

Christopher Canning: Were self-proclaimed?

Dr. Gold: Self-proclaimed—well, Marxists, and when they managed to come to us, I said, I don't know, it could have been that they met, but they were certainly very sympathetic to communism. But he not only braved the wrath of his associates but didn't bother them at all because he thought the doctors were members of the bourgeois class that are doomed to extinction [laughs].

So he didn't care about that, but he also agreed to work for the same salary as the rest of us. So I mean, he could have earned hundreds of thousands dollars even in those days and he was working on a very small salary and so, certainly in his case, the accusation of being a mercenary was very, very ill-judged. In the case of English doctors, we were earning much more than he would have done or anything, so we could be more justly accused for being mercenaries, but not them.

Christopher Canning: How long was your involvement? How long were you in Saskatchewan?

Dr. Gold: I was there five years.

Christopher Canning: So '62 to '67?

Dr. Gold: Yes, '62 to '67. So then, of course, I don't know how much you want to know that—so we go to a hospital and we've got our license to practice. That was okay and then the question was hospital privileges. Well, actually between you and me, you can be a general practitioner without having hospital privileges, but you generally need to work in a hospital to be a family physician. But, it was advantageous, particularly in a small town; there is a political point to be made and the hospitals refused a lot of us hospital privileges.

And so a royal commission on hospital privileges was assembled. I don't know whether you know about this, under the aegis Mr. Justice Woods. I gave evidence to this commission (I was denied hospital privileges) for two days and we subpoenaed the college files; it was revealed that people had been given privileges on no more than the recommendation of the head master, that they were of good character and they asked for hundreds of references and the head of city hospital testified that my training was a dog's breakfast [laughs].

Another doctor testified that my training did not equip me to practice

"prairie medicine." So anyway, Justice Woods at the end, with a very nice learned opinion, said, "Doctor, Gold had grounds for supposing that the decision to deny any hospital privileges might have involved political consideration." And he recommended that they re-review.

He was very diplomatic and so they gave us our hospital privileges.

Christopher Canning: And that was towards the end of your time at Saskatchewan?

Dr. Gold: It was in the middle. I can't exactly remember—but oh, this was great fun!

Christopher Canning: So I guess during all of this fun political time, somewhere brewing inside of you was, hey, I want to go back to school and do a PhD or something more.

Dr. Gold: You're absolutely right. Your instinct is right. Because, basically, I didn't like practicing medicine very much then, but I'll tell you why: see after I did my science degree at Cambridge and went to the London teaching hospital, it was a tremendous culture shock because I went from a universe of securely founded knowledge to all sorts of smoke and mirrors. There is a tremendous—even today, when people would talk about evidence based medicine, there was a tremendous amount of smoke and mirrors, which I found very uncomfortable so that I never felt when I was practicing medicine that I knew what I was doing in a scientific sense.

Christopher Canning: You always had that underlying scientific basis despite being a clinician.

Dr. Gold: Yes, I was always scientifically bred. I mean, I always thought or tried to think scientifically and so, I found it uncomfortable. I wanted really to go back and then, I talked to my friend, Ian Shine, the guy I had worked with who's book on St. Helena had helped to edit, and he told me, go and fly to Clark Fraser" and so I did; and by that time I had married.

By the way, I should tell you. While in Saskatchewan, I wasn't disturbed by the obloquy in which I was held by my colleagues. I was used to that and I mean, I expected that, but what I was really perturbed by was the sort of cultural desert. When I got to Saskatoon, there were two cinemas. One was showing King Kong meets Godzilla and the other was showing Dracula in the Girl's Dormitory and I thought, well, we really should—I mean, I felt that Saskatoon could benefit from a cultural transfusion, so I started a coffee shop called the Louis Riel Coffee Shop and there were queues around the block and at this coffee shop, I met my future wife.

She was doing a PhD in psychology. So I went to McGill. To cut the long story short, with my wife. She got a professorship at Concordia in psychology and I so, I having seen her through her PhD, she saw me through mine at McGill.

Christopher Canning: And did you apply then to work specifically with Dr. Fraser?

Dr. Gold: Yeah I went to see Fraser and I said, my interest was in biochemical molecular genetics and then he said, well you better go and see Charlie about that and so I saw Charlie.

Christopher Canning: He would have been doing teratology and cytogenetics, no?

Dr. Gold: He was doing biochemical genetics and--

Christopher Canning: So he said, go to talk to Scriver?

Dr. Gold: Yes. And then he said, he would be taking me on so I did a year of course work, which is very surprising to me because with an English PhD you don't do course work. If you went to an English PhD supervisor, what courses should I be looking in at, he says well, if you want to know anything, I mean, you're supposed to know everything, so your job is to find something new, but if there's something you feel you ought to know that you don't just feel free to audit any course you like.

So the fact that courses were required for a PhD was sort of a startling idea to me.

Christopher Canning: So here you are, age 35, with interesting experiences of being a ship's surgeon, political activism in Saskatchewan, and you're back in course work at McGill University.

Dr. Gold: Right, which I loved. I felt absolutely at home, during my PhD, I felt at home. The only way I didn't feel at home was, unfortunately, I am a tremendous klutz, and almost incapable of doing an experiment, so that was a bit of a handicap. And, eventually, because of the group, I came into a situation where I could apply what theoretical expertise I had, and have the experimental work done by people who were better at it than I was.

Christopher Canning: That a very nice segue into the group. And so we've traced years of your intellectual, political past and here we are in 1972.

Dr. Gold: Yeah, I started my PhD in 1967.

Christopher Canning: And you would have been finished in 1970?

Dr. Gold: I had it done by 1970 and I'm not quite sure what I did in-between; there must have been a hiatus between doing my PhD, because I went through my PhD fairly quickly.

Christopher Canning: OK.

Dr. Gold: I think two and a half years. Well, I would have had it by 1970 and, well, the group started in 1972.

Christopher Canning: In 1972. The application would have gone in the spring of 1972 and the funding came in the fall.

Dr. Gold: So I did some emergency work in the emergency room at the Children's Hospital, but I'm not quite sure what status I had or how I stayed on.

Christopher Canning: You have a 1971 publication here with Scriver on amino acid composition of hair in different racial origins.

Dr. Gold: I'd forgotten that one completely. I'd forgotten that one.

Christopher Canning: So I guess you were still doing some research with Scriver before that, or in the early 1970s?

Dr. Gold: I don't know how that—I can't reconstruct that one. I even forgot that I did that and I can't really reconstruct under what aegis I did that, whether I did that as a student. I couldn't have done it under the group because the group didn't exist then.

Christopher Canning: But here we are, you forming a relationship with Scriver. You did your PhD with him. You initially had interest in working with Fraser and these are the two founding members of the MRC Group.

Dr. Gold: Yes.

Christopher Canning: Founders of this project.

Dr. Gold: They really are, yes.

Christopher Canning: So how then did you first become involved? Can you recall being invited to participate in their research, or the Group more broadly?

Dr. Gold: I think that Scriver invited me to join the group and I said fine. I think it was a simple as that. I mean, the forming of the group was a really an amazing thing because apart from Charlie [Scriver] and Clark [Fraser], none of us had any real track record at all. I mean—who were the initial members of the group? It was Charlie, Clarke, there's Peter Hechtman and me.

Christopher Canning: Peter Hechtman and David Ronseblatt, who joined later in 1975 but was on the 1972 application.

Dr. Gold: David Rosenblatt.

Christopher Canning: He was written on this first application but he was in the States doing his

postdoctoral training in Boston.

Dr. Gold: So none of the three of us had any visible track record at all. So I mean, it's an amazing feat for them to have got us in and we really were non-entities.

Christopher Canning: Do you remember writing that application?

Dr. Gold: I don't think I wrote it.

Christopher Canning: Well, there's a long list of your work in keratin genetics and in the initial application, which I have a copy of, there is a five or six page description of your research in keratin genetics.

Dr. Gold: I don't remember that. I didn't realize I'd done that, but even then, I mean, there may have been a number of papers but scientific content of it was really very negligible.

Christopher Canning: Well, actually, I'm really interested in this because you were written in that in your first application.

Dr. Gold: You're telling me things now that I'd forgotten.

Christopher Canning: Well, interesting, because your work was written into the application as an exciting new area of genetics, which examined keratin proteins in hair follicles. So what was exciting about that research at the time and how did that influence the formation of the group? It seems that the MRC found your research compelling enough because there were actually two unsuccessful applicants on the application. Margaret Corey--

Dr. Gold: Oh I forgot about her, I didn't even—I'm not even aware of that.

Christopher Canning: And Hy Goldman.

Dr. Gold: Well, Hy Goldman was no scientist. I mean, he was a very nice doctor and that's about it. I mean, he was a very nice man. He was a socially very active guy in the Jewish community and so on, but not a scientist. He had no idea what science is. But Peter Hechtman hadn't done much, had he?

Christopher Canning: He was new out of his PhD as well.

Dr. Gold: And had Rossenblatt done anything?

Christopher Canning: Rossenblatt had just finished his PhD and he was doing his postdoc in the States in Boston. So, you had just finished your PhD, Rossenblatt was doing his postdoc, and Hechtman had just graduated as well.

Dr. Gold: I didn't realize I'd done anything significant before the Group. Well, okay.

Christopher Canning: So what was it about keratin genetics that interested you, or was interesting in the context of the group? Can you recall from that time? I mean, obviously this was your area in the group.

Dr. Gold: Well, I'll tell you what interested me. Okay, what interested me about it was that if you look at the keratin in hair, there are various groups of proteins that are high tyrosine proteins, high lysine proteins, but each of these groups has a very large number of individual proteins. So, I mean, hair is dead stuff. It's not biologically very important, but I had two questions. There were two questions that really intrigued me and one was, why the hell are there so many different proteins of a similar kind, right? I mean, that's a theoretical question, and secondly, how does the mutation of one—as became clear later on, the amount of all of these proteins is being reduced. The whole group of proteins is being reduced by about a half as we later showed with Susie [Tenenhouse] and another bit of work on the naked mouse where you really got accurate within the work on the naked mouse, which was an inbred strain.

Christopher Canning: This was a 1976 publication. I have this here with you and Dr. Tenenhouse.

Dr. Gold: There were a couple of them--

Christopher Canning: In biochemical genetics, yes.

Dr. Gold: The collaboration between—I'm sort of digressing a little bit.

Christopher Canning: We can come back.

Dr. Gold: I'm going to come back to it. I haven't forgotten what we're doing. The collaboration with Susie [Tenenhouse] was wonderful because she was a fantastic experimentalist. I mean, to see her do an experiment was like watching an artist at work; everything was accurate and precise and the interaction between us was a very good example of how a group works. I don't know whether you've interviewed her yet. I mean, she did experiments I could never have done as well myself, if at all, because I'm a total klutz in the lab. If I do an experiment, it's sure not to work. There are people like that who are not manually adept, but she was a fantastic experimentalist!

On the other hand, I don't know what she will say. I think I was able to see in the day and to suggest experiments that she may not have seen herself, but I don't know, maybe you can ask her what she thinks about that. I saw ways of interpreting the data that maybe she wouldn't have seen, or maybe didn't see it at the time.

So together with the theoretical aspect and the experimental aspect and I

wrote the paper and I'm a good writer more or less, I mean, I'm as good a writer as I am a bad experimenter [laughs].

Christopher Canning: So I see that Dr. Tenenhouse is involved here, but she doesn't come into the project until 1981. What can you tell me about that?

Dr. Gold: Well, there's a story about that.

Christopher Canning: I would love to hear it if you don't mind.

Dr. Gold: Well, first, let me just get back to why I was interested in keratins and I'll tell you the story about Susie. Well, so the thing that interested me was 1) why should all of these very similar proteins exist, I mean, when one could've done with one? This was a dead tissue, so why do you need it and did it have a biological purpose? And, secondly, how would a single gene modulate the quantity of a whole family of proteins, not necessarily one?

Christopher Canning: Amino acid chains?

Dr. Gold: Yeah, I mean. Yeah because the Bible says that one gene, one protein and this is one gene and about 12 different proteins reduced by half. So the thing that excited me was I thought, maybe we're onto a regulatory gene. There was a thing at the back of my mind. I don't know if that is what interested Scriver, but that's what interested me.

Christopher Canning: And at the time, what was meant by the regulatory gene?

Dr. Gold: Well, we knew how genes were regulated in bacteria with operon and so on. We knew quite a lot about the regulatory genes and viruses. In fact, we didn't know anything about regulation of genes in higher animals, so we didn't know whether higher animals had operons. We didn't think they did because genes with related function were not necessarily contiguous on the chromosomes as they are in bacteria, right?

But what I meant by a regulatory gene is some gene that controls the production of a large number of proteins. It was as vague as that, and the interesting question is, is there such a regulatory gene? And, if so, how does it work, right? I had no idea of this.

Well, eventually, it proved too ambitious a question to ask. I still haven't answered that question. In Toronto, we got onto analyzing a similar problem with the cat-mouse. This is a mouse that has a cataract in the eye and again, a family of crystallins is reduced by a mutation of one gene, so we thought, let's try and tackle that while we have very good molecular geneticists there, so I got Tsui Lap-chee interested in that gene and they discovered that, in fact, this was caused—the mutation was in one of the genes, the coding for one of the structure of proteins, so one of the gamma

crystalline. And so now, the question is, and I do think we have answered that question, why does the mutation in a gene encoding one of the family genes cause a reduction in the whole family?

So that question, honestly, to the best of my knowledge is still unanswered. So the story about Susie Tenenhouse is--

Christopher Canning: Just before we move there, I'm hoping you can expand on the topic of keratin. It's written into the 1972 application, but it drops off after that.

Dr. Gold: What's written into it?

Christopher Canning: Your interest in keratin genetics, because, obviously, you're no longer involved in the group in 1977 and no one is looking at keratin genetics after that.

Dr. Gold: No.

Christopher Canning: So what caused the decline in the interest of keratin genetics? Were there questions still unanswered or was keratin genetics too broad of a field?

Dr. Gold: Well, I think two were two causes; one is that we had taken the problem as far as our wits and our technology allowed us to take it, because to answer the more fundamental question would've required molecular genetics of a kind that wasn't yet available, right? Which brings me under another subject or question: why we should study human genetics at all, but that's another good question.

And then Susie Tenenhouse got interested in something else, because Susie was really Charlie Scriver's professional assistant. But she got interested in my genetics problem, and I think it was something that says a lot for Scriver; he didn't caveat that. He said go ahead if that's what interests you, work on that. Then she got interested in the phosphate rickets problem, so she started working on that.

Christopher Canning: Which Scriver was working on?

Dr. Gold: Yeah, and also because I started getting interested in something else. So Susie and I stopped being interested in keratin, Susie partly because she got interested in something else, I partly because I couldn't see where else to take it. I couldn't see how you could attack the problem any further and actually, when I got to Toronto, we did tackle it further with a different mutation but we didn't find the answer to the question of how a gene worked.

But then I got interested in the mathematics of screening and that sort of became quite a big project, and I got a lot of papers out of that because

every time they did screening, they used my mathematics or our mathematics and so I just got my name on a lot of papers through that.

Christopher Canning: So you made an interesting point a few minutes ago that this is how the group worked at the time, you were the theoretical side, Susie was the experimentalist, etc.

Dr. Gold: More or less.

Christopher Canning: Was Scriver more the experimenter as well?

Dr. Gold: He was the promoter.

Christopher Canning: What about Fraser, what was he doing at this time?

Dr. Gold: Well, Fraser, he's a wonderful man. I love Fraser; he's such a genuine guy. He's a very straight guy. He has no façade. I love people who don't have a façade and he would challenge you intellectually. You would think that he was the guy who'd come in to clean the board, and I think that's wonderful. The same with Tsui Lap-chee; have you heard of him? I worked with him in Toronto. I got him interested in the crystalline problem, but he was the guy who isolated the cystic fibrosis gene, right? And he was like Fraser; he would come into the lab and you would think he was the technician. He was actually a world famous scientist. So, I loved that about him. He really functioned—how would I put it? You know, it was really Scriver who was the engine of starting the group, and of course, he included Fraser because he was always a big figure in human genetics. It wouldn't have been a good idea to start a group and not have Fraser, not because there was much connection between what the two would do, really; he was interested in congenital defects, really; I mean in mice and men and women.

But, actually, again it turned out that there was an interaction because he was the one who suggested to me that I should look at the naked mouse.

Christopher Canning: Fraser suggested that.

Dr. Gold: Yes, He was on the Nature paper with me. I'd put him on the paper because he suggested that we look at that and that was a very fruitful suggestion.

Christopher Canning: Because that got you involved in the group as a whole?

Dr. Gold: Well, I had already been involved in the group, but it gave me tremendous angle on tackling this problem of one gene involving many proteins. So that's what I worked on with Susie.

Christopher Canning: Again, I want to come back to the early days of the group, because you were one of the founding members; it's great to get a little more perspective. But

before we do that, let's go to that story about Dr. Tenenhouse. So she was involved, obviously, in the early 70s, but wasn't a member of the group until the early 80s.

Dr. Gold: This is Susie.

Christopher Canning: Yes, Dr. Tenenhouse

Dr. Gold: Well, what happened was that she became a principal investigator after I left the group.

Christopher Canning: She was on the 1980 application, and was successful in 1981.

Dr. Gold: As a principal investigator? So that was in the middle of the term; well that must have been either the application after I left or two after I left?

Christopher Canning: Two, actually. You were not on the '76 or '81 applications.

Dr. Gold: Well what happened was that Susie was still kind of an adjunct, but she was a very, very good experimentalist. And—but she was just a hanger-on; I mean, she hadn't a status as a professor. Well, it is a status but it's a minor status of being a professional assistant, so she didn't have independent visibility.

And Scriver was not very good at promoting. He was very good at providing facilities for collaboration, but he wasn't much for promoting people's careers, right? So he didn't make any moves to get [Susie] tenure or on a tenure track. So her husband I knew very well; Alan Tenenhouse is quite a character and he was at the Montreal General Hospital. He was interested in calcium metabolism, which related to what Susie was doing, and he finally said, he said to Scriver, "well we should do something for Susie," and Scriver said, "Well, there's nothing I can do."

Christopher Canning: He said that there's nothing he could do? Interesting.

Dr. Gold: Well, I'm reporting Alan's comment; he said, "Come off it, Charlie!" Then he says, "you've got more power at the university than anybody else and a word from you and you can get her onto a tenure track." And so [Scriver] did and that's what got her onto the tenure track.

Christopher Canning: Was she interested in becoming more involved in the group when you two were publishing together in the mid-70s?

Dr. Gold: Well, she was very gentle. She was a very gentle and demure person, but I call her steel. She has ambitions, too, and I suspect she had expressed her dissatisfactions to her husband who was much more—what's the word, much more forthcoming in his opinions than she was. And I'm sort of

deducing this, but anyway, whatever the truth of that, Alan [Tenenhouse] told me that he had gone to Scriver and said that he'd better do something or…and then he did. It was as a result of that, I think, but I also think Charlie [Scriver] would have been quietly happy to keep her on a principal investigator and not give her a push for her own position.

Christopher Canning: Do you remember the procedures back then for applying for a group grant? The group formed just a few years after the MRC first granted group status, and what's interesting, I think, is that there was a stipulation in the awards guide that all members must be in the same physical environment. What was this physicality of the group like in the early '70s?

Dr. Gold: I think Scriver had to show that we had space for research, and to conduct this research; we had very crammed space, but we all worked together and eventually ended up in the same space. Even Rosenblatt, I think, he later deviated into something else, but I don't remember; my memory of those early days is not very good. Scriver was really enchanted and I'm not even sure to what extent I wrote part of the proposal. I mean, I may have done and I may not have done it. I don't even remember whether I wrote anything on it or--

Christopher Canning: If I showed you the application another time, would you be able to tell me?

Dr. Gold: Oh yeah, I should be able to tell you who wrote it, because Charlie and I write in completely different ways.

Christopher Canning: I will show you the application at one point.

Dr. Gold: Then I would know.

Christopher Canning: Yeah, okay.

Dr. Gold: Then I would know. I guess, Charlie would've said we were going to write something and I guess I may have, but I can't recall, I'm sorry.

Christopher Canning: I have heard that in for early applications, the director, which is Scriver and Fraser, were responsible for writing the applications. I don't know if that's what happened in your case, though, of course.

Dr. Gold: I really can't remember, but I would tell you immediately if I see the keratin part of the application, because Charlie and I had very different ideas on how to write on science.

Christopher Canning: Okay. I will show it to you the next time we meet. Do you recall the physical space as a group at the time? There was something built in the Montreal Children's Hospital, and, eventually, a laboratory was set up.

Dr. Gold: That's right. I think on the eighth or the seventh floor? Yeah, and it was a small place with not many separate offices. I mean, I didn't have an office and Charlie had a little office and Clarke was at one of the end and we were at the other end and we just had benches, open benches and students; we all crowded in this very small space.

Christopher Canning: Were you running experiments at the time then?

Dr. Gold: Oh yes! We did a lot of experiments in that space.

Christopher Canning: Did you have graduate students at that time?

Dr. Gold: Yes, I had several. I had three, but two of them, when I left the group, two of them were put onto somebody else.

Christopher Canning: I'm intrigued by your relationship with Dr. Scriver. What was it like during those first four or five years on the project? And how was the relationship, not just between you and Scriver, but also between him and the rest of the group?

Dr. Gold: He was the guru, you know.

Christopher Canning: Interesting. So, more specifically, what was your relationship like with him and the group as a whole? I mean, how did that affect the working dynamics of this group, especially during these early formative stages of the group?

Dr. Gold: My relationship, huh. Well, in the beginning, I admired him very much for his administrative abilities. Well, you see, what I admired about him was that he was very skillful in setting up the organization in medical care, particularly in relation to genetic diseases. And that was a theory, I mean, it was very interesting because I always participated in research in Saskatchewan on the delivery of medical care and I have a lot of interest in the logistics, politics and economics of delivering medical care, which is a very interesting subject.

And so, he was very good at that. He was just a consummate politician; I mean, he got Steinberg to put vitamin D in milk, which was an excellent contribution and attribute. So I started off by being a great admirer of his for about a year, and then I began to realize two things. One is that he didn't really know very much about science. I mean, not basic hard-nosed science. The other thing was, he was a bit of a con artist. I mean, I saw him on the one hand as a consummate politician and I saw him on the other hand as a sort of a Leonardo con artist. And I don't know whether you've had this view from anybody else, but that's my view of him. He was very preoccupied with his image and you know, when you're in a so-called clinical research, you have this tremendous temptation to represent yourself to

physicians as a scientist and to scientists as a physician, and I must say, I probably did this myself because you probably see from my CV, I gave a lot of lectures. But when I gave lectures, I still tried to stress how little we knew and so on, but Scriver wrote a fantastic amount of real bafflegab. I mean, stuff so extraordinarily, how should I say; I don't know, but real emotional garbage. You were amazed that he could get it published at all.

So he was very, very preoccupied with his own self-image and I mean, it was very obvious that he was very concerned with the welfare of the group, but the welfare of the group, I felt, was a mechanism to feed his own image. This is the way I saw it. Later on, I was concerned that I only had an adjunct appointment in biology and an adjunct appointment in pediatrics. So I said, well I said to Scriver, "I'd like to get on a tenure track." And it wasn't really for security, because I'm really not financially insecure, but it was really a matter of principle, more than anything, and a matter of having one's status recognized rather than being sure I could make a living, because I had my own income and I could always make a living as a physician, anyways. It wasn't that, although Scriver imagined it was. He said, "You know, I don't have tenure myself." So I thought to myself that this guy, whom I had previously taken to be a man of unimpeachable integrity had, in fact, a precarious apprehension of the truth caused, I believe, by the possession to an unusual degree of the capacity to believe what is convenient. That was my immediate reaction. It came as a shocking insight.

Christopher Canning: Wow. Okay. How long after the start of the group did this come about, a couple of years?

Dr. Gold: A couple of years. First year, I thought great and then after all--

Christopher Canning: You were fresh out of a PhD?

Dr. Gold: I was fresh out of a PhD and he got me into a wonderful group, you know; you have to recognize that. I didn't have to do a post doc, right? I mean, I went straight from being a PhD to being a principal investigator and that was an amazing achievement on his part. So there's that aspect. That was sort of the good part of his consummate political skills, I think. So when he told me, "I don't have tenure," I mean, I thought that this guy was playing games and he said, "Well, look, I'll be frank with you, it's going to be very difficult, if not impossible, and if you're really anxious about getting tenure, maybe you should think of going somewhere else. Because I don't think we will be able to pull that off, or it's very unlikely, but if we do well in the group, you've got a good future here in the status that you have; and if that's okay for you, that's okay, it is not then—I'll be honest, I can't do much." I would have accepted that. In fact, I would have said, fine, but he said, "I don't even have tenure myself." I said, my goodness!

I suddenly got this tremendous insight. It came as a shock. I'll give you the

only other instance I had with him. There was a guy I used to play chess with. This was when I was a medical student. He was a very pleasant rational guy and I played chess with him for about six months. We had nice tea together and we played chess in the YMCA and so on; he was a student of some kind. And one day, while we were playing chess, he said, "did you know by the way that the Jungian analysts are trying to kill me?"

I thought he was joking. I said, I thought maybe he was training as a Freudian and expressing his disagreement. I said, "haha, okay that's very funny." No, he said, "I'm serious," and it turned out that he was schizophrenic, but I had that kind of a shock. Not that I'm saying Charlie is schizophrenic, but the shock--

Christopher Canning: A realization?

Dr. Gold: Yes, that a man whom, as I said before, I had assumed to be a man of integrity turned out to be something different.

Christopher Canning: Wow. And did this scar your relationship with him?

Dr. Gold: Oh yeah, oh yeah, because I rumbled him, and in a way, he knew I'd rumbled him, but I played along and said, "That's devastating." That's bad because I knew he had tenure. I said to myself, "Why is this guy telling such an obvious lie?" So I went along and I played along and I said, "Wow, Charlie, that's very bad news." I played along because he thought I believed him, right? I said, "That's very bad news because, I mean if you with all of your achievements cannot get tenure, what hope do I have?" So I said, "Well, you know, I'm going to write to the Dean and see what my relationship is with tenure because I'm going to tell him if you don't have tenure, I'm anxious to get a tenured appointment; if you haven't got tenure, what hope do I have? What's my future in this university?" Charlie said, "Go ahead."

He didn't believe I was going to do it, but I did it! So I wrote a letter to the Dean, I said, I'm very disturbed. I told him I was going to do it. Scriver said, "Go ahead, do whatever you like," but he didn't think I was going to do it. I don't think he thought ahead in those terms, but I did it, so I wrote to the Dean and the Dean said, "Of course, well he has got tenure." Well, the dean said, "Don't worry, he has got tenure."

And I suppose he wrote to Charlie about this and Charlie was very sort of edgy at our next meeting and he said, "Well, you know I didn't know. I didn't know I had tenure," and I was like, he was just playing games. So then there were several incidents that I won't bore you with, so I thought--

Christopher Canning: Was this affecting the group as a whole or was this a particular problem between you two?

Dr. Gold: Well, it was, because I made a point of pursuing in a very nice way. I mean, I didn't shout or rave; I just pursued my point. And as Clarke Fraser would put it, you break down his arguments one by one. And that's what I did. I mean, but I don't know why he does that. But I'm not the only person who thinks this.

Christopher Canning: And obviously, you're all working in the same space at the time and you were conducting experiments on your individual projects that are contributing to this group.

Dr. Gold: Indeed, I think he could have arranged for my tenure as he did with Susie, but you know, I don't know if that's the case or not, but he treated the whole thing in a very deceptive way.

Christopher Canning: The whole thing meaning the whole group?

Dr. Gold: With me. But I was the one who pressed the issue because the way I read myself, and you understand the surface estimates are very precarious, so I think that I'm a fairly tolerant guy, but if I think that somebody was screwing with me, I get really tough. If I think somebody can't help it or is a bit irascible, I'll go along with it, but I feel that somebody is deliberately screwing me, I get very, very tough.

Christopher Canning: And you felt this at that time?

Dr. Gold: Oh yeah. Now, I don't know why he did it. You see, there were other aspects to our relationship. Well, the other thing that I got into—you ask me why I left? You see, he's a very strange man. He's a very strange man in many ways. Well, first of all, we're going back to where I left keratin. I left keratin for the reasons that I stated, but also because I got interested in the screening problem. Charlie had developed a two-test method of screening, but I read his papers and he used two methods and his two dimensions was screening for carriers of PKU and the carriers of Tay-Sachs, and I suddenly realized that he was misusing the data totally. I mean, in mathematical terms, he was using the data totally wrong, absolutely misusing it; and so, I told him this. I told him I was going to write a paper, and he said, "Fine, no problem."

Christopher Canning: What was your training in mathematics?

Dr. Gold: None really, but I mean, I did calculus in high school and that's all, but I have a sort of reasonably secure grasp of elementary mathematics. I never trained with that, but I mean, it's not such difficult mathematics. So one way he was using it wrong was, okay, it's a bit difficult, I mean, do you have any idea of probability theory?

Christopher Canning: Very basic.

Dr. Gold: Well, let me try to explain one very elementary way in which his mathematics were very dangerously wrong. He was screening for carriers of PKU, so he was using a test to screen random members of the population for whom the probability of being a carrier is maybe one in fifty. And also, normal healthy offspring of two carriers, in which case, the probability is two-thirds. If an offspring of two carriers got the same test result as an offspring of a random member, he would give them the same probability, but that's totally wrong because you start off with a higher probability even though your test result is the same, and the probability is higher because you can work it out by a thing called Bayes' Theorem. But not only that, he didn't think in terms of probability at all, you know. So I did this mathematical analysis together with some collaborators.

Christopher Canning: At the time of his work in screening?

Dr. Gold: Well after he had published his paper in Nature. And the interesting thing about it was, first of all, he totally accepted it. He didn't say, oh, I don't know; he didn't fight it. And he accepted it, and in fact, he talked about it to visitors or he mis-explained it because he didn't understand it; totally absurd, I mean, he was a co-author on this paper!

So, you can say, well, in a way you can say this shows great tolerance and benevolence of spirit. But, the thing is, the other strange thing, he totally accepted it and did not understand a word. I find that strange; that's very strange. So you can say that it shows tolerance and benevolence and greatness of spirit, which it does. But there's more to it than that and I can't explain quite what the more is. Because you would think that somebody's published a paper in Nature, and then get shown that it's totally wrong. And he doesn't understand why the other person thinks it's wrong. You'd think he'd go into them, no. He didn't really understand it.

Christopher Canning: How did it get published in Nature?

Dr. Gold: Well, Scriver got it published in Nature

Christopher Canning: But if the mathematics and probability were questionable?

Dr. Gold: Well, because it was in the early days and it was a good idea. It was a good idea to use two tests and I guess the person who read the paper maybe didn't think about the mathematical aspect. Lots of things get published; all sorts of stuff gets published. The other big question about the group is what did it actually accomplish? This would be interesting question, because I mean, it certainly accomplished orchestrating and organizing the care and detection of people with genetic diseases. I mean, it did that very, very well, probably better than anywhere else in the world. Okay, so if that was the

intention of the genetics group, it accomplished its goal. Did it achieve enough science? I don't think so.

Christopher Canning: The group as a whole?

Dr. Gold: No.

Christopher Canning: Throughout its 37 years?

Dr. Gold: Well, I don't know much what it accomplished. I mean, it wrote papers, lots and lots of papers, but the question is, how much genuine breaking through the frontiers of science was there? I don't know what happened after. Do you know of any? I mean, there certainly wasn't any when I was in the group either what I did or anybody else did. There was no discovering the T-cell receptor or identifying the gene for whatever.

Christopher Canning: Well, I'm going to read to you from the 1972 application. Here is what was laid out in the application as the goals of the research. Perhaps, then, you can tell me what was accomplished. The application states that the goals of the group were to discover the etiology of modes of inheritance, estimate genetic component of familial diseases other than Mendelian, study the genetic susceptibility of disease, and further the goals of genetic counseling.

Dr. Gold: Actually, I did something on the mathematics of genetic counseling; I did that. It's what I've just told you about, but I also did a sort of mathematical algorithm, so that given a whole set of information about members of a family; given the pedigree and sets of relevant information about each member of the pedigree, there was a sort of robotic algorithm you could use to calculate the risk of everybody without thinking. I think that that's mentioned in my application of clinical genetics, so I guess, I did something in genetic counseling in that sense.

Christopher Canning: And that seems to be a field that has trickled through from the 1970s until now; genetic counseling is still a major goal of medical genetics.

Dr. Gold: Well, doing the genetic counseling, yes, but anyway, go on with the goals of the group and I'll tell you more.

Christopher Canning: The etiology of the modes of inheritance.

Dr. Gold: I don't think we've discovered much about that. But I don't know; I'm not aware of the papers that came after me, after I was in the group. But do you know of anyone that did that?

Christopher Canning: This is what we're still investigating; it would be too early in this study for me to say what the group did or did not discover.

Dr. Gold: I mean, we discovered that in one dominant disease, there was a loss of a family of proteins, but that doesn't really tell you the etiology. It tells you something that happens in something that is dominantly inherited, but it gives no insight into the mechanism. Anyway, go ahead.

Christopher Canning: Well, in particular, you were studying ectodermal dysplasia?

Dr. Gold: That was a dominant inheritance.

Christopher Canning: That's a dominant inheritance, and so--

Dr. Gold: And the naked mouse. So what are the other goals?

Christopher Canning: The other goals were to estimate genetic components of familial diseases other than Mendelian.

Dr. Gold: We'll still can't do that, even with all of our modern molecular genetics; we're only just beginning to scratch the surface of that.

Christopher Canning: The morphology of chromosomes.

Dr. Gold: Were there any cytogeneticists in this?

Christopher Canning: During the early years of the group, and this is written into the formation of the group, was the merging together of cytogenetics and teratology, which was Fraser, and biochemistry, which was Scriver.

Dr. Gold: Well, Fraser doesn't do cytogenetics.

Christopher Canning: He was doing cytogenetics and teratology, if I recall correctly.

Dr. Gold: Was he?

Christopher Canning: Yes, in the 50s. I think he trained other cytogeneticists and did some work in that area.

Dr. Gold: Oh yeah, he did this, that's right.

Christopher Canning: So you have the cytogeneticist, the study of the morphology of chromosomes, and then you had biochemistry and pediatrics; this was the rhetoric of the first application, or the fields under which the group defined itself early on.

Dr. Gold: Oh pediatrics isn't a scientific goal, I think. It's a specialty in medicine. So it was a very applied group. In other words, it's sort of orchestrated and trimmed around the edges of genetic care. Now here's a fundamental question, why would you want to have a group in human genetics? I think it

would make more sense now, but think of that way. If you really want to study how genes work, the mechanisms or the sort of engine of life, you don't want to study humans. Why? I mean, not at that time. Maybe mice, e coli, or viruses, but it was really very difficult then that the state of knowledge of human genetics would make any scientific breakthroughs in human health, or by using human genetics as a vehicle for breaching the frontiers of science.

Christopher Canning: Obviously at the time, though, human genetics research was not necessarily motivated by the outcomes but by the possibility; these early years are filled with a promissory rhetoric.

Dr. Gold: Right. You see, at that time, human genetics was very clearly a field in which the possibilities for genetic, that the possibilities for advancing the understanding of genes was the most limited, right? There were two reasons, really, then, to study genetics. One was a narcissistic wish for self-contemplation and hope for medical advances.

Christopher Canning: That's what you would say were the goals of early medical genetics?

Dr. Gold: I would say part of it, yes, but if you would have asked the question…let's say the head of the Medical Research Council said to himself, "Why do I want to have a group in human genetics?" If I wanted to know about the fundamental advances in genes, I wouldn't pick humans. So he would say, well, the reasons for studying this human genetics is sort of a narcissistic goal of being interested in ourselves; there's nothing wrong with that, except it has nothing to do with science. And then, the other reason would be because it's relevant to medicine.

But the hope of doing anything fundamental in human genetics at that time was very small. Now I think there are two reasons why you would be interested in doing human genetics, from a scientific perspective. One is, when you've got the genome, and we do know a hell of a lot of phenotypes, I mean, we have a more detailed knowledge of genetically influenced phenotypes. So if you've got a whole sequence of genes with a tremendous repertoire of phenotypes, it gives you a good opportunity for penetrating the mechanism of gene action. Even so, we haven't got—well, it depends on whom you listen to, but we've got very, very little distance along the way, but it's going to come.

The other reason is, because it's a way of trying to find out the genetic basis of consciousness, because consciousness, part of the fact that we happen to be the ones who have it in this way, is in its own way a scientifically fascinating phenomenon. And if you can find out why we're not chimpanzees by looking at the difference in the genome between the chimpanzee and the human, you've got an idea, you've got a beginning, and what are the genetic differences that have enabled us to be conscious in a

way that a chimpanzee isn't?

And we've got now this human accelerated regions, if you've heard of them, where by very complex mathematical and computer methods, they've managed to identify regions of the human genome which have changed very rapidly from that of the chimpanzee over the last six million years. And when you look at these regions, you see that there are genes already known to be associated with speech and brain function. That's very interesting. So now, if I were going to put a group in human genetics, those are the two areas I would look at.

Christopher Canning: So the irony, of course, of what you're saying, is that it would be better to fund a group project in medical human genetics now as opposed to 40 years ago. And yet, why did the MRC fund the group for 37 years?

Dr. Gold: I don't know, do you know?

Christopher Canning: That's what we're trying to find out. Why would you say?

Dr. Gold: You should ask who made the decision? The other thing you should find out, but I should be presumptuous to tell you what to do, but what would be interesting to me is to find out why they stopped the group, all the groups, they stopped. Do you know why they did that?

Christopher Canning: I have no idea, but it's something we're going to look into. Interestingly, however, the director of the MRC in the early '70s, Dr. Malcolm Brown, was a friend to Scriver's parents. So that was a big reason McGill folks got involved with group research from the outset.

Dr. Gold: Political skill.

Christopher Canning: Of course, and there's obviously early politics concerning how this group formed. But there were other groups in Canada as well, both in Montreal and elsewhere, which concerned other areas of science.

Dr. Gold: Well, the interesting question is, is it good to have groups? That's a good question. And I think the answer is, if you have people who are really hot, but in different fields, you can be very, very productive, but if you have mediocrity in the group, there is a sort of potentiation of the mediocrity. So a group potentiates what's already there and none of us in that group, I think, were outstanding scientists. I mean an idea of a good group is the Perimeter Institute in Waterloo. This is the first time, I think, that Canada is starting to have a world-class university, in Waterloo. And then, of course, what's the other? The Weizmann Institute; this is an excellent example of a group thing.

Christopher Canning: Where is that?

Dr. Gold: The Weizmann Institute in Revohot, Israel, which is where I taught a few years ago. That is a good example. So that's about it; I've said it all actually. And I don't know whether you want me to say anymore.

Christopher Canning: That's great!

Dr. Gold: How long have we been at this?

Christopher Canning: An hour and a half, which is great.

Dr. Gold: I've said most of the things. By the way, I want to tell you about a few ideas; it's not really relevant, but I have a very, very new idea. I've been thinking about writing an article on this, and that is how medical care should be organized and it's quite clear to me what they should do. You've got to have a single payer. The reason that Obama had so much trouble is it's very difficult to start off if you don't have a single payer or state pay. You can do the Swiss thing where it's done by insurance companies, but it's tightly regulated and they're not allowed to make a profit in Switzerland. And interesting enough, even though they're not allowed to make profit, they still compete vigorously with each other.

But the way to do it is you have a single payer and then the state funds HMOs, which is an American invention. They had a bad rap recently, but they're very good. So, in other words, you get together all of the physicians and facilities you need to, say, look after 500,000 people, right, and the psychiatrists, health economists, nurses, psychotherapists, psychologists, general practitioners, pediatric, plastic surgeons, whatever you want and you get a group together. You know, presumably, the number of people who can be looked after the most verified specialist is probably a good denominator. So half a million people and everybody has to join one of these group's patients and then the government says at the beginning of it, look boys, we see you've got 500,000 people on your books and the tax payers agree to pay $4000 or $5000 a head for taxes for Medicare, so here is $2 billion, best of luck, see you next time!

It's as simple as that and you suddenly find the physicians would discover that nurse practitioners are the greatest thing since sliced bread. And the health education that works would be put in because it saves money and the stuff that doesn't work would be ignored. so that if they find they could save money by getting people to come in, but perhaps they'd be coming in and if they found it didn't do a damn thing to reduce their costs, we wouldn't come in for that.

That's the way to do it because if you—the government can't decide, so you have a board which has doctors on it, businessmen, health economists, patients, and the income of the medical care providers is all thrown into the

pot, so you've got a very good doctor and the board really wants to keep him, well they'll pay a little bit more. And if he' no good then we'd be happy to not raise his salary and he'll be gone. That's the way to do it.

Not only do I think it's the way to do it; it's the way it's got to be done because it's going to be the only solution. So what do you think of that?

Christopher Canning: You obviously know much more about this than I do.

Dr. Gold: I'm going to write an article on that.

Christopher Canning: That sounds wonderful. Are you still writing these days?

Dr. Gold: Well, I'm writing that article.

Christopher Canning: Great! Can I read it?

Dr. Gold: Not yet because it doesn't exist yet, but I mean, I'm going to submit it to the Globe and Mail as a focus article.

Christopher Canning: Fantastic!

Dr. Gold: So I think I've said my peace, unless you've--

Christopher Canning: I think you have too.

Dr. Gold: Questions you want to ask me--

Christopher Canning: Just as a wrap up question, did you stay in touch with folks? Obviously, you moved to Toronto in 1977 to start working out of there?

Dr. Gold: Yeah, and then I did some research there and then I got tenured there.

Christopher Canning: Were you still practicing medicine at the time?

Dr. Gold: No, I didn't practice medicine. But I got tenure, but then for family reasons, my wife was and in fact, she still is a professor of psychology, couldn't get a job in Toronto and so, I though I would come home and stay with the family and practice medicine instead. I did that for family reasons, but also because I didn't think I was going to make a kind of fundamental breakthroughs that I was really interested in making.

And so, I mean, being a tenured professor isn't that big a deal if you're not achieving what you think you'd like to achieve thought in terms of basic science that I wasn't doing what I really wanted to do. I wouldn't be able to do what I hoped I would do, so I said, okay, let me practice medicine instead.

Christopher Canning: Great, and so have you stayed in touch with anyone from the group? It sounds like you and Dr. Tenenhouse were--

Dr. Gold: Well, I met her at the dinner, and as a matter of fact, she sent me an email after the dinner because she discovered…have you heard of…it's a famous folk singer, called? I forget. She's actually a world-renowned folk singer and Susie had just read a book in which this folk singer had given me the credit for launching her in her career. We had this coffee house called Louis Riel in Saskatchewan, and so we had folk singers there and debates on Cuba and so on and there was this waitress…and I'm just trying to think of her name, it'll come to me.

Christopher Canning: A Canadian folk singer?

Dr. Gold: Yeah.

Christopher Canning: Joni Mitchell?

Dr. Gold: Joni Mitchell, yes, that's the one! That's it! But she was Joni Anderson then. She was a waitress in the Louis Riel.

Christopher Canning: Okay, wow, Joni Mitchell was a waitress in your coffee shop?

Dr. Gold: I'd forgotten this completely, but I'm giving you this as recounted in her book. So she wanted to sing and she came and I with my fellow owners auditioned her and the other two said, "ah, forget it," and I said, "no," because I'm a musician myself, "she has something here!" So I insisted that we give her a chance and she describes me in her book as a bespectacled man with an Oxbridge accent driving a jaguar!

Christopher Canning: Excellent!

Dr. Gold: So anyway, she was very popular, so she credits me with launching her career. I'm sure if I hadn't done it, somebody else would have done it. So I just sent an email to her agent saying I'd love to meet with her. So I was very happy about that. After that, I had a part--

Christopher Canning: In the formation in Joni Mitchell's career? Neat.

Dr. Gold: So Susie sent me this email and brought my attention to this book to my attention and she had abandoned that she had recently read. Also, I rang up Peter Hechtman to ask if he would like to come to dinner or something, but I haven't had any reply, but I'm on very good terms with them, yeah. I have no problem.

Christopher Canning: That concludes my questions for today. Thanks very much for your time, Dr.

Gold.

END OF INTERVIEW

Dr. Leonard Pinsky, July 21, 2010

Christopher Canning: My name is Christopher and I'm here with Dr. Leonard Pinsky on July 21, 2010. It is my great honor to be here with you, Dr. Pinsky, to discuss two main themes regarding Human Genetics. First, I would like to discuss your academic background, which ultimately contributed significantly to the growth of medical genetics in Canada and beyond. Secondly and perhaps more importantly for this particular study, I'm interested in your involvement in the McGill MRC Medical Genetics Group, which you joined 1981 and remained until 1990.

So let's consider your background first and then we'll go into more detail about your research. I'm interested in where you were born, where you grew up and where you did your early years of schooling.

Dr. Leonard Pinsky: That's pretty comprehensive, I must say!

Christopher Canning: You can go into as much or little detail as you wish.

Dr. Leonard Pinsky: Well, I was special in one way. [Laughs] As early as I could remember, from around the age of 5, whenever I was asked what I would want to be when I grew up, I said I wanted to be a doctor. I have no idea where that desire came from. I had no relatives or no friends who were doctors. I grew up in an era before shows with medical themes appeared on television weekly or more often than that. And so until this day, I have no idea of why I wanted to be a doctor, but from such an early age I wanted to be a doctor.

I remember, as a teenager, one of my friends fell in an awkward way on the street, we were playing with a football made of a disposable pairs of socks; we made it a football out of it and then played touch football, and one of the guys fell in a funny way and broke his leg. And I remember the first thing I did was I was so frightened that I ran away from the scene of the accident and I got about 10 yards away, and I said to myself, "Where are you running? If you're going to be a doctor, you can't start running away." [Laughter]

INSERT STORY HERE.

So that's my introduction to the world of medicine.

Christopher Canning: Or how you became interested in medicine?

Dr. Leonard Pinsky: Yeah.

Christopher Canning: And where was this? Did you grow up in Montreal?

Dr. Leonard Pinsky: Yeah, Montreal.

Christopher Canning: You were born here as well?

Dr. Leonard Pinsky: Yeah.

Christopher Canning: And how were you as a high school student? Were you inquisitive in the area of science at that time?

Dr. Leonard Pinsky: I can answer that with another good story.

Christopher Canning: We like stories.

Dr. Leonard Pinsky: I grew up in a part of Montreal that was unique in that. It housed most of the Jewish families that immigrated to Montreal in the very first five, 10, 15 years of the 19th Century, a great migration of Jewish families to New York and Montreal.

INSERT STORY HERE FROM WRITTEN NOTES.

Christopher Canning: So how were you overall as a high school student then? Were you a good student?

Dr. Leonard Pinsky: Yeah, I wasn't bad, but I wasn't a superstar either. Sports were much more important to me at that time.

Christopher Canning: And how were your parents? Did they push you to be successful?

Dr. Leonard Pinsky: No.

Christopher Canning: No?

Dr. Leonard Pinsky: No. My father couldn't believe that he had a son who was good enough or special enough to want to become a physician. They're little on the—so, no.

Christopher Canning: You started McGill, I see, in the early 50s?

Dr. Leonard Pinsky: I started McGill in 1952.

Christopher Canning: Okay. Enrolled in what?

Dr. Leonard Pinsky: I enrolled in what was then called—I think it was called a mixed something. It was for people like me who didn't know whether they wanted to go into the arts stream or the science stream. So believe it or not, McGill offered a mixed undergraduate bachelors program and I quickly found out that I was

not a great mixer, and that I was going to do a hell of a lot better in science than in arts studying Latin.

Christopher Canning: Right.

Dr. Leonard Pinsky: At that time, it was still prevalent among lay people to think that in order to be a doctor you had to know how to write prescriptions in Latin. [Laughter] It sounds stupid, but that's how much times have changed. That's how much the times have changed in my lifetime for sure and my professional career as well! We've gone from thinking that you had to write prescriptions in Latin to writing, as it were, personalized treatment, is now the word now, for rare individuals with inborn errors of metabolism.

Christopher Canning: Yeah.

Dr. Leonard Pinsky: That's the definition of what's happened as you and I sit here at the end of that genetic and scientific revolution.

Christopher Canning: Yeah.

Dr. Leonard Pinsky: I lost the train of thought. It will come back to me about being in high school. But we might get back to it.

Christopher Canning: That's fine, okay. So you finished your undergraduate degree in 1956. You did a Bachelor of Science?

Dr. Leonard Pinsky: Yeah.

Christopher Canning: And I see from there, you would have entered medical school?

Dr. Leonard Pinsky: Yeah, I did. Now, if you want to talk about that—I guess I should talk about the undergraduate school.

Christopher Canning: Please, by all means.

Dr. Leonard Pinsky: That's very simple; in '52, I entered McGill. I told you about the mixed program—I was a mixed undergraduate. It quickly became apparent that genetics was my love and I remember now, this is pre-1955.

Christopher Canning: Pre Watson and Crick!

Dr. Leonard Pinsky: Yeah, that's right!

Christopher Canning: Yeah.

Dr. Leonard Pinsky: That's how far I go back. McGill did not have an honour's program in genetics until I and two other students came along at the same time, and we

expressed a deep interest in genetics.

Christopher Canning: Okay. Was this in the Department of Biology at that time?

Dr. Leonard Pinsky: At that time, it was the Department of Genetics.

Christopher Canning: Okay.

Dr. Leonard Pinsky: Later on, genetics and biology and zoology or whatever it is, they all fused and they defused and unfused; the precise chronology I can't give you. Although they're easy to find out if you want to. I don't think they're that important. Except that to say that genetics had a hard time finding its way out from the cloistered part of the university through the exposed part of the university with all the excitement.

Christopher Canning: So what got you excited about clinical genetics then? If there wasn't a lot of excitement about genetics at McGill, what made you excited about it?

Dr. Leonard Pinsky: That's a very good question. I'm glad you asked that. It's one of the few things that I give myself credit for doing or thinking or whatever and it's precisely what you just asked. Somehow, I saw through the morass of accumulated information up to the mid 1950s, give or take. Somehow I saw that the Truth about the fact that if one person became ill and another person otherwise or similarly exposed didn't become ill, that there was probably some difference between them in the way they were made, genetically speaking.

Christopher Canning: And at that time, because this is before the visualization of DNA, so was it just the concept that an illness must be an inherited trait?

Dr. Leonard Pinsky: Right. I don't want to claim sitting here now that I foresaw that DNA was the bearer of genetic information and the bearer of information that determined whether one person became ill and another person did not. I'm not claiming that I knew it was DNA, but I knew that there was something new.

I didn't know but you know what I mean when I say I knew. "I knew" that it had to be something like DNA to achieve the effect that I had perceived.

Christopher Canning: Who were you working with during this time? Who else was in the faculty then who was interested in genetics? And not just that, but the excitement of the possibility that would have application to human medicine.

Dr. Leonard Pinsky: Yeah. There were just three of us, just three of us—one, two, three! And there were three in the first honor's genetics program and the next year, another person turned out to be a very important addition. So that's all I can really remember with certainty, and the individuals are noteworthy.

One of them was a man called David Rimoin, who went on to laudible accomplishments in the field of Human and Medical Genetics. I won't go into too many details; it doesn't matter but he certainly turned out to be a superstar.

And there was a second person that went on training in obstetrics and gynecology and there was me. And then the fourth person, the one who joined in our second year, was a woman by the name of Dorothy de Montmorency who went on to achieve considerable and well-earned accomplishments in human cytogenetics.

Christopher Canning: Okay, so let's move into your med school years. So you finished your undergrad in this mixed department of biology and arts and then you went on to med school. So you had this sort of burgeoning interest in genetics at that time and in its application to human medicine. And so, how much did that become a part of your medical training?

Dr. Leonard Pinsky: Yeah, okay, good. Well, I started medical school in 1956, so DNA was already the talk of the town.

Christopher Canning: Yes, of course.

Dr. Leonard Pinsky: And it didn't need me to make a lot of progress because in a sense, progress was waiting to be made and things started to fall rapidly into place about what DNA might be doing or RNA or stuff like that.

My involvement in the world of genetics during medical school was, besides being busy with medical school, I spent every summer right through medical school working with Clark Fraser. And during that time, I developed more and more interest in my belief that genetics was the answer to a lot of the world's medical problems and then just strengthened that as I went on.

Christopher Canning: And I see in your later medical school years, I think you finished in 1960. You published a really interesting paper on genetic approaches to comprehensive medicine.

Dr. Leonard Pinsky: I did.

Christopher Canning: And you were young at that time. You would have been 24 or 25 years old.

Dr. Leonard Pinsky: Yes, I was. Yeah.

Christopher Canning: And so, what sparked to you to write this, because it seemed like almost a proclamation of the necessity of doing genetics in medicine.

Dr. Leonard Pinsky: That's true. I did. And it not only seemed that way, it was. That's what it was. I thought I knew—

Christopher Canning: Yeah, I know what you meant by "I knew". [Laughter]

Dr. Leonard Pinsky: I thought I had recognized the answers to the world's great medical problems and I set out to stimulate the awareness of these problems in the medical field, and I wanted to convince others that I was right. So I just gathered this information, which for a third and fourth year medical student was a lot; there are actually two papers I published under the heading, "Genetic Approaches to Comprehensive Medicine" and the other paper dealt with molecular pathology. I think and the second one was "Prevention."

Christopher Canning: In fact, "Genetic Approaches to Comprehensive Medicine Prevention" came first, I see.

Dr. Leonard Pinsky: Yeah.

Christopher Canning: Correct. That was your first one in 1959. Then "Genetic Approaches to Comprehensive Medicine in Molecular Pathology" was in 1960.

Dr. Leonard Pinsky: Yeah.

Christopher Canning: Do recall what it was like publishing these? That's exciting obviously for young a medical student?

Dr. Leonard Pinsky: Well, it was very exciting. First of all, the relatively few people who read it thought it was very good and that made me very happy. And amongst those people were Clark Fraser and who I remember very laudatory and what else can I say?

Christopher Canning: At that time then, so this is still the early stage of medical genetics, what interested you the most about genetics? Or you don't have to prioritize them, but what areas interested you, say somatic cell biology, cell culturing, and biochemistry? These are all swirling around one another at that time.

Dr. Leonard Pinsky: Okay, good. So at that stage, I had to make—medical school was finished. I had to make some decisions. First one was to specialize in pediatrics because I had heard from enough people at that point by osmosis, that if you were going to get anywhere in academic medicine, you shouldn't start off with a way of subject like genetics. You just start off with something like pediatrics.

Partly because I had a natural leaning towards the kids; I loved to hug kids and it made me feel good. And probably because I did, as I just said, it was the strategic thing to do was to go and get ahead in academic pediatrics. And then gradually I veered off into genetics.

Christopher Canning: Right. And I guess that's why you ended up at the Lady Davis Institute. Is that—?

Dr. Leonard Pinsky: No.

Christopher Canning: Okay. That's a little further ahead.

Dr. Leonard Pinsky: That's a good deal further ahead.

Christopher Canning: So let's stick where we are then. We'll come back to that.

Dr. Leonard Pinsky: Yeah. We'll get there very quickly. I spent one year as an intern at the Jewish General Hospital. That's just an ordinary rotating internship. Then I spent one year at the Children's Hospital in Montreal, and then at that point, we moved. We refers to the fact that I got married at the beginning of that rotating internship and my wife was a medical student. If we were going to move, the right time was for her to move at the end of the second year in medical school and in my case, at the end of my first year of pediatrics when I did my internship.

So we ended up in Philadelphia and my wife went into Temple Medical School, and me at the Children's Hospital in Philadelphia called Saint Christopher's, which is not as well known but very good anyways. As the Children's Hospital that's associated with the University of Pennsylvania, which is called Children's Hospital of Philadelphia. So, once again, at the end of my second year in Philadelphia—

Christopher Canning: What year would this have been?

Dr. Leonard Pinsky: That would be 1964; it will become clear in a moment.

So we had to make another decision, and my wife was graduating from Medical School and I had to choose my next step and that's when I got into real science. Because at that point, I made the decision to learn some human somatic cell genetics at the University of Michigan under the direction of Robert S. Krooth.

Christopher Canning: Great. So you joined the somatic cell genetics group at the Department of Human Genetics at the University of Michigan, which is interesting because they already had a Department of Human Genetics at that time.

Dr. Leonard Pinsky: At that time, the only universities that had a Department of Genetics of Human Genetics, Medical Genetics—whatever you want to call it but had an identifiable department of genetics. The only ones in North America were several in the United States. One in Michigan, one in Wisconsin, one in Seattle, Washington and maybe one other; yes, I think that's it. And in North America, the only other one was Clarke Fraser at McGill.

Christopher Canning: Which wasn't technically a department at that time; it was just a unit.

Dr. Leonard Pinsky: Yeah, it had various names; I can't keep up with all the different name changes. But there was an entity; I call it an entity at the Hospital for Sick Children in Toronto, which was directed by a woman, Peggy Thompson, who was a not a physician but made important early contributions to Canadian medical genetics.

So she was "in" and in terms of the development of medical genetics, clinical genetics in Canada, she's important historically but not all that important; I hope all of this is not going to get published! [Laughter]

Not all that as important as some of the others in the Canadian genetics. Haste it to say that Peggy Thompson, although she was a non-physician and her husband co-authored what I think was the first successful and appropriately so, human/medical textbook in North America, and it came out in Canada.

Christopher Canning: Okay.

Dr. Leonard Pinsky: So I hope that Peggy won't be too mad.

Christopher Canning: So you're in Michigan at this time, in 1965-'66; you came back to the Jewish General in 1967.

Now, how much did this experience in Michigan influence your desire to start your own Centre for Human Genetics at McGill, which actually didn't happen until late 70's? Did you come back from Michigan thinking, and working with Fraser at that time, that McGill needed something more directly related to medical genetics?

Dr. Leonard Pinsky: Not so much more directly related, because it was directly enough already. Here's where this becomes interesting. For reasons which I still have not ever defined for myself, I felt that it would be important to help the—I felt that it was important to help the Jewish General Hospital to become a full-teaching hospital of McGill University Faculty of Medicine. And I felt that if I went to the Jewish to start a genetics program of some sort or another that I would be achieving my goal, which is to get the Jewish General Hospital to be accepted as a full teaching hospital of McGill University Medical School.

That's what motivated my choice of staying in Montreal. I had lots of opportunities, lots of offers to go to any number of medical schools at that time, because there only were three or four around, give or take a few, at that time, and there was plenty of opportunities for me to move either in Canada or United States rather than come back to Montreal, but I did. And when I did, I brought with me the skills that went with the knowledge and

expertise necessary for doing somatic cell genetics.

Somatic cell genetics was, or is, what it was supposed to be, and that is the study of the genetic mechanisms affecting physiology, of pathology, or whatever, using cells grown in bottles rather than in the uteri.

Christopher Canning: So at that time, is this when you started getting interested in androgen receptor genetics?

Dr. Leonard Pinsky: Okay, so yes.

Christopher Canning: So you're a student on somatic cell biology, cell culturing, and your particular interest was in sex differences and androgen receptors?

Dr. Leonard Pinsky: Yes, indeed. But maybe for the purpose of history here, I think it's very clear that, although at that time I didn't consider it to be earth shatteringly important, but in retrospect and let's say from the point of view this interview, I believe from the historical point of view that I was the first person in Montreal to grow human diploid somatic cells for the purpose of studying human diploid genetics disease.

Christopher Canning: Okay.

Dr. Leonard Pinsky: Period. The precise of year I'm talking about is I started to be an independent researcher in 1967. I think it's 1967.

Christopher Canning: That's when you were Director of the Cell Genetics Laboratory at the Jewish General.

Dr. Leonard Pinsky: Yeah, I believe that's the year I got my first MRC grant, competitive grant.

Christopher Canning: Were you running your own laboratory at that time?

Dr. Leonard Pinsky: Sure. And the work that I did at the beginning with androgen insensitivity represents the first entirely original work in Montreal using diploid somatic cells in cultures.

Christopher Canning: You have a 1970 article that was published in Nature called Enzymatic Differences in Cultured Fibroblasts; is that related to that research that you were doing?

Dr. Leonard Pinsky: Yes but it has a longer title.

Christopher Canning: Yeah, I mean, I may have just taken the introduction to the title.

Dr. Leonard Pinsky: Can we look at it?

Christopher Canning: Yeah, you can look at your CV here because that's obviously related to the research that you're saying that you're doing is that correct?

Dr. Leonard Pinsky: Yeah. Stressing the history here from—I think this is the place to do it, right?

Christopher Canning: Absolutely, yeah. Can you just read that out for the record?

Dr. Leonard Pinsky: What am I talking about here with Christopher is my early publications in somatic cell genetics to emphasize the historical truth about some of these things.

If you look at publication number 12 in my CV, you'll see that my first paper on my research on somatic cell genetics was when I was at the University of Michigan, studying somatic cells genetics, human somatic cell genetics, with Bob Krooth, and this was published in The Proceedings of the National Academy of Science (PNAS), the famous journal, in 1967, right?

Christopher Canning: So there was no one else that you knew of in Montreal that was doing similar research?

Dr. Leonard Pinsky: Absolutely not.

Christopher Canning: Yeah.

Dr. Leonard Pinsky: Absolutely not. That's in '67. The second paper, also '67, also in PNAS. These were very important papers, which we may have time to talk about in greater detail, or we may not, but I'll tell you why they're important.

Christopher Canning: Yes, if you can just give me a brief overview of why you think they're important.

Dr. Leonard Pinsky: But, for now, I'm going to go on for just for a second

Christopher Canning: Sure, yeah.

Dr. Leonard Pinsky: If we go on, I come to just two papers later, paper 14 and 15, you look at page 15. Do you recognize some names?

Christopher Canning: Of course, you're publishing with Hy Goldman and Charles Scriver.

Dr. Leonard Pinsky: Yeah, that's just right. And there it is in 1970; so there was a spread of about three years before the rest of the world, including my colleagues, were involved with somatic cell genetics.

Christopher Canning: Well, of course, Dr. Rosenblatt would have come on the scene a couple of years later doing very similar research, no?

Dr. Leonard Pinsky: Yeah. Very similar and very well but few years later.

Christopher Canning: At that time, he was doing his post-doc research in the States. So he would've come back in 1974 or 1975. So you're doing this about six or seven years in Montreal, previous to Dr. Rosenblatt's arrival?

Dr. Leonard Pinsky: Yeah, I believe so.

Christopher Canning: Okay fantastic. So this is great; this brings us to the late 60's, early 70's, which is when the MRC group first started to form.

Dr. Leonard Pinsky: Yes.

Christopher Canning: Now of course, you didn't become a member until the late 70's, early 80's, but what was your relationship like with folks there who were involved in the group in 1972? Did you hear about this group forming and what was your relationship with Scriver, with Fraser and some of the early members as well, such as Peter Hechtman and Renny Gold? What can you tell me about who was who at the time and what were your relationships like with them?

Dr. Leonard Pinsky: That's a great question but considerably harder for me to get into, or harder than some of the 70's we've talked about until now, which I could be much more precise about. The overall picture is very clear. My primary allegiance was to the Jewish General Hospital. By that time, the Lady Davis Institute for Medical Research had been built and I was its first so-called Staff Investigator.

Christopher Canning: Okay.

Dr. Leonard Pinsky: They didn't put the building up for me, but they put the building up to attract people like me. And I was the first one who was offered a job at the Jewish General Hospital and its research wing, the Lady Davis, and was offered not only a position and a job but as a teacher and as a supervisor of Pediatric Residence. And I did all of those things at one time in the beginning of that period.

My links with the people at the Montreal Children's Hospital we're very close and were activated, if you wish, by the fact that I participated in several collaborative research programs with people who worked at the Montreal Children's Hospital and other places.

And finally, my links with the Children's Hospital were strengthened even more by the fact that one day a week, usually on Fridays, I would go to the Children's Hospital and function as a pediatrician, geneticist, and dysmorphologist at the time. Seeing patients and conducting genetics

rounds with pediatric patients, whether it was just morphology or dysmetabolism or whatever, and those were important days in my career because as you can see, from what I just said that I had the best of both worlds. I was obviously accomplishing most of what I set out to do at the Jewish General Hospital. I was contributing a lot to appreciation of the Jewish Hospital's ability to function as a full teaching hospital. And at the other end, I was being a dysmorphologist, et cetera, at the Montreal Children's Hospital.

Christopher Canning: Alright. And so are you saying that your contribution was one both as a practicing physician but also related to your research, that your research was directly impacting and benefiting patients at that time?

Dr. Leonard Pinsky: Precisely, yes. That's when I got seriously involved with androgen insensitivity.

Christopher Canning: While we're here, then, can you just give me a brief overview of what that meant at that time? Sexual maldevelopment in boys and girls, that's what you're studying; is that correct?

Dr. Leonard Pinsky: Yes, but a particular aspect of it. I certainly was not studying the whole range of questions or problems in human sexual development, by no means. I got involved, if you wish, through the back door. I mean that respectfully; how I got involved is very simple. I wanted to see if I could find an expression of the problem that some individuals with androgen insensitivity have. And I wanted to see whether I could recognize whether a cell is able to respond or is unable to respond to the stimulus of male sex hormone, whether I could distinguish that difference in diploid somatic cell monolayer cell culture. Where in essence, I made an about turn, in a sense, and I went back to what lead me into somatic cell genetics in the first place.

Christopher Canning: Was this the type of research that you were conducting that led to your initial involvement in the MRC group, if we can jump up to that?

Dr. Leonard Pinsky: Precisely.

Christopher Canning: Yes.

Dr. Leonard Pinsky: Precise dates, I've never been too good with those.

Christopher Canning: You're written in on a 1980 application.

Dr. Leonard Pinsky: Was that the first time?

Christopher Canning: That was your first time; you became Director of the group in 1981, after the 1980 application.

Dr. Leonard Pinsky: Oh I see, okay.

Christopher Canning: And at that time, you would've been working with Peter Hechtman, David Rosenblatt, Charles Scriver and Susie Tenenhouse, but not Clarke Fraser because he had gone to Newfoundland temporarily.

Dr. Leonard Pinsky: Because these are the things that I can't normally keep track off. Well, okay. You got the answer. The reason, well, I think it's obviously self-apparent that at that time, I was invited to join the group and to become its co-director or whatever it was called. Obviously, at that time, my contributions to the viability and success of the group was important. How important it was is for other's to judge, but at least at that time, I would not have been invited to join the group if I did not have something to contribute to the group.

Christopher Canning: Do you think you weren't initially invited because you were at the Lady Davis Institute and not the Montreal Children's?

Dr. Leonard Pinsky: I can't say; I doubt it.

Christopher Canning: And I don't mean to speculate, either, but it was important, as Scriver said in the 80s, that everyone was in the same space; the MRC also needed researchers to be in the same physical location.

Dr. Leonard Pinsky: At various times, and I can't remember the details, but it's not important, but at various times and during my interaction with the Montreal Children's Hospital, I was invited to come and join the Montreal Children's Hospital Genetics Group and to leave the Jewish General Hospital, Lady Davis Institute, to leave it, which is normal that people changed their primary allegiances or something like that. But I never felt that it was important. I felt that it was more important for me to try and get the Jewish recognized as a full-teaching hospital than to switch.

Christopher Canning: So then after doing that, of course, then you do join the group in 1981. And I would ask, at that time, if you can recall, what constituted group research? What made the group a group?

Dr. Leonard Pinsky: This is a hard one, because I'm sure that there were lots of discussions sort of standing on one foot, the quick exchanges between colleagues that you treasure but that you can't always remember during the course of the day.

I can't help but believe that whatever I lost by not being a coffee cup away from five, six, seven, eight colleagues that were conceptually very close to my heart, I can't believe that I wasn't—I must believe that I was losing something by not being in immediate contact with my closest colleagues, conceptually.

Christopher Canning: Being physically separated influenced a sort of conceptual distance?

Dr. Leonard Pinsky: Yes! On the other hand if you ask me, on a day-to-day basis, did I miss or did I feel that my progress was being hindered or hampered by not being part of the Children's group, physically part of it? I can't say that's true. I didn't suffer. And I didn't suffer because I didn't keep myself separate from the rest them. I sought and found plenty of readiness to help to communicate, to share. I mean I was always welcome, more than welcome.

Christopher Canning: Do you recall what that was like at that time? Would you have meetings together as a group? Do you remember meeting during your eight years with the project?

Dr. Leonard Pinsky: The only meetings that we would have, that I remember, were either the rare formal meeting, administrative purposes I guess. If there were regular meetings then there were some regular meetings that I didn't know about. [Laughter]. I don't know what else I can say.

Christopher Canning: I found a very interesting document from 1987. So you were still a member at that time. This is obviously after the Centre for Human Genetics had formed. And Scriver wrote a letter to the groups stating that the group needed more of a molecular genetic approach. Now, do you were recall that conversation at that time in the mid-80's when the molecular biology was starting to become more of a focus, because he seemed always worried that the group wasn't going to be funded again if molecular biology didn't pick-up, if you didn't pick-up new members; do you recall?

Dr. Leonard Pinsky: No, I don't remember the details but it sounds very much like we could have weld in worrying about it at that time. I can't honestly say that I know the details. As a matter of fact, —let me think for a moment. I mean by the mid, you were talking about—you said '87?

Christopher Canning: Yes, 1987.

Dr. Leonard Pinsky: By that time, I don't think it would've been well established that we needed to do biology, cell biology. I'm not sure if I can contribute to that.

Christopher Canning: Okay.

Dr. Leonard Pinsky: I tell you that one thing maybe—no, that's a little later. When we started to get involved in molecular biology and I remember the genetics group at McGill was feeling very much out of it because it didn't have a strong -- we didn't have a strong group in gene mapping, at the beginning, as it were, in molecular biology. That came in and sort of swallowed everyone up except half a dozen and or so big time operators who saw how to get around that problem.

Christopher Canning: You said that you worked for Fraser in the earlier years but what was your

relationship like with Fraser and Scriver throughout the project and throughout your time while working in Montreal?

Dr. Leonard Pinsky: Overall I can say is that I was always welcome. And I valued the "welcomeness," if there is such a word; I wasn't shy by using it. I frequently saw the letters of recommendation from them on my behalf. Later on, I used to joke about the fact that I had begun to write letters of recommendation or nominations on their behalf for various things, so the tables had turned.

Christopher Canning: Jumping back a bit, do you remember writing in the 1981 application at all? Do you remember submitting it? I'm wondering who helped put together the applications. I've asked a few folks and I think it was usually charged to the director to help facilitate gathering all the different research profiles and CV's. Do you recall how that was organized?

Dr. Leonard Pinsky: No, as a matter of fact the only thing that I do remember is that for the purpose of writing a budget, there had to be some coalescence between the budgetary needs of person A and the budgetary needs of person B. And it didn't make sense always, or it often didn't make sense to have separate budgets for the same kind of expenditures, and so the needs of several people would coalesce and they would be fused. The budget would come out as a joint or fused budget but aside from that, I can't recall.

Christopher Canning: It looked like a very complicated process. The applications were 100s of pages thick.

Dr. Leonard Pinsky: As a matter of fact, it used to be that there was no page limitation on the size of regular MRC grants; when I say regular, individual grant requests. But later on, I think maybe in the early 90s, I'm not sure now exactly, but quite sometime ago now, the grants were restricted to 10 pages or something like that and you had to get fitted into the mold and—but I remember back in, say, '87, '86 or those days, I wrote MRC grants that looked like books!

Christopher Canning: Yeah they look like books, they do.

Dr. Leonard Pinsky: You know 40, 50 pages and those were the days [Laughs] when you made one typing mistake and the whole thing that you couldn't—there was no copying, there was no xeroxing, there was no; it's hard to believe. It's hard to believe. Once stupid mistake on a typing error, either involved the transposition of letters or something like that, oh my!

Christopher Canning: Looks like that. How are you doing for energy level and time here?

Dr. Leonard Pinsky: I'm fine.

Christopher Canning: You're good? Okay great.

Dr. Leonard Pinsky: It's getting dark in here though.

Christopher Canning: It is. We have a thunderstorm rolling in.

Dr. Leonard Pinsky: So maybe we can turn on a light?

Christopher Canning: I'm okay. I have light from the widow here.

Dr. Leonard Pinsky: Sure?

Christopher Canning: On the 1987 application, it said that the group had achieved a level of interdisciplinary scholarship through the combining of cytogenetics, somatic cell genetics, biochemistry, physiological genetics, clinical genetics, and population genetics. This is a very broad question, but can you explain this relationship for us? What we're interested in is how did these fields merge and was the group successful in being interdisciplinary in their approach to all these different components of genetics?

Dr. Leonard Pinsky: Okay, I think I can answer the question from my point of view as Director of the Centre for Human Genetics as well as my one term chair of The Department of Human Genetics, where David Rosenblatt is. I think that I was not privy to any of the strategic discussions relating to the need for greater interaction or amongst these ten or so different branches of genetics that you just rattled off a minute ago.

I don't have anything particular to add that. I mean anything that I could say to add to that would be just superfluous; I just can't imagine. Maybe when I finish saying what I have to say now, you may stimulate me to come up with some more answers. But when I was the Director of the Centre for Human Genetics, which I was for 15 years I think.

Christopher Canning: 1979 to 1994?

Dr. Leonard Pinsky: Yes. There I had considerable opportunity to affect and to effect change or maturation or development or growth. It doesn't matter which word you use but I was able to do it in several ways. First of all, but necessarily so much in the importance, not so much first in importance but historically, there never was a very good relationship between Clarke Fraser and the original Department of Genetics and the rest of the people in what later became known as the Department of Biology.

So that Clarke Fraser's office as nominally his academic home was always considered to be foreign to the rest of the biologists, to the rest of the geneticists. When I took over as Director of Centre for Human Genetics, I worked very hard and I think successfully at marrying we human geneticists

with all the other genetics that was going on in the greater Department of Genetics or in the Department of Biology, which change its names back and forth. So that I did, I tried hard, I worked hard, and I did achieve considerable success.

Christopher Canning: Was that your intention behind the Centre for Human Genetics when you helped form it in 1979?

Dr. Leonard Pinsky: Yes.

Christopher Canning: Or was that the consequences of the Centre, or maybe a bit of both?

Dr. Leonard Pinsky: It's good question. I'm not sure how to answer to that. I don't how to answer that question.

Christopher Canning: Let's go back to the first one then: What was your intention behind forming the Centre for Human Genetics in 1979?

Dr. Leonard Pinsky: Yeah. I was given the mandate to do that.

Christopher Canning: To do that, right. So underneath this, were you thinking what there's all these different areas of genetics and human medicine could benefit by bringing these scientists together and doctors together and pediatricians and everyone who was interested in it? And you feel that that was what happened with this Centre?

Dr. Leonard Pinsky: Okay. On one side, from one point of view, we were not very successful in attracting new blood, new academic blood to our pre-existing groups, entirely because we just didn't have enough money. We would make a submission after submission after submission seeking more money and very often we would fail. We felt this was primarily because we did not have departmental status.

Christopher Canning: You couldn't grant a masters program, a master's degree in genetics, for example?

Dr. Leonard Pinsky: We couldn't but later on we could. That's one of the one of the accomplishments. As a matter fact, our success in these domain coincided with an explosion and the need for and the demand for research level positions.

Christopher Canning: I see that you didn't continue on with the group in 1990. Do you recall why, and where did your research go from there?

Dr. Leonard Pinsky: The reason I didn't continue in 1990 was that, to my great chagrin, my part and the part of two other members of the group were not funded by the MRC, and the reasons that we're given for the decision not to fund it were

earth shatteringly false.

Christopher Canning: Can you tell me what those were?

Dr. Leonard Pinsky: Sure, the group that was sent by the MRC to act as external judges, the external reviewer, I guess they called it, included a young man who was, and I have no idea where he is now, a junior staff person or I think maybe just a senior post-doc in the laboratory where androgen biology was studied and to my knowledge is still studied by a man called—I shouldn't name his name. It would be easy to identify whom I'm talking about because there is no other person than he, who is the leader of the Androgen Metabolism Biology Genetics study group in Canada. So this post-doc type of person was sent, as I imagine, by the MRC; I imagine representing the laboratory, I guess, the operation that he can have. And to make the long story short, the review that he wrote and I read it, the review that he wrote, which was negative, did either contain false assertions or did not contain proper appropriate positives.

And the consequence was that it got blocked off, at the same time Dr. Fraser's component was discontinued and there may have been a third person and I'm not sure.

Christopher Canning: I think that's it. Yes, that was Fraser's last term and yourself.

Dr. Leonard Pinsky: There wasn't a third?

Christopher Canning: Not by the looks of things, but I can't be too sure.

Dr. Leonard Pinsky: Okay.

Christopher Canning: At the time, it would have been Rosenblatt, Rozen, Scriver, Skamene, and Harriet Tenenhouse. So it just seemed like MRC changed direction?

Dr. Leonard Pinsky: What I've given you up till now is -- what can one say except that I believe that I was royally screwed and by the hand of someone who remained in the background but who was calling the shots. And I will never be able to "prove" it, but in my heart, I know our research was internationally competitive and the criticisms leveled by this person who after all was simply mouthing the words of his boss.

Christopher Canning: Seems like you have a quite strong memory of that time.

Dr. Leonard Pinsky: Well, it was very sad time I think in my life. I regained my MRC grant one or two years later and held it until I retired in 1999.

Christopher Canning: Fantastic.

Dr. Leonard Pinsky: So I got it back in 1991, I think.

Christopher Canning: Okay.

Dr. Leonard Pinsky: And I had it through the next eight, nine years.

Christopher Canning: How did this departure from the group impact, or not, your relationship other members of the group?

Dr. Leonard Pinsky: Well, first of all, it made me feel terrible. It was sad and costly in terms of well-being and the ego support and it was costly to people in my family. You don't put your heart into something and have it wiped out unjustly, very much unjustly without paying a price; well, what can I say?

Christopher Canning: Well. I'm coming to the end of my questions. I have some broad theoretical questions that I would like to conclude with and you can answer as specifically or generally as you want. In your opinion, what is some of the most major advances in medical genetics influenced chiefly by the MRC group?

Dr. Leonard Pinsky: Compared to?

Dr. Christopher Canning: In general, in the broad spectrum of medical genetics. What do you think this group offered?

Dr. Leonard Pinsky: I have not pre-planned an answer to that question so I hope whatever comes out makes sense.

Christopher Canning: Like I said, we can skip this question.

Dr. Leonard Pinsky: Yeah, please.

Christopher Canning: Would you like me to move on to another question?

Dr. Leonard Pinsky: Yeah, let the first one simmer for a while.

Christopher Canning: Okay, in your opinion, what ensured the group's longevity?

Dr. Leonard Pinsky: Oh, that's easy. I guess it's related to the first question, too; they are related. What ensured…?

Christopher Canning: Ensured the group's longevity? It was that longest group funded research project in medicine and Canadian history.

Dr. Leonard Pinsky: How can you fight with success? [Laughs]

Christopher Canning: Which is related to the first question, how do you measure success to

ensure longevity?

Dr. Leonard Pinsky: And that explains why I knew it was going to be tough at the end. Look, undeniably, undeniably, and I think this is true universally, if one or two people, I was going to say guys but nowadays because it's women just as easily. I believe that if one or two people who are so superstars right from the start become associated with your group, you can't lose, man! I mean how can you lose? Clarke Fraser had the foresight to ask what is now considered to be a simple question, in his case, if you inject this amount of hydrocortisone into this mouse strain and the same amount of hydrocortisone into another mouse strain, the two strains differ dramatically in a percentage of a hydrocortisone they get when they're injected by the teratogen hydrocortisone, which isn't a teratogen most of the time because its a drug most of the time; that's good.

But if you give too much of it to inbred strains of mice then you get cleft palate. He had the brains say, "Okay, so I'm going to study the genetics of susceptibility to hydrocortisone and induce cleft pallet and then best strains in mice." Nobody had done it before.

You know I used to have an expression, an aphorism, on the label to the front of my office door, which went something like, "when you've done this and you've done that, the rest of them will say that they always knew that what the answer was." I didn't say it very well but you know about the expression. And that's true in his case. Now, it seems like utter simplicity. But when he did it, it was absolutely novel; even about 15 years and 20 years ago, genetic factors determining susceptibility to birth defects, it was barely, barely accepted. Now, we take it for granted.

Christopher Canning: Yeah.

Dr. Leonard Pinsky: It was barely, barely accepted. So the first part of my answer to -- I'm doing better than I though I would be -- first part of my answer is, if you're going to build a successful department or whatever you want to call it, get yourself a few superstars early on and ride with the winner. And then Scriver comes along and he's a superstar in another area. It hadn't been done before. It's not that others have tried and haven't been done before.

I mean others could have discovered that what Clarke Fraser did; it's not as if the whole world is waiting for him to discover it. The same as with Scriver; I mean everyone was waiting for inborn errors to be found. But he found them he studied them and characterized them. He was also a wonderful speaker with a beautiful delivery. How can you beat that? And between you and me, I'll bet you that not many people will give you that answer, but I think it's the real truth. Tell him that I think he is a real superstar.

Christopher Canning: Well, it's recorded here forever and ever.

Dr. Leonard Pinsky: Well, yeah.

Christopher Canning: I think that's a fantastic place to end if are you good ending here?

Dr. Leonard Pinsky: Yeah.

Christopher Canning: Okay. Thank you very much for you time, Dr. Pinksy.

END OF INTERVIEW

Dr. Emil Skamene, August 5, 2010

Christopher Canning: My name is Christopher Canning and I'm here with Dr. Emil Skamene on August 5, 2010. It's my honour and privilege to be here with you, Dr. Skamene, to discuss two main themes regarding Human Genetics.

First, I would like to discuss your academic background, which contributed to the growth of Medical Genetics in Canada and beyond. And secondly, and perhaps more importantly for this particular study, I'm interested if your involvement in the MRC/CIHR Group in Medical Genetics. First, can you just give me a quick overview of where you're from, where you're born, where you grew up?

Dr. Skamene: I was born in Galicia in 1941. It was part of Europe, which often changed rulers, especially in the 20th century – it had a very strong Jewish population then and belonged to Poland before the war. When I was born, it was a part of Soviet Union (as a result of the infamous Hitler-Stalin pact) and it was a victim of German invasion and of the Nazi program of Jewish extermination, the Holocaust. I was saved by being smuggled out of there as an 18 months old infant, to the home of my adoptive parents in Prague. I lived in Prague from 1941 until 1968. I received all my schooling in Prague and I have my MD diploma from Charles University in Prague and the PhD degree from the Czech Academy of Sciences, [also] in Prague. In 1968, during the invasion of Czechoslovakia by Russian and other Warsaw Pact armies, I left. I didn't want to stay in an occupied country. I went to the USA and did 2 years of postdoctoral fellowship at the Harvard University in Boston. From there I have been recruited to McGill in Montreal.

Christopher Canning: I would like to come back to this in a bit because I want to ask you a little more about your postdoc training at Harvard. So what was your medical training like in the Czech Republic at the time?

Dr. Skamene: Yeah. Well, it was Czechoslovakia, then.

Christopher Canning: Czechoslovakia, of course. So let's go there first; I guess you finished your medical degree first?

Dr. Skamene: Yes, I went to medical school when I was 17. At that time, it was a six-year course, as it is common until today, in Europe. I had my MD degree at 23. During my medical studies I already started to participate in research, first in biochemistry and afterwards in immunology. When I finished my medical school, I enrolled in a PhD-like training (called the Candidate of Science Program) at the Czechoslovakia Academy of Science, in the Institute of Microbiology and Immunology.

Christopher Canning: So, how much was genetics a part of your medical training, and was it

common in Czechoslovakia at that time?

Dr. Skamene: No, it was not, the school curriculum, just like everything else in our life, was fully under the Russian control – and the "party line" was that it was the environment which dictated the evolution, and that environmentally induced traits were inheritable. It was known as the "Lysenko doctrine" after a Soviet biologist who was the Minister of Education under Stalin. Genetics was treated as a "no-no' but like in every such situation there was an underground, out there—

Christopher Canning: Was it actually an underground? Obviously, it was taught in universities but was it hush-hush?

Dr. Skamene: It was very much hush-hush, and especially Mendelian and Morganian genetics was not taught. But, I got a good dose of genetics from very bright professors who offered this forbidden fruit to us in cafes, their homes or their labs at night. It was exciting for us, partly because it was prohibited. Some of these professors were removed from the university and otherwise persecuted; such was the norm in all walks of life.

Christopher Canning: Were you reading research that is coming out of North America or other parts of Europe?

Dr. Skamene: No. Well, not when I was a medical student. I could not read or speak English; my second language was Russian.

Christopher Canning: And then when you finished med degree, where did you have some genetic training in genetics during your medical training?

Dr. Skamene: Very little.

Christopher Canning: Was genetic medicine anything in Czechoslovakia at the time?

Dr. Skamene: No.

Christopher Canning: So then what made you interested in genetics and medicine? What was it in you that said I would like to do genetics and medicine, if it wasn't very big in Czechoslovakia?

Dr. Skamene: Well, as I said, there were many—"underground extra curricular lectures and lab exercises". They were in other walks of medicine and science as well (e.g. psychiatry). I would participate in the biology/biochemistry/genetics activities of this type and I met there these two or three professors who were just fantastic.

They made things so clear and made sense of the environment influence of phenotypes, which, without the basis of genetics, were so difficult to

comprehend and accept as such. So with their teaching it became much clearer and I said to myself that this was something I'd like to pursue in more detail in the laboratory.

Christopher Canning: Is this your PhD research?

Dr. Skamene: Yeah, and it was very much dependent on the use and knowledge of genetics.

Christopher Canning: Absolutely, yeah. So at the time it seems this is the meeting of Darwin and Evolutionary Theory with Mendelian genetics?

Dr. Skamene: Yes, indeed.

Christopher Canning: You mentioned this but I'd like for you to maybe elaborate a little more. How much did the Czechoslovakian government support genetics at that time or was there a change after you left? Because I've seen that you've subsequently won awards in the Academy of Science in Czechoslovakia?

Dr. Skamene: Well, now, the former Czechoslovakia (the Czech Republic and Slovakia, when they separated in the early 90s) is a fully democratic region with open borders and very much a part of EU.

Christopher Canning: So when was that shift in Czechoslovakia?

Dr. Skamene: You know, it's tough for anyone to imagine the kind of governmental control of life that was exerted there. Same thing, in a way, as you see now in an autocratic Saudi Arabia, which wants to block Blackberrys, because they are losing control over what people are thinking.

So you know the genetics was very much in collusion with the communist doctrine and so, simply, was not taught. Textbooks of biology would not have formal genetics material at all.

Christopher Canning: And this would have been—what years were you doing [Voice Overlap].

Dr. Skamene: Well, when I was doing my PhD [1964-1968], it already was a bit different: several countries of eastern Europe's communist block (Hungary, Poland, Czechoslovakia) have gone through the period of having somehow more sophisticated, while still communist, rulers, who allowed some degree of liberalization (eg the famous "Prague Spring" between 1966 and 1968 under A. Dubcek). All these liberation movements were subsequently crashed by military invasions of Russian armies.

Christopher Canning: Was there any discussion of genetics, of what was happening elsewhere in the world or if they just ignored genetics entirely?

Dr. Skamene: Yes, at that point the "underground" became public and a much different biology was taught. Unfortunately, not for long, in the case of Czechoslovakia it all ended again in 1968, and everything returned back to darkness, suppression and totalitarian rule, for the further 21 years.

Christopher Canning: So then at that point, you decided to go to Harvard to do your post doctoral training. Is there are a particular reason why you—?

Dr. Skamene: Yeah, my PhD thesis was not really in genetics; it had to do with the development of immunological system; it was the generation of diversity. And again, you know, as it was taught at that time, the reason you developed diverse ways to handle environmental attacks, bacteria or viruses, cancer cells, was because the system was molded by exposure to it.

Christopher Canning: Simply environmental?

Dr. Skamene: Right. And then suddenly when I did my thesis to look at the particular class of antibodies, it became clear that all the information for diversity was already present in the germ line. Two of my publications [provided] an experimental proof of it, from my PhD thesis research were published in Nature. Something unheard of at that time —

Christopher Canning: Yeah, from Czechoslovakia.

Dr. Skamene: But I was so fortunate to do my PhD research with such a scientific genius as Milan Hasek, my supervisor. He narrowly missed a Nobel Prize!

Christopher Canning: In immunology?

Dr. Skamene: Yes, in immunology, for having discovered an immunological tolerance. That story is a diversion of our interview but it is so interesting and so telling. Professor Hasek was a founding Director of an Institute of Experimental Biology and Genetics where I worked on my PhD research. The Institute prospered very much and it prospered because the Director was really a believing communist and he was able to amass a great funding from the Government as well as a complete freedom of scientific inquiry. Hasek made a trail-blazing basic discovery about immunological tolerance but he totally misinterpreted the implications of it, still being very much a Lysenkoist biologist. His experimental observations were, however, solid and ground-breaking. Peter Medawar (England) got the Nobel Prize for that discovery and he publicly acknowledged Hasek's priority (as well as Hasek's misinterpretation of results) in his Nobel acceptance speech.

Christopher Canning: Well that is interesting about the Nobel Prize and the politics of that. It's a whole different story I guess.

Dr. Skamene: So you are asking me—

Christopher Canning: You're talking about the publication.

Dr. Skamene: Yeah. So, I published in "Nature," and of course, you know, once you publish something in ""Nature" you become someone. So it was immediately read by everyone who reads Nature, but by everyone in the west. And you know, the brain drain activity with the United States and other countries was as active as it is now. So within couple of months of those two publications, I started receiving letters from the United States and from Western Europe [asking me if I] would do post doc with them; I accepted the offer from Harvard to start October 1, 1968.

August 1968 came and I suddenly realized that I would not be able to go because of the Russian invasion and subsequent occupation of Czechoslovakia. However, I managed to sneak through the border. It was a second "survival "in my life.

Christopher Canning: And where did you go?

Dr. Skamene: I went to Germany. My mother, a medical doctor, was an extremely bright woman. Some of her patients happened to live at the German-Czech border; they let me to sneak through.

Christopher Canning: Your mother was medical doctor as well [Voice Overlap]?

Dr. Skamene: Yeah, a doctor. My [adoptive] mom was a professor of medicine in Prague.

Christopher Canning: So she has no doubt influenced your interest in medicine?

Dr. Skamene: Listen, I was sixteen at the end of high school. I was a good student. I knew nothing about what I wanted to do. But, know a smart Jewish woman, said, you know, you go to medical school. So I went. If she said, "you go to a law school, I would have been a lawyer, today.

Christopher Canning: So here you are.

Dr. Skamene: Yes. I gave them stories in the medical school entrance interview, how I always loved medicine and wanted to be a doctor, but I was being basically directed by someone who knew me better than I knew myself.

Christopher Canning: So at what point did you actually say to yourself, this is what I'm going to do for my life? At what stage?

Dr. Skamene: No, I loved it from the beginning as soon as I came in. It was so different from my regular high school. It was just so interesting, so I knew it was a good choice.

Christopher Canning: So more detail about Harvard. You were there for a couple of years and what were you researching? Was it still in immunogenetics?

Dr. Skamene: Yes, it was still in immunogenetics. There, I was very much influenced by Henry Winn. He was a fantastic mouse geneticist. There, I was indoctrinated in mouse immunology and mouse genetics.

Christopher Canning: So you have many publications on mice immunology?

Dr. Skamene: Yes, quite a few from that period. After two years there, I was appointed a research assistant and I was able to write a grant to the [National Institutes of Health]. I wrote a grant under my name and the professors' name, Russel's and Winn's. It was a huge grant application and the NIH sent a site visit.

Christopher Canning: To where?

Dr. Skamene: To my lab at Harvard at the Massachusetts General Hospital. Several scientists came and looked at the environment to see whether what's written was really doable, etcetera. I think they have done it because it was—something was not usual, I guess,—that someone who was at Harvard for less than two years, submitting a grant which was excellent.

Christopher Canning: Yeah.

Dr. Skamene: So, they came. One of the site visitors was Phil Gold from McGill. He was an internationally recognized immunologist and was a member of various committees at the NIH. So, he was part of the site visit team. The site visit went well and the grant was awarded. But Phil had done something which is sort of no-no under these circumstances. He gave me his business card and said "phone me [at] the hotel".

So I phoned him and we had dinner, and he said this is a nice work and what do you want to do with your life, etcetera. And he basically said, "Don't waste you time at Harvard, come to McGill." We had a discussion about combining medical practice with research, something that interested me. Prof. Russell, the chair of our Department at Harvard was really not very supportive of my idea to get an American license to practice medicine and to combine the two activities. He wanted me to direct the departmental research labs.

Christopher Canning: It's a sign, obliviously, that you were doing good research.

Dr. Skamene: Yes, but when I was talking with Phil [Gold] I said, "How would that work in Canada?" He was very much an MD & PhD. He said, "Well, you would come and do this and that and we would give you an opportunity to do your

exams and to get your license." I liked what I heard.

He asked me to come for a short visit to McGill. And you know, I liked it here, I liked his group at the Division of Immunology; Phil Gold said, "Look, if you were to come we would make you immediately a research associate like you are at Harvard and, at the same time, would set up a modified intern – resident clinical rotations to allow you the qualification for licensing exams.

Christopher Canning: Very interesting, which takes me to my set of next questions. I would like to move in to the actual time of the MRC group. So this is 1972, the year the Group formed. You have Scriver, Fraser, Reynold Gold, Rosenblatt, and Hechtman. Were you aware of their research in genetics or were you involved mainly in immunology?

Dr. Skamene: I was more involved with an immunology but, actually, my second grant already was on genetics of susceptibility to infection. I knew about the McGill geneticists you have mentioned, but nothing about the MRC group. I knew they were interested in what I would call today Mendelian or monogenic traits. They were interested in newborn malformations; they excelled in biochemical genetics, e.g. Tay -Sachs disease. You know, one gene—one disease phenotype.

Christopher Canning: Suck as PKU.

Dr. Skamene: Another "one gene problem," okay? As I was starting my own research project at McGill I decided to look at something new, at that time. I found that some inbred mouse strains are very susceptible to infection, while other strains were resistant. I started to breed the mice and investigated how their genes of resistance/susceptibility genes travel through generations. But, it never came out as a one gene trait; it was just very complicated.

Christopher Canning: Okay. So you were working with multiple gene systems rather than their single gene phenotypes?

Dr. Skamene: Yes, I had no interest to pursue the single gene traits since it didn't apply to my system, which was looking at the inherited variations of immunology.

Of course I knew about the geneticists at the Children's Hospital; I would go to their lectures. They started to take interest in my own research and I was being invited to their lectures and rounds. In the 90s, the Canadian funding agencies launched a program of National Centres of Excellence (NCE) and the McGill group of geneticists (mainly Scriver and Gravel) spearheaded the formation of one of the national NCEs in genetics. Since there was a required element of translational genetics of major health issues it was very difficult to build such Center on monogenic traits such as PKU.

So, they started to recruit people with other research in the general sphere of genetics. Scriver invited me in, and of course, it was a great privilege for me. So, I became one of the principal investigators of the NCE in Genetics. I think it was about the time they needed to renew the MRC Group in Genetics and I got invited to join them. Also, I think Rima Rozen joined the group at that time with her research on genetics of…

Christopher Canning: Folate metabolism?

Dr. Skamene: Yes, folate metabolism. If I am not mistaken, Roy Gravel was also recruited about the same time.

Christopher Canning: 1990 would have been Clarke Fraser, David Rosenblatt, yourself, Harriet Tennenhouse, Charles Scriver, Rima Rozen and Roy Gravel.

Dr. Skamene: Yeah.

Christopher Canning: And what we haven't mentioned yet is that—so in 1990, you were recruited into the group, but in 1988, previous to that, you started your own Centre for Host Resistance. Can you give me a background of what constituted that, how was that formed? Did that in any way affect your profile in terms of the Group wanting to recruit you?

Dr. Skamene: I am sure it did – my Centre at the MGH used mouse genetic tools to understand mechanisms of resistance to a variety of infectious agents, listeria, mycobacteria, malaria, salmonella, to name a few. Once we started to unravel the genetic and immunologic issues, I realized we need to expand my group of scientists to also include biochemist, microbiologist, epidemiologist, statistician, pathologist etc. I was fortunate to have been given resources to do this recruitment. So, we ended up with having one of the first truly multidisciplinary research centres at the Faculty of Medicine, in the early 90's. In essence, my scientists had a "home" academic appointment in various departments of the Faculty of Medicine, but their "research home" was physically based in the research laboratories of the Montreal General Hospital. Our research was going well, we started to get substantial grants, individual, center grants and program grants. We were, and still are today, really well funded.

And at that point, the Montreal General Hospital decided to build three new research floors on the top of the Livingston Hall, one for me, one for Aguayo's research in neurology and the top floor for mice – a "mouse hotel".

I think because I was able to put that together, got it funded and created all that infrastructure, I have become of interest to anyone who was trying to form any multidisciplinary centre. I don't know why exactly, but I know that Charles Scriver called me once and said, "Would you come with us as a

member of the MRC Group in Genetics?"

Christopher Canning: That was my next question. So you're building this profile for yourself from 1988 onwards in the Centre for Host Resistance. You're obviously settled and you get a call in 1989 to get ready for the '90 application. So what was that like to get that call from Scriver? What was he saying and what was his motivation?

Dr. Skamene: I don't really remember exactly, but you need to understand that an active research life is full of connections, groups, links, networks etc., whether they be virtual or physical. To become a member of something, doesn't mean that one has to abandon what one is doing. I was in the period of rapid development. I don't know what exactly Charles said but I am sure it had to do with my experimental strategies on how to dissect these multigenic traits into series of unigenic systems that interact. So that became attractive as an expansion of their purely monogenic themes, which were extremely important but from practical point of view pertained only to a tiny proportion of the population.

In my case, I was dealing with something which is a major struggle for populations and continents and, although scientifically, I was not that kind of giant that Scriver or Fraser were; I had projects which were very interesting to them because it was a way to look at common diseases of adult life. I am sure they did not think that they have Nobel Prize candidate joining them. I think for the MRC Group this became a natural extension. In research you are funded almost entirely by public funds, so scientists must forever explain to the public that you want to do something [that] is going to help someone one day. To say that we can help understand how people get tuberculosis was quite attractive from the public point of view.

Christopher Canning: Yeah. Interestingly, in 1987, you weren't a member of the group at the time but he—

Dr. Skamene: I was not a member.

Christopher Canning: No.

Dr. Skamene: Okay.

Christopher Canning: In '87, [Scriver] wrote a letter to the group saying that they needed more of a focus in molecular genetics. So it appears as though, like you were saying, that there was this slight shift or crisis to say the Group needed to expand from this monogenetic focus. So it seems like these factors are all lining up to invite someone like you?

Dr. Skamene: Yeah, but I really don't remember exactly. A lot of stuff in the organization of science is done opportunistically. We're very fond of each other, Charles

Scriver and myself.

Christopher Canning: I was just going to ask you, what was he like as a person to work with at that time when you were first recruited?

Dr. Skamene: He was a God but very, very nice one and very interactive, open to suggestions, very quick and critical thinker.

Christopher Canning: There was also a discussion in the group around this time that everyone needed to be in the same physical space; the MRC wanted people in the same research centre so that everyone could collaborate. And there was some worry that the MRC wasn't going to fund the Group. Do recall any of these conversations about the physical space of the group? Here you are at the Montreal General, and they are all mostly down at the Montreal Children's Hospital.

Dr. Skamene: Yes, there was definitely. But we, in fact, checked with the MRC and they said, you know if you can show the reason why this would work, there's no problem. These scientific constructs are geographically often virtual — and I'm talking about my life at McGill.

Christopher Canning: Everyone's all over the place.

Dr. Skamene: I know that very well from my period as the Scientific Director of the MUHC [McGill University Health Centre] Research Institute (1998-2008); I was the first, founding director. When I was selected and appointed by the MUHC, I asked the CEO of MUHC for keys to my Institute. He said, "What institute? There is no Institute." I became a Scientific Director of some 1000 scientists working at 65 laboratories all over the MUHC campus [Montreal General Hospital, Royal Victoria Hospital, Montreal Children's Hospital, Chest Institute]. To be able to interact with my scientists, I had to go to 65 places. I was able to do it once every year, in addition to everything else the Director has to do.

Geographic proximity is very important. New buildings which were recently built at McGill as well as the upcoming central campus of MUHC Research Institute will certainly have an extremely positive influence on productivity and the quality of scientific life. There is nothing like rubbing shoulders with your colleagues or having coffee with them. Even if you're only 10 minutes away, in winter, you just don't go.

Christopher Canning: So if you weren't physically in the same location, what did it mean to collaborate? What did collaboration consist of in the group during your four years? Did you publish with anyone? What could you say contributed to the development of the group?

Dr. Skamene: Well, I was pretty much left to do what I was doing. We had some

collaboration with Harriet [Susie] Tenenhouse; I was working on osteoporosis in mice and rheumatism but in fact not to the degree that we would have even papers with them. So it was pretty peripheral participation.

Christopher Canning: So according to the application, you were studying macrophages?

Dr. Skamene: Yeah.

Christopher Canning: Great. And then you were working on genetic responses to parasites; so the genome of a parasite, versus the genome of the host?

Dr. Skamene: Right.

Christopher Canning: And this is how you're written into the application, I suppose. So how did this research contribute to a group in medical genetics?

Dr. Skamene: Well, it's hard to be specific about dynamics of the group. You know you don't have to actually do experiments together to benefit from each other. Whenever there was a group meeting, I would be exposed to new science, which I didn't really study before; they would be exposed to what I was doing. We had student's seminars, so my students would go to the MRC group student meetings, etcetera.

To be very frank, it contributed to the notion that the group was expanding into medically and politically more important areas. It was very good for me because they had a lot of resources, intellectual, first of all, as well as banks of cells and tissues, which are very helpful to me. But, really, it was more an intellectual stimulation than anything concrete, research wise.

Christopher Canning: Yeah, fair enough. Do you recall writing an application for that? Do you remember when Scriver asked you or do you—because there are some discussions that the director put together the application, do you remember?

Dr. Skamene: I've written so many applications in my life. It's always like that, that the director writes it; I've written many applications as a director of this or this or that. It's always with an input from the members.

So I'm pretty sure I was asked to contribute my part and as far as I recall, big chunks of the write up were taken but big chunks were also cut, when it became too technical and it was impossible put in. But I don't really remember writing that one specifically.

Christopher Canning: Fair enough; it's a long time ago now. Do you recall the overall dynamics of the group? How it moved along? How it functioned? Obviously, they were enormously successful in terms of publications and seminars and speakers.

What were they dynamics, if you can recall?

Dr. Skamene: Well, Scriver was very much a dominant person there. Throughout, Fraser was present but not that much as Scriver; I don't know whether Gravel was there at that time.

Christopher Canning: He didn't come on until the next application, 1994.

Dr. Skamene: And he came through the NCE [Networks of Centres of Excellence] interactions.

Christopher Canning: Yeah, I guess Rima—

Dr. Skamene: Rima was becoming very important during presentations—but again the dynamics, the interactions of the group at the Children's I could not judge.

Christopher Canning: Yeah—

[Voice Overlap]

Dr. Skamene: That's okay, that's just life.

Christopher Canning: Yeah, it's just interesting. And not to sound like I'm pressing, but you came in for four years and your research is not very similar to everyone else's. Everyone else is doing PKU, folate metabolism, and vitamin B_9 and B_{12}, and then you come in with this multi-genetic approach. This, to me, is very interesting.

Dr. Skamene: Just one term, right?

Christopher Canning: One term in 1994, yes.

Dr. Skamene: So I guess it did what I was supposed to do and what I believed was important. As far as my life with the Group, it was not anything of priority in my life. When you called me for an interview I even had to check my CV to remember the dates and the players.

Christopher Canning: And obviously to others, then, Rosenblatt was involved in this group for 37 years so this was his orbit right? And same with Charles Scriver, he was—
[Voice Overlap]

Dr. Skamene: Yeah I just don't have a single publication with the Group,

Christopher Canning: Yeah that's interesting. May I ask and why you didn't continue with the group in 1994?

Dr. Skamene: I probably wasn't asked to participate or probably they had now Gravel and

other people who fulfilled the need for more medically relevant genetics research.

Christopher Canning: Okay. Well, then when the 1994 application was submitted, it was Gravel, Malo, Nadeau, Shoubridge, Rosenblatt, Rozen, Scriver, and yourself. You were on the application but you didn't continue with the group in that year, do you recall?

Dr. Skamene: I'm sorry. Their home was very harmonious but it has never become my home. My home was always the MGH [Montreal General Hospital].

Christopher Canning: Right and you—yeah, you went there for a few years, contributed what you could, took from it what you did and went from there.

Dr. Skamene: Yeah, that's right.

Christopher Canning: Okay, fair enough. So I just have a few general questions. In you opinion, and I'm asking everyone this, why do you think the MRC group was so successful from 1972 to 2009?

Dr. Skamene: So when you say successful, what do we mean? Is that like being renewed or what?

Christopher Canning: Well, that's my second question: how does one define success in science? You could measure success in the longevity of the Group, or you could measure success in the actual discoveries. So what discoveries have been made by the group that, in some way or another, contributed to the benefit of medicine with genetics, or in biochemistry and molecular biology? So what are the measures of the successes of this group, or groups more generally?

Dr. Skamene: Well, you know—I kind of make life; it would still be different now because now, the questions you just asked, what did you do for the person on the street are really being asked much more than those times. But those times, I remember number one was—there were just very normal criteria of success, how much funding were you able to get other than the group. The group was like to grow money to have co-facilities, which would have not to be paid for from grants, to have banks of specimens which would not have to be paid from the operating grants, to have meetings which cost money, etcetera.

But as far as the real scientific success, I think the group had fantastic ability to raise research funds. I don't know what it was, but, as I calculated, it was number of dollars per head. They published to lot of papers and then important ones; I'm not going to tell you which—you know I think some of the public health consequences of Scriver's treatment, prevention of metabolic diseases was something which showed the world, showed

everyone, politicians the value of medical genetics. If you find the gene, you can correct the problem. It did work for PKU and few other things but it has always been said that it can be done and will be done for everything else beyond 2010.

That premise has not actualized, yet. For example, we are able to look for breast cancer genes but we have not put this to practice; the cancer genes we know are just a part of the multigenic architecture of that disease, which will need another decade or two to unravel. So, now, the real practical impact of this multi-genic medicine is much less than it was [for] the PKU impact where you have it clear, one gene, one enzyme, tell you how the child is. That was very, very powerful.

We have not solved the genetic mystery of the breast cancer or heart disease yet. In my own case, we contributed the ability to recognize susceptible to infection, even before the exposure but are not still able to say who's to be vaccinated or not.

However, both the scientific community and the public became aware, based on the research of the MRC Group, as well as others, of course, that what we have inherited from our predecessors is identifiable, the genes and gene-regulated biochemical pathways could be found, could be manipulated and eventually used for diagnosis or treatment.

The role of the Group as a super training environment cannot be underestimated. An army of MSc and PhD graduates can attest to it. The Group's fiscal situation allowed for much more strategic student selection and commitment to their stipends.

Christopher Canning: Would you say that there is more pressure to demonstrate the actual success of medical research, or that there is basic research for basic research sake?

Dr. Skamene: You know that but people, generally, don't. I will give you an example: we have published the basic science discovery of a gene regulating susceptibility or resistance to mycobacterium infections in 1982. It has taken over 3 decades of hard work, of many PhD theses to unravel the phenotypic expression of this gene on an organismal, tissue, cellular, molecular and structural level. Only in 2010 we can say that we know medically-important homologues of these processes in humans and can modulate the host response in favor of the host.

So the fact that there were few examples in the group of the research really making difference in lives, I think it would not happened without the group because these thing are used as waving flags to create something—if you frankly ask me if there's any [research] that was done which would not have been done, probably not but [it] made for much richer university life, which

is in fact [what] we are here for. We have students and we want to see things happening. We want to have debates and so the group is very important; so, if the applications come every four years, the group would say, look how many papers they published. It's very difficult to say from the application, how many, would you have published, have you not had this money. So as I said, sure and they bring the people in, they change the focus. It's been used politically very well. I'm not saying that it was—it's not differently nonsense, absolutely not. People could say the same thing with my centere. There are lots of opportunities in there but we need to use whatever we can to basically win the final amount of resources that are available so, if [Scriver] didn't do it someone else would have taken it so we might as well.

Christopher Canning: Great. One final question: I know you have to go but do you have any idea why the MRC or, now, the CIHR stop funding groups? Do you have any idea? Were you involved in the any other group, MRC grants or CIHR grants? But do you know why they stopped?

Dr. Skamene: I think with the time of final resources, they—someone has said exactly what I just did: this is a group of fantastic individuals; the money they contribute is being fantastic. Anyway, it's certainly not because they want to fund the researcher, on the contrary, they want to fund an—I for once think that that's not the way to go but all the big organizations here and United States go that way; they want to fund the mission oriented, big science research now. So they could put their money to accounts or this or to that rather than basic science groups.

Christopher Canning: Which is a problem obviously, in my opinion. If you don't have the basic research to support that, what is this research going to add if we're just focusing on big science? I don't know, that's —

Dr. Skamene: Big science – if a student came to me and gave me a good scientific reason why he wants to study the color of the wings of a mosquito I would think about it, but I would not tell this guy you cannot. So you know that there are enough people in these systems who let the curiosity driven research continue to flourish. There's a lot of basic research going on certainly here at McGill; not everywhere, but here the tradition is strong. I can tell you that not a single Nobel Prize discovery was made by mission oriented, applied research orientation; everyone who discovered something really important was a fundamental researcher.

Christopher Canning: Thank you very kindly for your time, Dr. Skamene.

END OF INTERVIEW

Dr. Peter Hechtman, September 30, 2010

Christopher Canning: My name is Christopher Canning and I'm here with Dr. Peter Hechtman on September 30, 2010. It's my honor and privilege to be here with you, Dr. Hechtman, to discuss broadly two main themes regarding Human Genetics.

First, I would like to discuss your academic background, which contributed to the growth of Medical Genetics in Canada and beyond. And secondly, and perhaps more importantly for this study, I'm interested if your involvement in the MRC/CIHR Group in Medical Genetics, which you joined in 1972, the first year of the group, and were a member, as a understand, until 1987.

Dr. Hechtman: Yes.

Christopher Canning: So as I mentioned I have a few introductory questions. First, can you just give me a quick overview of where you're from, where you're born, where you grew up?

Dr. Hechtman: I was born in Brooklyn, New York. I went to High School in Englewood, New Jersey. I was an undergraduate at McGill and majoring in biochemistry. I took a masters degree in biochemistry at the University of Minnesota; that brings us to 1966. Then I came to McGill and I did a PhD with Charles Scriver; at that time it would have been the Department of Experimental Medicine. Following that, I went back to the States. I spent two years at Albert Einstein College of Medicine doing a Post Doctorate fellowship, working with Dr. Richard Soffer and learning enzymology.

Christopher Canning: Fantastic. We're going to come back to where you were in your postdoc and early career years, but first of all, what sort of expectations did your family have in regards to your schooling and academic success when you were younger?

Dr. Hechtman: It was absolutely taken for granted that I was going to University. My father had great scientific ambitions in his youth, but they would have directed toward physics. And when the depression came along and he wound up doing other things. So I was meant to rescue his dream, except that by the time I came through university, biochemistry was the cutting edge of science, or so it seemed, rather than physics. So, that's where I went.

Christopher Canning: Interestingly, biology was meeting physics at that time in some respects.

Dr. Hechtman: Well, that wasn't all that clear to me but I guess what was clear was that the ultimate answer to all biological questions lay in biochemistry; at least that's how it seemed back then.

Christopher Canning: What about as undergraduate student: what were your ambitions? Were you're interested in science this early on?

Dr. Hechtman: I think there was no question that I was headed towards science as a professional career.

Christopher Canning: Right. And you didn't do any medical training. Is that correct?

Dr. Hechtman: No.

Christopher Canning: No. So what sparked your interest then in the science of medicine, or medical genetics, in those early days?

Dr. Hechtman: Well, I guess at some point it became apparent that the market for biological scientists lay within those fields of activity that had some practical application. Basically, being agricultural or medical -- medical was a much bigger enterprise. I mean that was where you could expect to find jobs and opportunities.

Christopher Canning: Did you have any interest in medicine in your early days of work in genetics and biochemistry?

Dr. Hechtman: No, I had a very mistaken idea about what physicians did. I thought that they took care of patients. Later on, I came to realize that what they did was they wrote papers about patients, which I was doing myself and I probably could have done it for more money, had I gone into medicine; but I didn't quite understand that at the time I made the important decisions.

Christopher Canning: And how did you end up coming to meet Scriver and working with him when you came to do your PhD?

Dr. Hechtman: Well that was kind of a personal matter. My wife and I were not able to be in the same place in the first year or so of our marriage. She couldn't get accepted at medical school at Minnesota where I was. So it became apparent that, therefore, I would have to go to McGill. And I wrote to some friends at McGill asking them whom they might suggest as a PhD supervisor. Several names where suggested—

Christopher Canning: At McGill specifically or in Canada?

Dr. Hechtman: No, at McGill specifically, but as I said my wife was at that time in medical school at McGill.

Christopher Canning: Right.

Dr. Hechtman: So my friends suggested several names at McGill and I came. I met some of them. I think I met with Scriver at a Federation meeting in Atlantic City.

And he was the one who seemed most congenial.

Christopher Canning: Did you know about his work previous to your interest in coming to Montreal?

Dr. Hechtman: No, I not heard about his work before but he indicated to me a problem that he was working on. It had to do with vitamin dependent enzyme deficiencies. That is to say, patients who had enzyme deficiencies but it could be treated by large doses of vitamins, particularly vitamin B6. And he had a particular theory about the mechanism by which this occurred. He had suggested that there was a new mutation affecting the binding site of the vitamin-derived cofactor and that this resulted in the reduced affinity of the enzyme for the vitamin-based cofactor. So that if you could load up the cells with higher amounts of this cofactor, you can get the enzyme to work a little better. You could possibly boost residual activity from 1% to 4% and that might make the difference clinically.

So I kind of sat down and thought about how I might use bacteria with --

Christopher Canning: When was this?

Dr. Hechtman: We're now talking about 1966 when I was making arrangements to come to do my PhD with Scriver. Anyway, I suggested a biochemical approach to proving or disapproving his suggestive mechanisms of vitamin dependent inborn areas of metabolism by constructing a bacterial mutant with this type of metabolic defect.

Christopher Canning: Interesting, Okay.

Dr. Hechtman: He liked it, so he gave me an opportunity to try it. And the fact is I was not able to make it work. So I was left with some interesting bacterial mutants that offered me the opportunity to investigate another area of research that he had a strong interest in, which is amino acid transport.

Christopher Canning: Right.

Dr. Hechtman: And so I used these mutants to do that and I got my PhD thesis with Scriver on that amino acid transport in bacteria.

Christopher Canning: Fantastic. And what was your relationship like with Scriver as a PhD student and beyond? How was he as a supervisor, for instance? Because he was an extremely ambitious and well-respected scientist at the time, right?

Dr. Hechtman: Yes. I guess it didn't take long for me to think that he was somewhat overreaching himself. That is to say, he wanted to be able to bring science to bear on medical problems, but his grasp for basic science was perhaps better than most physicians, to be sure, but it was not quite enough, I think,

to supervise PhD students who were doing basic science work. So I felt somewhat on my own. However, he was quite helpful with finding other sources of help. For example, I spent six months up here in the [Department of Human Genetics] learning to work with mutagens because he found me another person to help supervise that part of my work.

Christopher Canning: Did this research, then, influence your involvement in the early years as a group? I see that you finished your PhD in 1970, after which you went to the United States for your postdoc. Did you know at that point that you would be coming back, or that you would be invited into this group as a contributor to the basic science?

Dr. Hechtman: No, I didn't know that. I kind of felt that the United *S*tates offered much more opportunities and that I was kind of anxious to take advantage of them and hope to go on to academic career in the US, but my post doctoral fellowship turned out to be a difficult experience. And I found myself, shall we say, much more dependent upon my friends back in Montreal than I would have liked to be because my post doc supervisor was not particularly interested in helping me out.

Christopher Canning: And that influenced your decision to then come back to Montreal?

Dr. Hechtman: Yes.

Christopher Canning: And so how did you get on that first Group application to the Medical Research Council?

Dr. Hechtman: Well, [Scriver] made me an offer and I had no other offers going.

Christopher Canning: Interesting. What was that offer? What did he say?

Dr. Hechtman: That he was putting the group together.

Christopher Canning: OK.

Dr. Hechtman: And that I might become a member of the Group.

Christopher Canning: Can you tell me the story about the formation of the Group? From what you understood at the time, why did Scriver and Fraser want to form a group?

Dr. Hechtman: Well, I guess I was in the United States where a lot of the planning work was being done. So I couldn't tell you very much about it. And in fact, I would say even my -- the research proposals that I came to be involved in were not really written by me; they were written by Scriver.

Christopher Canning: I did hear that. As it turns out, Dr. Reynold Gold actually said the same thing. He doesn't remember writing his section in 1972 for the first

application for Group status. So you didn't write that application?

Dr. Hechtman: No, not that one. I kind of pretty much slipped into what Scriver had suggested.

Christopher Canning: Okay. And how did you feel about that? Were you just happy to become part of the group?

Dr. Hechtman: I think so. I wanted a job and this one [was] an offer.

Christopher Canning: Interesting. So you came back to Montreal 1972 and the Group gets funded. Where were you located and what was the space like at the time?

Dr. Hechtman: The first year was a little difficult because the space was on the second floor of the Montreal Children's Hospital, the same laboratory in which I did my PhD work. There was an expectation that the hospital was going to develop new space for us in what used to be the nursing residence. And eventually they did, but it took about a year to come about. So in the first year, I was fairly isolated. I was up here [in Human Genetics]. Actually in the room just across the hall.

Christopher Canning: Was that an issue for the group at the time, about where to work? Because I understand there was some stipulation in the grant that everyone needed to be together in a single space defined by the parameters of collaborative research.

Dr. Hechtman: In the first year or first several periods of the grant, yes, that was the case. But subsequently -- particularly when Pinsky, whose lab was at the Jewish General Hospital, came on board -- those rules tend to be relaxed and you know there was a point when it became quite decentralized.

Christopher Canning: Indeed. I would like to ask you a few questions about the other members of the group at the time. What role, as you understand, did all these folks play: Fraser, Scriver, Gold, and later Rosenblatt? What was this coming together like, what did each person contribute to the formation of this group?

Dr. Hechtman: Well, I have to say that I may be missing something in the sense that the way I recollect, but we all pursued our own research programs. We shared the space. We shared equipment, basic big equipment. We had each other to consult on various technical things but there was hardly any overlap between my research and Rosenblatt's. He developed tissue cultures. It's one thing that he seemed to have learned in Boston. He brought that kind of expertise with him and you know -- at some point my research began to be quite dependent on tissue culture but this was basically a case of sharing resources.

Christopher Canning: What about Gold?

Dr. Hechtman: Gold. He -- what did he do?

Christopher Canning: Yes.

Dr. Hechtman: He's a bit of a difficult character. I'm not sure how much I want to kind of go on record about him.

Christopher Canning: That's absolutely fine. As I understand it, he was doing keratin genetics at that time.

Dr. Hechtman: He was; I always had certain skepticism about the preliminary results that he based his hypothesis on. Nevertheless, he did raise certain issues, which I don't think the leaders had thought out when they put the Group together. And that is this: we all came as people whose salaries were paid from the Group grant, okay? But this is soft money. Now some of us, the younger guys, didn't think a great deal about that initially, but Gold was not a younger guy. He was somewhat older.

Christopher Canning: He was around 40 at the time, if I recall correctly.

Dr. Hechtman: Yes and I really don't know what kind of promises had been made to him, but whatever they were, he announced very early in the game that he was not contented to be indefinitely on soft money. He wanted to be an employee at the University. He wanted a hard money salary and an academic appointment in a department. And he became quite a nuisance about this. He made it the center point of all interactions with him. Eventually he didn't get it and he went to Toronto.

Nevertheless, he did awaken in my mind the fact that, "Yes. This is something that I should strive for myself." And so that was a problem with the group -- the career path was not clear from being essentially a research associate to becoming a professor. Well it wasn't clear how that was going to be managed.

Christopher Canning: Was it unclear to you as well at the time?

Dr. Hechtman: Actually, at the very beginning, I didn't give it a thought. But over the years with Rennie [Gold] pushing and pushing on this issue, I have to say it did sink in that, yeah, this is something I should consider, since everyone want stability and security in his career.

Christopher Canning: Who did you publish with in the Group, because obviously you said that you were doing different research programs at the time? Who would you have published with in your early days and how did it that work? How did publications happen in the early stages of the Group?

Dr. Hechtman: There was certainly no requirement that you clear your publications with the bosses. You publish and submitted what you wanted to, when you felt it was ready. There was no centralization of publications.

So I published with graduate students, or sometimes with technicians on a paper. Now, you might see one or two papers that Scriver and I published together. And I have to say it came about -- because as you already know -- I stopped being a member of the group in 1987. Essentially I lost my funding. I had projects going at the time. And I -- it was necessary to find ways to limp along small grants from here or there, but also one of my graduate students was paid for by Scriver. So, I thought it was diplomatic to put his name on the paper. Also, it was the case that I wrote a paper or two dealing with issues of Tay-Sachs screening to which he contributed ideas or data.

Other times when I published, and you might see the name, Andermann on some of my papers, Eva Andermann. She is basically a neurologist, a neurogeneticist. She traveled throughout Quebec to discover French-Canadian Tay-Sachs Disease, and so I felt whenever she furnished me with a patient, which is usually meant cells from the patient, and I investigated that patient, I owed her a name on a publication. It's the way it works in medicine. You know, your papers are just heavy with names of doctors who do a little test or for a patient you'll write. But mostly, I was the only academic on the papers. The others were students or technicians.

Christopher Canning: And you were doing the basic science? So for instance, you're on a neutral amino acid transport publication in 1970 that would have been your PhD research, I guess. Scriver's name is on that. You're doing the basic science for this?

Dr. Hechtman: Yes, but that's the way it works; if you are a graduate student you publish it with your mentor. It's a feather in his cap that you've been able to do the work. I think there are three such papers from that thesis. Now, one of which has a name Middleton as well. Middleton was the guy who taught me how to use mutagens. I worked at his lab for six months. I mean, there's so much sensitivity in the research world about who gets to be on papers that my policy has always been to anticipate trouble and put names on of everybody who might be remotely offended if I left them off.

There's a paper in there called "More Than One Mutation Defines Tay-Sachs Disease in French Canada," something like that. You'll notice a dozen names on it. They're all doctors who sent me cells of Tay-Sachs disease patients. That's all they contributed but --

Christopher Canning: So at the time, then, the collaboration between basic science and genetics and medicine was not necessarily in the science, but in the fact that they're providing you with cell lines or whatever you needed?

Dr. Hechtman: Or sometimes performing specialized lab tests. That just the way it was, and continues to be, done.

Christopher Canning: Sure enough. According to the first application you submitted to the Group, it states that your research was situated within biochemical genetics, developmental biology and differentiation of cellular functions. Can you describe to me what this means and how it fit into the early picture of the Group?

Dr. Hechtman: Well this was a Scrivernarian in invention that I --

[Laughter]

Christopher Canning: Scrivernarian invention? Can you be more specific?

Dr. Hechtman: Yeah. Well he, you know -- before he went to medical school, he was an English major. And he does have good language skills. He knows how to invent terms and play with language. I can remember at the time saying, what is this development all about? I don't know anything about developmental biology. Oh! It's development of an enzyme. If you actually read the research proposal, it was based on an idea that an enzyme Hexosaminidase B is converted by a process of adding sugar residues into Hexosaminidase A. That turned out to be a totally mistaken idea of the relationship between these two enzymes. But, that's what we thought at the time and so this was Scriver's idea of "development of an enzyme". So I said, "Okay."

Christopher Canning: And that was the first you had heard of what developmental biology was as you're doing biochemistry?

Dr. Hechtman: Well you know I heard about developmental biology from various courses but it wasn't anything that I would ever plan to have any expertise and you know--

Christopher Canning: Okay, even though you're written in the application as the expert in developmental biology?

Dr. Hechtman: Well if you would turn off a tape recorder, I would say there was a lot of what I prefer to call "imagination" in science. I'm sure you're aware of that.

Christopher Canning: This is what we like to study. We study --

Dr. Hechtman: Imagination?

Christopher Canning: Well maybe not that word but the processes behind the making of scientific facts.

Dr. Hechtman: Science fiction.

Christopher Canning: Well, sure, in some cases it might be considered fiction, but there are real, concrete processes behind the making of facts, as you suggest. As sociologists of science, we're interested in these processes.

Dr. Hechtman: Okay.

Christopher Canning: There is some fiction to science of course, and there's a lot of interesting politics behind how science happens, so to speak; that's what we're interested in. So, as a researcher of science, I like hearing this stuff. That's great!

Dr. Hechtman: Now it may have occurred to you that of the three younger members of the group. Well, Gold, myself, and Rosenblatt, we were all students of Scriver. And there's no question that this was very paternalistic enterprise. Now of course, Fraser was not a student of Scriver. Fraser would be even senior to Scriver but you could not put together a genetics research group at McGill, at the Children's Hospital, without Clarke Fraser.

Christopher Canning: I want to go back to Fraser. He is obviously critical, in an often-understated way, in the formation of medical genetics in Montreal in particular, and in Canada more generally. So, how did your research in biochemistry contribute to his research in cytogenetics and what was that relationship at the time?

Dr. Hechtman: Well the answer is not one little bit. I think it would be a mistake to say that Fraser was doing cytogenetics. It is not out of the question that as the Chief Clinical Geneticist at the Children's Hospital that clinical cytogenetics fell under his purview, but I am not aware that he had any skills as a cytogeneticist. He always hired someone relatively senior and in fact, the first person who ran it was Michel Vekemanns who was a former student of his. So, I think Fraser's interest had to do with dysmorphology, more things like that. That was closer to his heart.

Christopher Canning: Right. So did you have much communication with him at the time as a member of the Group?

Dr. Hechtman: Not often a lot. I mean, you know administratively we would meet to discuss various problems.

Christopher Canning: What was he like as a co-director, co-leader of the group?

Dr. Hechtman: Much more remote as I say; Scriver had a paternalistic finger in things and Fraser pretty much left you alone. Scriver was more a man with a mission. Fraser was a man with a profession.

Christopher Canning: Interesting phrasing. What areas of medicine were you interested in then as you're coming to McGill? You're still doing basic science, but were you surrounded by clinicians? I see that you eventually got interested in Tay-Sachs disease; how did you end up studying Tay-Sachs and what aspect of basic science did you study?

Dr. Hechtman: Well, it's not really that I eventually got interested in Tay-Sachs. I kind of started with Tay-Sachs.

Christopher Canning: Can you briefly explain what that is?

Dr. Hechtman: Sure. It belongs to a category of diseases called Lysosomal Storage Disorders. A Lysosomal is an organelle which is a bag of enzymes that break complex chemicals down. And mutations in the genes for anyone of these enzymes result in a failure to breakdown a particular chemical and in the case of Tay-Sachs disease, the mutation affects an enzyme called Hexosaminidase A.

Christopher Canning: Hex A?

Dr. Hechtman: Hex A. And the failure to make this enzyme leads to an accumulation of a storage product called the GM2 ganglioside. And, eventually, this accumulates to such large amounts in the brain that it pretty much kills all the neurons and the child who was affected with the condition is left with complete paralysis, loss of mentation, loss of reflexes, complete loss of cerebral activity. They usually die by the age of three, four years of age.

Now, why it came to such prominence in those days was because there was a particular community in which the disorder was a hundred times more frequent than others and that was the Ashkenazic Jewish community.

Christopher Canning: Yeah I see that you worked with the Quebec Genetics Network in Montreal.

Dr. Hechtman: Yeah and that brings up another issue.

Christopher Canning: We'll come back to that.

Dr. Hechtman: Okay, so it became important because we have a target community with a serious level of frequency. We had a way to screen for the carrier state and to prenatally diagnose the affected fetuses. In other words, we had a scientific solution to practical problem. So it became the subject to a lot of intense research.

Now, I think people in medical scientists are only telling part of the story when they talk about the idea that their science is going to contribute to the treatment or the cure or the prevention of disorders. While it is not untrue,

the point for our day-to-day work is the idea that inherited disorders or any disorders offer you an opportunity to find that how things normally work.

So going back to the Quebec Network for Genetic Medicine, this was another Scrivernarian invention, which I think kind of illustrates the reason why the [Medical Research Council] was always fascinated by Scriver. And that is, he presents the idea of a seamless web between basic research and delivery of health care services, okay? And what Scriver did was fill in a lot of the administrative gaps between research and medicine. So the Quebec Network of Genetic Medicine was an organism that was supposed to take newly developed basic research turned it into ways of preventing genetic disease. For example, by screening for Tay-Sachs or Thalassemia carriers, in the case of phenylketonuria [PKU] and various other disorders, performing neonatal screening followed by dietary treatment. So he was good at putting these things together and selling them.

Christopher Canning: Do you see it not just as selling but also as a potential to eventually help with our understanding of health?

Dr. Hechtman: Well absolutely. Sure. There's no question that The Quebec Genetics Network became a model for other jurisdictions for other places in Canada. People from the United States asked him, "How did you do it? How did you put this together? How did you sell it? How did you twist people's arms? How does it work? How does it get funded?

Christopher Canning: And this is the early days of single gene Mendelian disorders? PKU, Tay-Sachs --

Dr. Hechtman: That's pretty much all we knew about medical genetics in those days.

I mean, there was -- when you go to teach on the graduates of course, you have an awareness that there are other things out there. There are you know -- cytogenetic abnormalities. There are polygenic conditions but really nobody, back then, knew how to investigate polygenic conditions.

So even though I was hired to be a researcher, I would want to say that I had the grand view of the things that Scriver had but I did participate in Tay-Sachs screening to the extent that the network went out to high schools where there were a lot of Jewish students. For Thalassemia, they went to high schools where there were a lot of Greek and Italian students. I wasn't involved in that. I went with technicians who were there to draw blood samples but there was also an assembly of students who needed to understand what this program was trying to accomplish and I was the guy who got up and explained to them what Tay-Sachs is and what they're being tested for and how that can help eliminate the disease. And what terrible things can happen if you don't get tested.

So I participated at that level. And as well, the screening was done by an automated system run by a couple of technicians using serum. But, there were people who waited until they were pregnant. And you could not screen them using serum because the pregnancy hormones affect the results. So we had to do it using white blood cells, which was a manual procedure. So I was the one who did that or supervised it. Similarly, [there were] various other lysosomal disorders, other than Tay-Sachs, beta-galactosidase deficiency, fucosidase deficiency, Gaucher's disease, a whole bunch of them. The technology for enzyme measurement was virtually identical to that of Tay-Sachs. And when a prenatal diagnosis comes up, I was the one who did that.

So, there was -- in this Scrivernarian model, my work to some extent fit with that idea of combining basic research and delivery of health care.

Christopher Canning: Was there some dispute at the time between the bench and the clinical? In other words, was there always the understanding that if you did clinical or you did basic science bench work that you would have to make the link between the two? As I understand it, this is what medical genetics was and still is.

Dr. Hechtman: Ah, disputes? Well, okay, you could not ever have a PhD who decides that he wants to go out treating patients. It's against the law, period. But you do have the opposite process. You have physicians with no research training who decide wouldn't it be good to get involved in basic research? And they tend to have a pretty hard time of it. A certain amount of, shall we call it, trade union jealousy always occurs.

Another kind of conflict, one particular department [that] always has a hard time making diagnosis is, of course, the neurology departments. First of all, they can't do anything about most of the patients they have, but if they can get the diagnosis, the marquees light up and they have a parade. So everytime they got a patient who they don't know how to diagnose, they started pushing me, "Could you do this test? Can you do that test? Can you do every single test you can do on these people?" And otherwise, there was a strong push that I thought these guys have to use my lab as a screening lab for just about anything and I guess they thought I was living in an ivory tower and unwilling to contribute to clinical work. And that became a little bit of the problem for me I suppose.

Christopher Canning: So you have all these physicians from department saying, "I need this research done. These enzymes [Voice Overlap]."

Dr. Hechtman: Well it wasn't research; it was screening. And it wasn't really all these departments. It was mostly the neurology department.

Christopher Canning: Interesting.

Dr. Hechtman: But anyway, it was something that I managed to work out.

Christopher Canning: I'm going to shift gears a bit here. According to some documents I obtained from Dr. Rosenblatt, there was some dispute in the group in the 80's regarding the Group's direction and competitiveness, especially in area of molecular biology. So there was this mid 1980's or early 1980's understanding that biochemistry in some way or another needed molecular biology to continue being successful. Can you speak to this time?

Dr. Hechtman: I think -- well, in terms of what you told me. He's pretty dead on with that. I mean, I don't know–how he thinks about the details of it but he's quite right. When I signed on the early 70's, biochemistry was going to be the answer to everything. But it didn't take long -- let's say 1978, maybe '79, that the first papers came out in which it was apparent that molecular biology was now a lab science that could be applied to all kinds of biological or medical problems and give you answers a lot quicker and a lot easier, just to give you one little example—

Christopher Canning: Please, yes.

Dr. Hechtman: One of my ongoing projects that I had later on in my career was the investigation of a disorder known as Prolidase Deficiency. Now I had two students working on that, one in the early 70s and one in the middle 80s. What they both needed was some pure enzyme to work with. The first one obtained literally buckets and buckets of outdated human blood and passed the extract through a series of about eight different purification columns to wind up getting 10 micrograms of pure enzyme to work with.

The second one cloned the gene, put it behind the strong promoters, stuck it into a bacteria, added something to the beginning of that enzyme that affinity column would recognize, and in three days she got 50 milligrams of pure enzyme. Now without knowing anything about this problem it should be evident that you can do a lot more investigating with 50 mg than with 10 micrograms. I think that's just an example of how much easier things were made by molecular biology. Nevertheless, I don't know if the group had its eyes focused on me as a guy who was going to make them into molecular biologists. If they did, they must have been disappointed because I don't take to new technology very easily.

And so, I think in the early 80s despite a fair bit of writing about it, we really did not manage to pull ourselves up by our bootstraps and convert ourselves into molecular biologists. The people who did achieve this at that time was the group at the Children's Hospital at Toronto. They developed a very strong molecular biology program.

They had Rod McInnes, who is here now, Roy Gravel who was part of the

group, Don Mahuran, quite a few other people whose names I can't remember now, but there's no question that in terms of molecular biology competence, that group raced way past what we were able to do.

Now, cut down to 10 years later like everything else, molecular biology becomes easier, particularly with the invention of a technique called PCR. So at this point, almost anybody can be a molecular biologist. So we did kind of catch up but there's no question that we kind of we were faltering in that area, in that most important area in the early 80s.

Christopher Canning: That was exactly the tone of the letter that Scriver sent out to the Group. I think that's in 1985 or 1986. It seemed almost like a panic that the Group needed to pull up their bootstraps, as you suggest, and learn this new technology in molecular biology.

Dr. Hechtman: Yes, indeed.

Christopher Canning: And I think this is why Rima Rozen was eventually brought into the Group. She was an emerging and very talented molecular biologist, according to Scriver and others.

Dr. Hechtman: Yes, she had been a graduate student of Charles Scriver's and then went off to do a post doc where she became a molecular biologist, the same way as I went off to Albert Einstein to learn what was the cutting edge technology of the early 70's, enzymology, she 10 years later or 15 years later went to acquire training in molecular biology which made the kind of person that the Group needed.

Christopher Canning: Which, as I understand it, ultimately changed the direction of the Group. Obviously, biochemistry is still important but did you see the direction of the group change in the 80s?

Dr. Hechtman: Well, yes and no. I was no longer a member of the group by the mid-80s, but I continued to work at the Children's Hospital at the same bench, surprisingly, for 15 years following. My being removed from the Group, I continued to run the Group's training budget; that's the money we used to pay graduate students. And nobody said that they have problem with that. I participated in the seminars and whatever. I didn't vote on how they're going to spend money but you know -- they kind of accepted me as -- I don't know what they call it, a grandfather?

So, the Group did change and my work certainly changed. It becomes more involved with molecular biology with looking at genes directly.

Christopher Canning: Right, okay. And as you just mentioned off hand, can we call the medical genetics Group a group? In other words, how did you define yourselves as a group? And how did you see the Medical Research Council defining

research groups at the time?

Dr. Hechtman: Well, we may have worked on different disorders but we all worked on the same category of disorders. That is they were all single gene mutations causing clinical disorders with the idea of at first understanding them and to see if treatments were possible to do that. So there was that common theme and I think part of being a group as well was that we all brought into the Scriver approach of a kind of a seamless web between research and the treatment. I think all my other colleagues would have been comfortable with that idea.

Christopher Canning: So what made the Group a group?

Dr. Hechtman: [Laughs] Funding.

Christopher Canning: Defined by the funding model of the MRC?

Dr. Hechtman: Yeah.

Christopher Canning: And was there some discussion in the Group about how to maintain your groupness in order to be successful on future applications?

Dr. Hechtman: I don't think that we thought about this in any terms other than publish a lot of papers; you know, that's what gets you funded.

Christopher Canning: In your opinion, why was the Group so successful for so many years? What ensured its longevity as a 37-year funded group?

Dr. Hechtman: I think that they certainly took on new people who made significant contributions to human genetic research. First one, I guess would have been Pinsky, and at some point Emil Skamene from the Montreal General Hospital Research Institute was in the group, although he wasn't involved in the group for long; he certainly had built an incredibly successful group at the Montreal General that was interested in genetic factors in infectious diseases. So that was a very significant area.

Well you mentioned Rozen, you mentioned Gravel, but aside from the individuals that were brought in, that expanded the expertise and expanded the number of professionals working there, I think part of the story had to do with was going on in the world of medical science. That is to say human genetics was increasingly moving into the forefront of medicine.

When I signed on, if you added up the 3000 known genetic diseases, they still would have accounted for extremely tiny fraction of medical disorders. It had become increasingly possible to investigate the genetic components of major diseases. One thing that came along, for example, was Hypercholesterolemia. Now we are talking about a single gene disorder

which affects very large number of people and which effects susceptibility to coronary artery disease. So the things that were being discovered were moving genetics into the mainstream of medicine from an obscure specialty dealing with rare and exotic diseases. And I think the MRC wanted to be involved with an area of science that was becoming more and more important.

Christopher Canning: And they wanted to make sure that they were funding this type of medical genetics to show that Canadian researchers were involved in this important, and to some extent still emerging, work.

Dr. Hechtman: Definitely.

Christopher Canning: Great. At the symposium last November, Scriver said that the group was a "grassroots organization." Can you speak to this and was this the case when you were involved?

Dr. Hechtman: I am not exactly sure what he meant by that.

Christopher Canning: He meant it was a bottom up group that formed and grew from the bottom up. I just thought that it was very interesting that he called the group "grassroots."

Dr. Hechtman: I guess I have a hard time understanding what exactly that means. I just don't know what it means.

Christopher Canning: Okay, that's fine then; I'll move on. You've kind of spoken to this, but what are the some of the major advances influenced chiefly by the Group? What major breakthroughs or discoveries did the Group influence as whole, or individual members in their respective research domains?

Dr. Hechtman: I tend to answer that in terms of medical rather that research achievements.

Christopher Canning: Interesting. Can you explain the distinction between the two?

Dr. Hechtman: I think that my own work has contributed to the understanding of how the active sites of a clinically important enzyme like Hexosaminidase A work. There are three amino acids at the center of this active site. My lab discovered one of them. My lab and another lab jointly discovered the second. And other lab discovered the third. So I think that is a scientifically important piece of work but the virtual elimination of Tay-Sachs disease had nothing to do with that fact. It had to do with the increasing application of genetic screening. While I've also contributed to this effort it has nothing to do with research.

I think Rima Rozen has done some important work in showing that a fairly frequent polymorphism in a gene that she's working on is related to

susceptibility to a fairly large number of different complex or conditions. So she's developed a fairly good model as to how one gene acts within the context of complicated conditions that ultimately involve many genes and maybe environmental factors.

Christopher Canning: Is that MTHR?

Dr. Hechtman: Yes.

Christopher Canning: It just been linked to breast cancer as well?

Dr. Hechtman: Well that one is new to me because I've been out of the loop for 10 years but that was certainly quite a few other things that Cardiac disorders, and it was of them that I remember I was involved.

Christopher Canning: Well, I like the distinction that you're making; that science for science sake is inherently beneficial in the sense that it contributes to the growth of scientific knowledge. But at the same time, there are so-called medical benefits that come as result of the basic science. So I guess what I'm getting at is that it's hard to designate or clearly mark the benefits of what you're doing necessarily because you're basic scientist; your contribution is your research.

Dr. Hechtman: Well, let me put the question in terms of the work that I was doing. I think at the time when Tay-Sachs disease had a frequency of one in 3600 among Jewish births, the MRC was very interested in learning about the properties of the enzyme Hexosaminidase A that was at the root of the condition, okay? Today, the Jewish community and other communities have bought into genetic screening. The frequency of the disease has been reduced by 90%.

But, nevertheless, there remained significant research questions to ask about this enzyme. Is the MRC still interested in this anymore? I don't know.

Christopher Canning: Interesting. I have a few more questions. Did you know the Director of the MRC at the time, not know to him personally but Malcolm Brown, the director of the MRC. Do you recall him as a figure in science at the time?

Dr. Hechtman: Not very well though. I mean I might have seen him in a podium once or twice.

Christopher Canning: Okay. What are you working on now? Are you retired?

Dr. Hechtman: I've been retired for 10 years.

Christopher Canning: So do you still do any publishing? Do you still read in the area?

Dr. Hechtman: No. I really got out of the loop.

Christopher Canning: Happily so?

Dr. Hechtman: By at large, yes. I do things that amuse me. I take humanities classes at McGill. I sell used books on the internet. I go out at a bicycle riding and I play with my grand children. I do things that I enjoy.

Christopher Canning: Fantastic. Okay that concludes my questions. Thank you very kindly for your time.

END OF INTERVIEW

Dr. Eric Shoubridge, October 8, 2010

Christopher Canning: My name is Christopher Canning and I'm here with Dr. Eric Shoubridge on October 8, 2010. It is my privilege to be here with you, Dr. Shoubridge, to discuss two main themes: first, I would like to discuss your academic background, which, of course, contributed to the growth of medical genetics in Canada; secondly, and perhaps more importantly for this particular study, I'm interested in your involvement in the MRC/CIHR Group in Medical Genetics. I will ask you a few specific questions, but this is generally a conversation about who you are, what you've done, your involvement in the group, and your research in general and how that fits into a medical genetics framework.

So, first of all, can you just give me an overview of where you're from, where you're born, where you grew up?

Dr. Shoubridge: I was born in Toronto in 1951. I grew up in Scarborough called "Scarberia" by those who grew up there. I moved to Montreal when I was 17. When I was in Grade 11 in high school in Ontario. When I moved they stuck me back in Grade 10 because I couldn't complete the requisite government exams after one term in grade 11 here.

And then I got caught in the first year of CEGEP. I went to McGill CEGEP, which was like McGill had been since time immemorial but they called it CEGEP. So I ended up doing five years at McGill for my undergraduate degree.

I was interested in evolutionary biology at the time, so I did a lot of biology courses, and a few math courses. I wasn't sure what I wanted to do as a graduate student; but I knew I wanted to do graduate studies, and I knew I wanted to do biology. Actually, I knew I wanted to do biology from the get-go.

Christopher Canning: From high school?

Dr. Shoubridge: From when I was kid. I love biology. I wasn't sure exactly how that would end up, and at one time I thought I wanted to be a marine biologist. I guess because it kind of looked glamorous. I saw films of Jacques Cousteau on his boat the Calypso saying "Philippe, bring up a bottle of red wine up from the hold and we'll look some plankton."

I actually entered the marine biology program at McGill at that time, then I realized that this wasn't what I wanted to do because there was really no way to perform experiments; the field was largely descriptive.

So I looked around for a supervisor and a guy named Bill Leggett asked if I

would consider doing a PhD under his supervision. Bill is a fisheries biologist who later became the principal of Queens University.

That was 1974. As I did all my undergraduate at McGill I wanted to go somewhere else for a year at least to just get a little bit of a different perspective on life. So Bill phoned up a friend, Peter Larkin, at UBC, and asked if he would take me under his wing for a year, and he agreed. Peter was brilliant; he could pack the house giving a course in statistics, so that gives you an idea what kind of teacher he was.

Christopher Canning: For statistics?

Dr. Shoubridge: Yes statistics. So I went to UBC for a year. The project with Bill was going to be on fish that he had studied called the American shad, which is a big sports fish on the East Coast in the US. It's like big herring and they are anadromous fish like salmons, so they migrate up the river to spawn, and that's where the fisherman catches them.

He had some money from fisheries organizations to do work on what determines whether they spawn once and die (like Pacific salmon) or migrate back to sea after spawning to return the following year (like Atlantic salmon). Just about that time, some studies had came out showing that there is a lot of natural genetic variation in populations, as evidenced by the presence of so-called isozymic variants. Everybody had thought that there wasn't that much natural genetic variation for reasons that escape now. Given what we now know I think if people went back and looked it again they might say, "What were they thinking about? Of course there are a lot of natural variations out there at the genetic level."

And I said wouldn't it be neat to try to look at this and these populations of fish and see if we could correlate such genetic variation with the life histories of the fish? The life history of the fish was as follows.

In Florida, the fish are like Pacific salmon. They migrate up the river once and they die. And then once you get up to Newfoundland, there are like Atlantic salmon; they migrate up the rivers to spawn and back to the ocean four or five times. They will go back to the ocean then back the next year, back to the ocean and back next year. And I said that's pretty neat, you know. They adopted this different kind of life history strategies, what's the basis for that.

Christopher Canning: Yeah.

Dr. Shoubridge: So I was totally naïve; totally, totally naïve. And I said oh yeah, there's

always natural variation out there in populations. There's a phenotype with this fish, a really interesting phenotype; maybe we can sort this out. Maybe the metabolic basis for this will become evident somehow when we look at the genetic variation in the different populations. Clearly, I didn't know what on earth I was doing.

Christopher Canning: Did you know biochemistry?

Dr. Shoubridge: No, not much, almost nothing. I took the basic course that almost -- I think everybody in biology at McGill was also obliged to take a 200-level course, in cell and molecular biology, but I was no biochemist. And I didn't have much in genetics. I had some population genetics.

Christopher Canning: Okay.

Dr. Shoubridge: The course in population genetics was given by Kurt Sittmann, a professor in the biology department. He was really a brilliant guy, and I just got turned on by the course; it was just a lot of fun.

And another guy named Peter Grant, who ended up in Princeton, taught a course in evolutionary biology. So these things kind of all fit together. Here is this evolutionary adaptation, this fish; there was clearly some population genetics going to be involved. And there was another population of this fish and it was slightly different species in the Gulf of Mexico that was thought to have interbred with the ones in the Atlantic Coast when the Florida Peninsula was under water. And then when Florida emerged, I can't remember what geological era now, the late Pleistocene I think, the populations were isolated and couldn't interbreed.

So I had access - I mean we even caught fish in many of the major rivers on the east coast of North America, sometimes by myself, sometimes with the help of fishermen - that was an amazing experience.

Christopher Canning: This is your PhD research.

Dr. Shoubridge: This was going to be my PhD; it ended up being my Masters Degree.

Christopher Canning: Oh, okay.

Dr. Shoubridge: And then I went to the West Coast and caught fish in all the rivers there. These fish were not native to the West Coast, but in the late 19th century, the US Fisheries Department decided, in their wisdom, that they would just take young fish and scatter them across the continent.

They had a number of hatcheries on the east coast. And then they would put small fish, the larval fish, in 45-gallon drums, put them on a train and took them across the United States. So whenever they saw water, like the

Mississippi, they would just dump some of them. Can you imagine? I mean nowadays, people would be horrified.

They ended up at the Columbia River in Washington when they hit the west coast and they seeded it with American shad and another fish called the striped bass, neither of which were native to the West Coast and the fish established themselves. And so the other question was, what did these fish do? Did they take on that kind of life history that the fish had in Connecticut for instance in Northeastern New England and in Canada or were they like the Florida fish? I thought it was a pretty neat evolutionary story.

Christopher Canning: So how did their new environment influence new phenotypic traits?

Dr. Shoubridge: Exactly, yes, and then I had hoped to determine the genetic basis for the life history strategies We were using differences in electrophoretic mobility of enzymes as a proxy for genetic variation because nobody had solved any genomes by then. The assumption of course was that this variation had a genetic basis.

So I started the project and I quickly realized how naïve the whole thing was. I still think it was a great idea but I didn't have the tools. I didn't have the tools to do it, and my supervisor Bill Leggett didn't really have the background to advise me on the project either. I realized I needed more training, and that this wasn't going to turn into a PhD for me.

That's when Peter Hochachka, who was a zoologist, actually a comparative biochemist interested in biochemical adaptation, came to give a talk in the department. I spoke with him and told him that I wasn't that happy with where I was, and that I wanted to do something different. He said, "Why don't you come and work with me?" So I did, I went back to UBC to start a new PhD.

I gave myself three years finish my PhD. And so I did; I finished in three years, and I had that really interesting project. I worked on fish, goldfish, which sounds pretty mundane. But they are actually rather remarkable metabolically in that they can live without oxygen, completely without oxygen, at low temperatures, such as they would encounter in a pond frozen over in winter. And even though they have no oxygen, they produced carbon dioxide. Carbon dioxide is the normal end product of oxidative metabolism in us (and in all vertebrates).

Christopher Canning: Of course, yeah.

Dr. Shoubridge: How they could produce carbon dioxide without oxygen was a complete mystery.

Christopher Canning: Through some others cellular process?

Dr. Shoubridge: Long story short, I figured out they make ethanol.

Christopher Canning: Right.

Dr. Shoubridge: So they're like the yeast of the vertebrate world.

Christopher Canning: Interesting.

Dr. Shoubridge: That was pretty neat story.

Christopher Canning: Okay.

Dr. Shoubridge: I learned a lot about how to do biochemistry, how to study metabolic pathways and had done a lot of radiotracer work to sort out the anaerobic pathway to ethanol in the goldfish. It took me a year or so to do that entire tracer work. At the end of that year, somebody published a paper showing that using nuclear magnetic resonance, you could actually look at metabolic pathways in vivo if you had an NMR machine. So I thought, boy that I just had to learn how to do that because what took me a year could have been done in an afternoon.

Christopher Canning: Yeah.

Dr. Shoubridge: What I didn't know at the time, because of course it was not emphasized in the paper was that NMR is a very insensitive technique, and only under special circumstances, like packing ten to the ninth bacterial cells in a tube, is this an afternoon experiment. So I was still naïve and naively I went off to Oxford to do a post-doc with a guy named George Radda, who, at the time, was one of the gurus using a nuclear magnetic resonance in living systems. I spent four years doing a post-doc there. And I think at the end of it, I realized that there was a very limited future this technique. And as a biologist, you really don't want to hook your wagon to one technique. As soon as somebody develops another technique, you are passé. You're out of the picture.

Christopher Canning: Makes perfect sense, yes.

Dr. Shoubridge: But then Bill Feindel who was the Director of MNI (Montreal Neurological Institute), and a former Rhodes Scholar, had a great interest in any technique that could image the brain visited me in Oxford and asked if I would consider coming to set up Nmr at the MNI. Long story short, he recruited me to come back here to just set up NMR spectroscopy with a neurologist named Doug Arnold, who was doing a fellowship in the Radda. So we did that.

I came back in 1985, and we spent a few years doing NMR. I had a high field

machine and developed some systems where you could look at cells. But, you know it was just too insensitive a technique. I realized that I wasn't going to be able to look at anything really interesting biologically, or to discover anything really fundamental.

Christopher Canning: Are you still working with fish at the time or other organisms?

Dr. Shoubridge: No, no, no. Now we were working on humans with neurological diseases, mostly people with brain tumours.

Christopher Canning: So where in your thinking or career did you say, well, I want to start working with humans?

Dr.Shoubridge: Actually at the same time we were imaging patients I developed some cell systems, cultured human cells to look at metabolic pathways, trying to use the technique to investigate metabolic regulation; so really the same kind of questions I was asking using fish. But I finally had to admit something that I had known really before I came back to Canada; this wasn't going to go anywhere for me.

Christopher Canning: There are a couple of those "this isn't going anywhere in your career."

Dr. Shoubridge: Yeah, exactly. I needed to do something at a more basic level. That was in 1988, about three years after I came back. And just at that time a technique called the polymerase chain reaction was developed, and that was going to revolutionize genetics.

Christopher Canning: Molecular biology?

Dr. Shoubridge: Molecular genetics -- yes, because now you could amplify any piece of DNA.

Christopher Canning: Right.

Dr. Shoubridge: Before that you had to know how to clone DNA and I had essentially zero training in that area.

Christopher Canning: Yeah.

Dr. Shoubridge: Two other events catalyzed my decision to change direction. A colleague of mine, George Karpati, who unfortunately has died last year, had several patients who had interesting metabolic diseases, thought to be mitochondrial dysfunction. And the very same year, somebody in England had published in Nature, an article showing that there were mutations in the mitochondrial genome of these patients. They had mutations that were involved in a metabolic disease that didn't allow them to use energy properly and this resulted in a very interesting neurological phenotype called Kearns-Sayre Syndrome. Their extra ocular muscles were paralyzed,

their eyelids drooped, they had exercise intolerance and some of them had cardiac conduction defects. And so George convinced me this might be an interesting group of patients to work on.

That was really my transition to human genetics.

Christopher Canning: This seems to be a general trend in the shift in the group too. From 1972, most of them are working on biochemistry and metabolic diseases. Come to mid-80s, during this molecular biology revolution, the schools were changing quickly…

Dr. Shoubridge: I wasn't really trained at any of the schools; I just followed my nose. It looked like a really interesting biological problem, so we did on the job training; we learned how to do molecular biology on the fly.

We learned a lot of it from a colleague of mine, Ken Hastings, who is still a couple of doors down from me at the MNI, and from many other people, mostly in the McGill System

Christopher Canning: Right.

Dr. Shoubridge: In the 70s you couldn't buy a restriction enzyme. You had to phone up a guy who could clone one and purify it in his lab. Now, it's a few bucks to buy tubes as stuff. In the late 80s PCR changed everything, and that was our entrée into human genetics. And I said this sounds pretty cool because it relates it to what I've been doing. It's metabolic disease, it's metabolism, but now it's in humans and now it has a genetic basis.

I started off working on diseases that involved mitochondrial DNA because at that time, that was quite easy to work on. It's a small genome. It's only 16 and a half thousand base pairs as opposed to three billion in the nuclear genome, and there were patients who had neurological diseases who happened to have mutations in that genome.

Christopher Canning: Single gene mutation?

Dr. Shoubridge: Some of them were single-base pair mutations.

Christopher Canning: Single-base, right.

Dr. Shoubridge: Yes, there only 13 protein-coding genes in mitochondrial DNA. There are 22 tRNA genes and two ribosomal RNAs, representing a kind of skeleton apparatus for translating those 13 proteins, which happens in the mitochondrial compartment itself. They are all integral components of the oxidative phosphorylation pathway, which is the pathway that allows us to use oxygen to produce energy.

Christopher Canning: Yeah.

Dr. Shoubridge: Those are the diseases that we've ended up studying since then. As I mentioned it was easy to work on mitochondrial DNA because there are thousands of copies of it in every cell, so that is where we started.

Christopher Canning: Who is the "we" that you are speaking of -- you and the lab or you and your colleagues?

Dr. Shoubridge: Me, my lab. We just started doing it. Luckily, I managed to recruit a couple of people who were really good. I say lucky because nobody really would come and work with me as molecular biologist or as a geneticist because I had zero track record in the field at that time. We were curious, and after all it isn't rocket science. You can't just go and be an astrophysicist tomorrow because you'll open up the first page of astrophysics 101 and you've got to know how to do a Leplace transformation or something like that, and you realize that you do not have enough math to even understand what they're talking about.

But I think in biology, it's a pretty level playing field. If you're curious as a biologist, you can learn how to do almost anything.

Christopher Canning: What was the climate like around the time that you became interested in mitochondrial DNA? What was it like in other places in the world? Was it becoming more popular, or were you kind of on the fringes of that work?

Dr. Shoubridge: It was just becoming popular because as I said in 1988 the first mutations were found. People had known for a couple of decades at least that there were families with neurological phenotypes that appeared to be maternally transmitted. And it was known since 1980 that mitochondrial DNA was transmitted maternally in mammals. There is a single example of the medical literature where that's not true, but by and large you get all of your mitochondria and all of your mitochondrial DNA from your mom. In retrospect, it's curious why people didn't look earlier on because it was, even then, a relatively simple genome to analyze.

Ironically, the patients in which mitochondrial DNA mutations were first reported were sporadic cases, but they had very particular skeletal muscle pathology. They have tons of mitochondria in some segments of their muscle fibers. This huge amplification of mitochondrial numbers made the fibers look kind of moth-eaten because some of the contractual apparatus had been replaced by mitochondria. So there was clearly something going on.

Christopher Canning: Was it an over replication of the -- ?

Dr. Shoubridge: Yes, it was. Nobody really understands it completely, but it looks like an

attempt by the cell to compensate for the mutation in the mitochondrial genome that's causing the defect in oxidative metabolism, resulting in intolerance to exercise or easy fatigability.

And if you'll look in those mitochondria, it turns out they're full of mutations. So what's happening is a kind of positive feedback loop. Normally, there is continuous crosstalk between the nucleus and the mitochondria in muscle to establish how many mitochondria the muscle needs to do the work it is being asked to do.

So if you want run marathons, you've got to train. And as part of training, you upregulate the number of mitochondria because marathon running relies almost entirely on oxidative metabolism. So you need more mitochondrial volume in your muscle cells in order to support that level of work. If you're a couch potato on the other hand, those signals aren't there, and the number of mitochondria decreases.

Christopher Canning: Those signals are coming from nuclear DNA.

Dr. Shoubridge: No, they are coming from metabolism in the cell. We don't know exactly what the nature of the signal is, but something tells your muscle cells that they don't have enough capacity to do what you're asking them to do, so they have to rebuild. If you de-train, then the muscle cells we have got too much capacity and they downsize.

What we think happens is that the mutations in mitochondrial DNA end up sending the same signal to the cell. And the cell just says, "Gee, we don't have enough capacity. We've got to make more mitochondria." However, the templates (mitochondrial DNA) are bad." And so they keep making more and more defective mitochondria without ever solving the energy demand problem- a vicious cycle. So you end up with this characteristic pathology – accumulations of dysfunctional mitochondria.

Christopher Canning: In skeletal muscle?

Dr. Shoubridge: That's in skeletal muscle. We don't know whether the response is the same in other cell types, because they are not often biopsied. Skeletal muscle is easy to biopsy, and it's easy to culture, so you can actually work on it in the lab. What we actually culture are cells called satellite cells. Everybody's muscle contains these dormant cells, which sit on the periphery of muscle fibres. If you tear your muscle, which happens all the time, you need to repair it. When the tear occurs, some magical things get released; nobody knows exactly what, waking up the dormant cell. The dormant cell decides to divide and it's like a patch kit. New cells come in and fix the muscle tear and re-establish function. The stem cell goes back and remains dormant for the next insult to your muscle.

Christopher Canning: Great. How did you get interested in the neurological sciences, then? How did you end up in a neurological institute?

Dr. Shoubridge: By accident.

Christopher Canning: Really?

Dr. Shoubridge: Truly by accident.

Christopher Canning: Okay. So this wasn't a planned transition?

Dr. Shoubridge: I had actually had a grant to go at the University Ottawa and work on the biology department.

Christopher Canning: Is this right after your post-doc time?

Dr. Shoubridge: Yes, when I was deciding where to work, I applied for an NSERC start-up grant, I can't really remember exactly what the program was, but at that time, the government had this kind of stimulus program to hire young people into universities. They especially wanted women in science faculties, but the program was basically for anybody, but you have to have a departmental sponsor.

At that time, I still intended to do NMR and it seemed to me that they weren't going to have the resources to do that because you needed to buy a machine, which was a few hundred thousand dollars. That was a fair amount of money for the biology department to put up and I didn't think that that was really going to happen.

And at the same time, Bill Feindel, who has actually an office on the corner here had visited Oxford because Doug Arnold, who was a neurologist from the MNI, who's also back here, had gone to the same lab to learn how to do NMR. And he thought it would be great if he could recruit both of us. And I said, well I like biology and I don't want to end up working for a doctor. I don't want to be a technical guy supporting some MD's research. He said, "No, no, no, no. That's not going to happen. You can have your own lab." And I said, okay let's try it. So that's how I ended up in a neurological institute.

And if I hadn't ended up here, there's no way I'd be working on disease, there is absolutely no way. That's the amazing thing about this place. Penfield, who set up the MNI thought that if you put guys who are neurosurgeons or neurologists in with basic biologists, who are curious, the biologists would end up working on some aspect of disease. So what he managed to do was to create a place where one could recruit basic scientists to work on important neurological diseases just by putting them together in the same container with clinicians.

Christopher Canning: I have a question on that point. Is that relationship good between the bench and the clinical? Do you find in your experience in the neurological institute -- and I'm soon going to move on to the questions with the group, but do you find that that relationship was good between the bench and clinical aspect?

Dr. Shoubridge: It's great here. I mean I would never have gotten involved in the disease world if a clinician who saw patients in the neuromuscular clinic hadn't got me interested in doing it. I would occasionally go down to talk to the patients myself to explain what we had found and what we were proposing to do.

There are still no treatments for most of them in fact, so a lot of what we were trying to do was to provide the right genetic diagnosis, so at least we would know what we were working with. There are some things that can moderate the symptoms in some cases, and there have been a few clinical treatment trials. My sense is that it is very important for the patients to know exactly what it is they have, what genetic mutation, even if there is little that can be done about it right here and now.

So the goal from the clinical perspective was finding out the genetic basis of the disease, and then we would take over from that and say, "well, if they've got this gene mutation, why does this gene mutation produce this particular disorder? What's the gene product doing?" It was really good marriage in that way.

Christopher Canning: Okay. Can you then speak more about your diagnostic facility? I'm interested in how that works, how patients are referred to you, what those tests are, what the outcomes are of those tests.

Dr. Shoubridge: We initially got involved with it because George Karpati, the man who got me interested in this field, wanted me to set up diagnostic tests. So I set up a lot of biochemical tests before there was much genetics. We did that for a few years, and then I realized that, at least in the adult population, many of the biochemical tests weren't really that valuable. They were in some cases, especially in the mitochondrial disorders, what we found was often low-end normal enzyme activities and it wasn't really telling us anything more that the pathology was the telling us, or the clinical phenotype was telling us, or eventually the genetics was telling us, so we stopped doing that.

And at about that time, the FRSQ started a program in collaboration with Hydro-Quebec, which they called Technology Transfer. The idea was that it would set up sort of expert labs to transfer results from research labs to the clinical environment. So if tomorrow we found a mutation in a new gene that was producing a neurological disease and patients came here, we could now offer that test to any patient, essentially immediately.

Christopher Canning: How would you know it was producing a certain disease if it's coming from the lab?

Dr. Shoubridge: A physician would call and say, "Look, I've got a patient and it looks like they have some kind of mitochondrial disease. Can you try and figure out the genetic basis?" At the time this was still mitochondrial DNA. We would sequence candidate genes and in many cases we found the mutation. Those in whom we did not became research questions.

We had to apply to the FRSQ for a grant every year for the privilege of doing diagnostic testing. I always got it and we provided the testing for free for anyone who requested it. The program ran for five years. We were at the point where we would get probably 200 to 250 referrals a year from patients from all over the place. At the end of five years, the FRSQ said, "Okay, that's been a really successful program. Now, we're going to stop that and we'll just do something else."

So I went to the hospital and I said, "Look, here is what we have done." First of all, we have provided a service to the patients who have come here. We have established ourselves as experts in this field and that has given the institute some kind of profile. And now, the program was stopped. We no longer have the funding so don't you think it would be smart just to set up a small lab?

And I must say, you know the funding was $42,200.00 a year, and we did tests from anybody for free. That, I think was an amazing bargain. And the hospital said, "No, we're not interested. That's not part of what we do."

Christopher Canning: That's it? Wow.

Dr. Shoubridge: Yeah. So the hospital guys are just worried about the hospital budgets and they don't think about the broader picture of the institution and where it sits vis-à-vis Montreal, Quebec, Canada and the world. That's not part of what those guys think. They're just looking at the ledgers, and focusing on the bottom lines. To be fair they are forced into doing this by the Health Ministry,

And so I approached the people at the MNI and they said, "Yes, we can do it if we do it on a kind of cost-recovery basis." And so that's what we've been doing ever since. We still lose money, but I think it is important to provide the service. And again, we would serve all comers. So some hospitals like SickKids in Toronto said, "Well, we can't afford that." And I said, well if you can find somebody that does it for free, let me know and I'll outsource all of our testing.

Christopher Canning: Yeah.

Dr. Shoubridge: Because we were doing it for peanuts relative to what the U.S. diagnostic labs would charge, something like five to ten times less. Now the Quebec Government has changed all the rules again. They have decreed that we can no longer bill between hospitals. And in fact, we're not even allowed to do the test because we're not an accredited clinical diagnostic laboratory. We're doing it in a research lab essentially and we need new rules.

I certainly agree that they do need some evidence of quality control, that the results that come from a lab that can be trusted. I think that testing could still be done reliably in the context of a research lab, but that's not the way it's going to happen. So what we have to do now, if we want to continue, is to set up dedicated molecular diagnostic laboratory,

Christopher Canning: Are these are for all late-onset disorders?

Dr. Shoubridge: No. They're all over the map.

Christopher Canning: Okay.

Dr. Shoubridge: They really are. So after the first mitochondrial DNA mutations were reported many new mutations continued to be uncovered at a rapid pace for about a decade or so, associated with a huge variety of clinical phenotypes, presenting from shortly after birth to late in life. The whole other area of mitochondrial disease, which was nuclear, coded genes remained relatively unexplored. There are probably 1000 to 1500 proteins in mitochondria that are encoded in the nuclear genome versus 13 encoded in mitochondrial DNA. Nobody knew much about those vis –a-vis mitochondrial disease .And so at the time, I thought maybe it's time to look, but the question was how?

In North America, a pedigree would look like mom and dad, who were complete normal, and a child who died early on, sometimes with a normal sibling. Usually, they were born normally and they would die in the first weeks, months or first years of life, sometimes a brain disease, sometimes a heart disease, sometimes a liver disease. And so the question was, how do you figure out what's wrong?

Christopher Canning: Right.

Dr. Shoubridge: At that time genetic linkage was all the rage, but we did not have big families so that was out of the question. It was clear to me the only way to solve it by functional complementation. The biochemical defects were predominantly be transmitted as recessive traits, so we reasoned that if you could somehow put in a normal copy of the gene, perhaps from a cDNA library, you could rescue the defect in the patient cell line.

Such an unbiased genetic strategy seemed to be necessary because there are just too many candidate genes, many of which are completely uncharacterized.

Christopher Canning: You don't know what the DNA is producing, the proteins to make the genes?

Dr. Shoubridge: Correct. We don't know which genes are necessary and sufficient to produce a functional respiratory chain. We know a lot of them, but we certainly don't know all of them. So I thought, what genetic material are we going to put in? We first tried cDNA libraries, but that was just too technically challenging. And so I thought, if you could put in a normal chromosome from an anonymous donor, cell line we could at least map the gene defect.

Christopher Canning: The whole chromosome?

Dr. Shoubridge: The whole chromosome, you could figure out whether the normal copy of the gene in that chromosome would rescue the phenotype, right?

Christopher Canning: Right.

Dr. Shoubridge: And if you put in all the chromosomes one at a time then you could figure out which chromosome was carrying the defective gene. There is a technique called microcell-mediated chromosome transfer that had been developed by people who were mostly interested in cancer, in mapping tumour suppressor genes. One or two groups in the world had created a bank of mouse cell lines that stably carried single human chromosomes.

They were tagged with a selectable marker, which confers drug resistance. After the chromosome transfer, in order to remain drug resistant, the patient cells had to keep the human chromosome. So we could ask whether or not the biochemistry that was defective was now rescued in cells receiving an extra copy of a normal human chromosome. So that's the functional complementation; you're complementing the functional defect in the cell line.

That's when I started to get involved with the group. The group was reapplying for one of their MRC grants.

Christopher Canning: This is a perfect segue into 2000 and 2001; so that's where we are.

Dr. Shoubridge: Yeah, that's right. So that was the project I put in and they said it can't be done.

Christopher Canning: That was – initially, though, you applied in 1994.

Dr. Shoubridge: Yeah.

Christopher Canning: And didn't get into the group at that time.

Dr. Shoubridge: Correct.

Christopher Canning: Okay.

Dr. Shoubridge: That was based on that. So they said it couldn't be done.

Christopher Canning: Okay, the MRC said that?

Dr. Shoubridge: Yeah.

Christopher Canning: But the group was obviously supportive.

Dr. Shoubridge: Absolutely, the group was supportive. They thought I was perhaps naive, and I am not sure whether anybody knew if it would work for sure. But they thought it was a good idea for me to be in the group or I suppose that they wouldn't have invited me.

Christopher Canning: Can I get you to be more specific? How did you become involved in the group? How did they know what you were doing? How did you know them? What happened there?

Dr. Shoubridge: Everybody knows Charles Scriver. And I bumped into Charles now and then and we started to discuss what it was I was doing. We were both doing biochemical genetics – the subject the group was really founded on. And Peter Hechtman was still there.

Christopher Canning: And David Rosenblatt?

Dr. Shoubridge: David Rosenblatt; so I knew David, and I knew of his research in vitamin metabolism – also biochemical genetics. I guess I was the new kid on the block then, you know, up the street in a different hospital, happened to become interested in human metabolic disease by this unusual confluence of events that happened in 1988 and 1989. And so, it was just pure serendipity that I ended up in the group.

Christopher Canning: Okay.

Dr. Shoubridge: So they invited me to join the group because nobody in the group was doing what we were doing, but it clearly fit in the general theme of the group. We had started out on adult diseases just because of where I was, here (the MNI), and this is an adult hospital. And so the patients we saw were adult patients mostly with mitochondrial DNA problems.

So the ones that are the nuclear problems tend to be very severe diseases in

infants. So what you don't know probably about the genetics of mitochondrial DNA, but I told you a little earlier.

Christopher Canning: I don't know a whole lot about that.

Dr. Shoubridge: It is a thousand copy genome in most cells but the number of bad copies, with the mutation, can vary from cell-to-cell.

Christopher Canning: Okay.

Dr. Shoubridge: So, it is very unlike nuclear genes. In a recessive disease you inherit one bad copy from your mother, one bad copy from dad, every cell has got two bad copies.

Christopher Canning: Got you.

Dr. Shoubridge: But with mitochondrial DNA because its thousands of copies, some cells will have no bad copies, and some cells can have a huge number of bad copies. And everything in between.

Christopher Canning: What's causing that?

Christopher Canning: We don't really know why wild-type and mutant genomes segregate differently in different cell types. The rules seem to be very complex because they depend on which mutation is there. There are huge differences amongst different mutations. So, that's why probably the adults who have mitochondrial DNA mutations survive because there can be selection for and against the bad guys in different tissues. And so, what you're seeing are the people that actually had enough ATP production, enough energy production to survive. The symptoms they present with represent, at least in part, the tissue-specific accumulation of mutant genomes.

But many of the children don't survive because they have two bad copies of a nuclear and it's a severe disease right from the get-go.

Christopher Canning: Right.

Dr. Shoubridge: They are usually born normally because we think that oxidative metabolism is relatively unimportant utero – it's mostly glycolytic metabolism, possibly because it is a relatively oxygen poor environment. But once they are born and they hit molecular oxygen that's when they start to get into trouble.

Christopher Canning: Interesting, okay.

Dr. Shoubridge: So that's how I got involved initially with the group, to study these severe childhood biochemical defects, but the MRC rejected the proposal.

Christopher Canning: Okay. Do you know why? Do you know what they said at the MRC?

Dr. Shoubridge: Yes, they simply said it wouldn't work. And then I sent the same proposal to the March of Dimes birth defects foundation, which was the foundation that funded the research to conquer polio. After polio was eradicated, I think they looked around for something else to fund. And said well, there are many other birth defects, so why don't we support research related to birth defects in general. And so they funded the project. We did it and we published it in Nature Genetics as an article, which is like the best genetics journal out there.

Christopher Canning: So this is after your '94 application that was or a couple of years after that?

Dr. Shoubridge: Yes. So this got published in '98. So we showed it could be done.

Christopher Canning: Yeah, which is obviously amazing.

Dr. Shoubridge: It was amazing, yeah. So then they funded it.

Christopher Canning: So in 1994 you weren't successful. Then you weren't actually on the 1998 application in the group.

Dr. Shoubridge: No.

Christopher Canning: Was that because you were still doing your own independent investigation with the March of Dimes?

Dr. Shoubridge: That's correct.

Christopher Canning: So this was somewhat related to Leigh Syndrome?

Dr. Shoubridge: To Leigh Syndrome, exactly.

Christopher Canning: Yeah.

Dr. Shoubridge: Yeah.

Christopher Canning: So this is your big kind of breakthrough.

Dr. Shoubridge: Yeah, that was the big breakthrough because we showed that you could solve a gene defect like this. And the reason it worked -- well, clearly the theory was right. But, I must say that I worried about whether or not parts of the chromosomes would have been silenced sitting around the mouse cells for years, and would never be expressed when put back into a human cell, but that wasn't the case.

Christopher Canning: Meaning, it would have to be epigenetic?

Dr. Shoubridge: Exactly, exactly. And so that worked. That didn't seem to be the case, although I mean that's still possible that that would happen in some disorders. The power of the technique turned out to be, that you could map the gene defect to a rather small region of the donor chromosome.

Christopher Canning: What does this mutating cell do with the third chromosome?

Dr. Shoubridge: Well I don't really know the answer to that. So, it does a lot of weird stuff. Sometimes the chromosome fragments; some of it just gets lost, or a piece of it gets hooked onto another chromosome. Sometimes the third chromosome will stay there, apparently in its entirety. And I don't know how it comes together with the two other chromosomes and segregates. But what seems to be the case is that these events happen very early on in the experiment, and after that, it remains relatively stable. So whatever happened happens and the cells deal with it.

Christopher Canning: Fascinating.

Dr. Shoubridge: It is amazing. And so for this experiment we got the two-cell lines from patients with Leigh Syndrome from, Garry Brown, a collaborator of mine in Oxford, and he got a whole collection from Denise Leigh, the neurologist who described this disease in the 1950's in England. Both patients had died from the disease, which is associated with cytochrome oxidase deficiency. I said, if you can give me those two cell lines, my lab will find the genetic basis for the disease because we have an idea about how to do it.

Christopher Canning: Yeah.

Dr. Shoubridge: So he gave us the cell lines and we mapped the defect to chromosome 9. Then we went through a bunch of independent transfers of chromosome 9 and managed to find one clone where a little tiny piece of the end of the long arm of chromosome 9 that had integrated into some other part of the genome, and that was all, everything else in chromosome 9 was missing.

And on that piece of chromosome 9, there was a gene that has a homologue in yeast that had been partially characterized and produced a mitochondrial phenotype. And we said this is it, we have got it.

And so we sequenced the gene (Surf1) and all the mutations we found were nonsense mutations, either stops or splice site mutations, all predicting that the patients would be null for the protein. We then developed an antibody to the protein and then the blots all showed that there was no detectible protein. So all the patients were essentially knockouts for this gene.

Christopher Canning: The gene just wasn't producing particular proteins.

Dr. Shoubridge: Yeah, because of the mutations. The mutations, all either produced premature stops in the protein, so they would be translating on it and would stop and so that's unstable; or they would be a splice site mutation in it, so that something got spliced inappropriately and then produced the premature stops.

So that's what got us back in to the group.

Christopher Canning: So in 2001, you said let's apply to be a part of the group again or did they say why don't you come back because this is a great thing that you've done? Do you recall that conversation?

Dr. Shoubridge: No. [laughs] I don't actually. They were going to reapply and I think probably David Rosenblatt phoned me and said, "You know, why don't you join the group again." I think Peter Hechtman had then left the group if I recall. I can't remember.

Christopher Canning: In 2001, Rima Rozen was the Director; Gravel was on the application, as was Andy Karaplis, Mark Trifiro, Susie Tenenhouse and Robert MacKenzie. Rosenblatt temporarily left the group, I think, because he didn't get funding. He then got it again six months later and rejoined the group.

Dr. Shoubridge: Right, I think Rima asked me to join the group. That's my recollection of it, but you know we'd see each other at human genetics events, and you know they were going to reapply and it looked like it would be appropriate for me to come back into the group. But, I honestly can't remember the details.

Christopher Canning: Right. Do you recall what the application process was like at that time? Did you have to write your own application?

Dr. Shoubridge: Yeah.

Christopher Canning: And then, you all submitted it together. So, do you remember going through that?

Dr. Shoubridge: I do. I mean at that time -- at the first time when I wasn't successful, we applied as a group. And I think it went in as a group grant.

And then and we were site visited. The second time around, this time when were successful; I don't think we had the site visit if I remember correctly. But we all applied for individual grants and then there was a group grant. Individually we had to be successful with our own pieces to be part of the group. But the group put in a grant talking about why it was useful to be a group.

Christopher Canning: Right.

Dr. Shoubridge: Now, what was its groupiness? Why would it make --

Christopher Canning: Great, which is what I'd like to talk to you about.

Dr. Shoubridge: What is groupiness?

Christopher Canning: Indeed. I like that you used that word. In your opinion, what was the Group's groupiness?

Dr. Shoubridge: So I would say that groupiness before this was better than groupiness after the actual application because we would rarely see some members of the group, those at the Lady Davis, for instance. David [Rosenblatt] was the person with whom I interacted the most. And he was working on B_{12} deficiencies, on which he is the world expert, and the same kind of technologies that we'd use to solve the gene defects there, because they are also autosomal recessive disorders with a cellular phenotype.

So we transferred that technology over to his lab. And it wasn't really that successful with the first student he had because he couldn't make it work on the cells for some reason. They did make it work and they mapped one of their gene defects. As it turned out their competitors/collaborators also found the gene, by yet another method, but it all fit together.

We used to have regular meetings and so it would be interesting to find out what everybody was doing. But we weren't working as a kind of team, focused on the same thing because we all had our own individual projects. And so the dynamics would shift a lot. So some people who were working more closely on a particular area like, Bob MacKenzie was working on folate metabolism and single carbon metabolism; so he and David [Rosenblatt] and Rima [Rozen] obviously formed a kind of sub-group in that area.

And I was working on metabolic diseases using technologies that David could use. And we developed some vectors that were useful for expressing cDNA's and retroviruses in primary human cells, so we shared those technical aspects of things. But from a real fundamental biological point of view, there wasn't a lot of overlap.

Christopher Canning: What made the group a group, then?

Dr. Shoubridge: That's a very good question. [Laughs] You know, it was partly a functional group and partly a dysfunctional group I think.

Christopher Canning: I'm curious. Can you speak to both of those points?

Dr. Shoubridge: Yeah. So I think what made the group -- for David and I it was obvious because we're working on metabolic diseases and we could share reagents

for them. But the biochemistry was completely different; however, some of our students shared things. So that was part of a group, but that was pretty miniature. For Rima and David and MacKenzie, who are all interested in folate metabolism basically; there was clearly a link. But for the other two guys --

Christopher Canning: Mark Trifiro and Susie Tennenhouse.

Dr. Shoubridge: Well Susie was at the point of leaving. I guess she was part of it, but she was going to retire.

Christopher Canning: Okay.

Dr. Shoubridge: Because she was working on phosphate metabolism.

Christopher Canning: Right.

Dr. Shoubridge: And, so she was more associated with -- not Mark [Trifiro] but Andy Karaplis, who was working on bone. So they were kind of off doing their own thing. And so we weren't really a group in that sense, I don't think. We are all working on different aspects of metabolic problems. And so it was interesting to hear whatever other people were doing, but to be quite honest I don't think that we ever -- I don't think we ever shared things that really moved our science forward as an entire group.

Christopher Canning: Interesting, OK.

Dr. Shoubridge: I really don't think we ever did that.

Christopher Canning: Okay. What role did Scriver have at this time? Obviously he was retired, but…

Dr. Shoubridge: Zero.

Christopher Canning: Because it's been agreed upon that obviously Scriver and Fraser, the founding members of the group, were hugely influential. Was he still around saying, "Hey, maybe you should think about this, maybe you should think about that?"

Dr. Shoubridge: No. Not that I know of.

Christopher Canning: Nothing that you know of. So the torch was literally passed to Rima Rozen?

Dr. Shoubridge: Yeah.

Christopher Canning: … who is a PhD student of Scriver, anyway.

Dr. Shoubridge: That's correct.

Christopher Canning: Yeah.

Dr. Shoubridge: And so was David, I think.

Christopher Canning: I think so, yes.

Dr. Shoubridge: David Rosenblatt -- he worked with --

Christopher Canning: He came back to work with him after his post-doc.

Dr. Shoubridge: Yeah. He may not have pitched but he worked with them.

Christopher Canning: Yeah.

Dr. Shoubridge: Yeah. I don't know what exactly -- under what -- maybe a fellowship or something.

Christopher Canning: A fellowship just before his post-doc but he went to the States and recruited back in 1975.

Dr. Shoubridge: Yeah, right. So that was before me.

Christopher Canning: Right.

Dr. Shoubridge: I landed here in '85 and didn't get associated with these guys until very late in the game.

Christopher Canning: So do you know Dr. Scriver well?

Dr. Shoubridge: Yes, I do.

Christopher Canning: Yeah?

Dr. Shoubridge: Yeah. No we bumped into each other-- and in fact now he has these books.

Christopher Canning: Yes. I've see them online too.

Dr. Shoubridge: Yeah. So, I'm now editing with another guy named Grant Mitchell who is a geneticist at Sainte-Justine the whole series on mitochondrial diseases for Charles' book. And he was always trying to get me to write the chapter in and I -- so I didn't, to make a long story short [Laughs]. Somebody else had written it. He wanted me to write the other different one and keep the other person in there; I just didn't think it made sense to do that. Well he said, "You have a totally different perspective on all of the stuff", which was true. But I said, I don't like the way it's configured. I said, that's not going to

work.

And then Grant phoned me up last year and said they're reorganizing this book. And it's going to be an online book, not a paper book. I think that makes much more sense because by the time you organize a mammoth event like this and it comes out on paper - well, science just moves way too fast now for that. So, it's a good reference book to have because there's a lot of history. I used to have a great book on Somatic Cell Genetics, which I read a long, long time ago and maybe that's what gave me the idea about the chromosome stuff. Somebody "stole" it from me. "Can I borrow that book?" and it never came back.

But it was about the early days of who was involved in all this stuff. And to me, it was fascinating because all the names of the medium, the media that were used in the lab like Dulbecco's medium or this guys' medium or that guy's medium; they were actual people of course who developed all these things. You go back and read and you find what their challenges were at the time, which is stuff that we just take absolutely for granted now, what they were thinking about in trying to solve those problems.

And yeah, so history books are great like that. But you can't -- as a reference book it is good. So you learn about the history, which you are not going to learn in papers. You can just print this PDF in the printer, so you have to be interested in that sort of thing. But I think to keep for the geneticist who wants to know -- I've got a patient with this kind of phenotype, what's known about that? They want to go online and find out like what was updated last month on that disease. So I think it makes a lot more sense.

And I think it's probably easier to get people to do the writing of that if they know they can update it easily. So what we've done is divide it into bite-size pieces. So somebody's going to take, you know write a chapter on this biochemical defect and this one and this one and this one, all associated with the same problem -- mitochondrial problems. But it's not going to be like hundred pages with a thousand references. So, it's not huge task for somebody to do that. That doesn't really make sense. It makes sense to get the people who've done the most in one particular area; the experts, if you will, write their little piece and then keep it updated. So that's the way the books going to evolve.

Christopher Canning: Coming back to the group, did you publish with any of them? Did you have any collaboration with -- ?

Dr. Shoubridge: We published two papers with David. I never published with Roy [Gravel], who was still a part of the Group. So we published two papers with David, I think.

Christopher Canning: Yeah. What was it like being a part of the group and not being a physician? Was that an issue at all?

Dr. Shoubridge: Not at all.

Christopher Canning: Because most of them are training -- not all.

Dr. Shoubridge: No, Roy is not a physician. Rima is not a physician. Bob was—

Christopher Canning: The later folks are not actually. So the early days --

Dr. Shoubridge: No, the early days everybody was --

Christopher Canning: Yeah.

Dr. Shoubridge: And every -- they are MD's or MD PhD's.

Christopher Canning: It's interesting.

Dr. Shoubridge: But in fact, Mark is a physician of course and David, but Bob McKenzie not Rima not, Susie Tennanhouse was not, I am not.

Christopher Canning: You were all trained biochemists or molecular biologists.

Dr. Shoubridge: Yeah, we trained ourselves.

Christopher Canning: You trained yourselves.

Dr. Shoubridge: Yeah.

Christopher Canning: I'm interested in that. You spoke to this a bit, but what was it like coming into health not being trained in health, do you know what I mean? Especially for the group, in the context of the group, what contributed to our understanding of health from the scientific perspective?

Dr. Shoubridge: I don't ever think I looked at it from that perspective, to tell you the truth; I've just always looked at it as a fascinating biological problem and I just happened to get involved in genetic diseases.

And the problems were no less interesting than discovering that fish without oxygen make ethanol. We could discover a brand new gene. Nobody ever knew about it, that nobody knew that disturbing that function could cause this neurological disease. And I think that's fascinating. And the gene, we discovered was something called SURF1. And so, what does SURF1 do?

Christopher Canning: Yeah, I've seen that.

Dr. Shoubridge: Its part of a locus called the Surfeit locus that was discovered by a guy in England, I think in the early 1980s. And he called it Surfeit because there were five genes in a really tiny piece of DNA. And at that time, it was the densest packing of genes that anybody had found. He said there's a Surfeit of genes, this locus; so they called them Surfs.

And they were conserved back to birds. So birds had the same thing and beyond that, they were all over the map.

And as far as anybody could tell, nobody really knew what the function of any of them was at the time. And as far as anybody could tell, they had nothing to do one with the other, and that's true. They have nothing, apparently nothing to do one with the other. But they were in this little cluster; that's still a bit of a mystery. And today we still don't know what the exact function of Surf1. It probably acts as an accessory factor that allows the enzyme to add a heme group to its catalytic core.

So, it's this kind of widget, I would say. It's something that increases the efficiency of the addition of heme and allows you to make the enzyme in a very efficient way. If you have none you can still make some enzyme and get by for a while until the body experiences some stress, like an infection for example.

So we find the new gene and now everybody can screen for that gene and its great people can get a diagnosis; it's medical genetics. And so, if you want to do the pre-implantation and direct diagnosis or a conventional amniocentesis and find out whether you're carrying an affected fetus with the defect, or only put in embryos that have at least one good copy of the gene, you can do all that. It opens up all these reproductive options, and you could diagnose children who have got the defect and say absolutely for sure they've got this disease because of a particular mutation. To me, that's a bonus really. It's like an add-on. But what drives it is my innate curiosity about --

Christopher Canning: As a scientist?

Dr. Shoubridge: As a scientist, what's the genetic basis for this and why does it produce this disease, and how does the thing work at the molecular level.

Christopher Canning: Would you call yourself a medical geneticist then?

Dr. Shoubridge: No.

Christopher Canning: But you do medical genetics?

Dr. Shoubridge: I do.

Christopher Canning: Interesting.

Dr. Shoubridge: Yeah. But I wouldn't say that's not my -- if somebody asked me what are you? I would say that I am a biologist. I'm interested in biology. I'm interested in living things and how they work. And I happen to work at the genetic level -- after all of the ups and downs, you know different points where I realized I wasn't getting anywhere – like with NMR, where I was limited by a technique.

Chemists do that kind of stuff. You know there are crystallographers and people who do some fancy kinds of spectroscopy. The techniques are sometimes so sophisticated that they end up doing that kind of thing, and that's what they like. And lots of people come and say, "Please could you do NMR on my favorite protein" because we want to solve the structure; and so they do that kind of thing. But as a biologist, that doesn't get you anywhere. I am not saying that structure is not important, it is crucial, but it only part of the puzzle.

I like to work on living systems and I think the genetics now is so powerful that it allows you to figure out what's wrong and it allows you to manipulate it, you can put in mutants. You can do all kinds of experiments to try to figure out what a particular gene is all about, how does it work and why do mutations cause it not to work, what part of a biochemical system is it involved in. And ultimately, you like to find out some way to fix it when it is broken.

Christopher Canning: Yeah.

Dr. Shoubridge: But some of the diseases -- I mean, especially these pediatric ones are so severe that some of the patients die of degenerative brain disorder. But if you manage to conquer that problem, and that's a hard problem to conquer, you know a year later they might end up with a heart disease or a liver disease.

And so you'd be constantly just trying to keep them alive. And you have to ask yourself, I think as a person, as a human being, is that a life? And is that where you really should be putting resources toward or should you take the subset of those patients who actually have reasonable quality of life and try to make their life better, and then try to make it possible for parents have normal babies and avoid really the catastrophic things.

Christopher Canning: That seems like a bit of shift from the early years of the group in early medical genetics from 1960's and 1970's, where you had clinicians and scientists and it was one; it was one job to try and make people better.

Dr. Shoubridge: Yes.

Christopher Canning: And now it's more, like you say. the study of living systems. Would you say that about was a spirit of the later years of the group?

Dr. Shoubridge: I think so.

Christopher Canning: You're all very well-respected scientists, but if you look at the applications, it kind of shifted from the physician-scientist to more individual molecular approaches, as seen in the recruitment of Rozen, Gravel, etc.

Dr. Shoubridge: But I think it's because the tools were there, right?

Christopher Canning: Can you elaborate?

Dr. Shoubridge: I mean, once you have -- once you can manipulate the genome, once you can look at the genome, sequence the genome, manipulate the genome, now you can essentially do anything to a living system because that's the basis of the living cell. Whereas before, you could look at an enzyme; so what are you going to do? So you could do enzyme replacement. Try to make more of an enzyme somehow by some small molecule.

But the tools were limited. But once the molecular revolution happened then you could ask all kinds of questions that you couldn't ask before. And so I think the shift was been driven by the tools that were available more than somebody thinking about how to do it or how to organize the group.

Christopher Canning: Okay.

Dr. Shoubridge: You know to some extent, we scientists dependent upon technologies. We're not slaves to it. But, I constantly like reading about how somebody's got a new method to do whatever. There's a little article in Nature about molecules that allow you to look at fluorescence in cells or a signals from it. And so somebody has developed this microscopic technique called Second-Harmonic Generation or something like that. So there are these compounds that are inorganic compounds -- I even forgot what they are. There was titanium in one of them or boron or something else that actually if you hit them with two photons at once will emit a light at a wavelength that's way different than what went in. But, it's not fluorescence. And so you can detect this with some kind of fancy microscopes.

So there's no background of living cells. They say we could use these in living cells as markers. But the problem is you have to actually hook them up to biomolecules and then get them into the cell. But nonetheless, there is all this fascinating stuff that kind of goes on around you, that allows you to look at problems you couldn't look at before.

Christopher Canning: Right, which actually makes it more difficult to apply that to medicine because it makes everything more complex; the irony of the increase in

technology has black boxed what we can do and what we know.

Dr. Shoubridge: Right.

Christopher Canning: Which makes the application to medicine that much more difficult.

Dr. Shoubridge: It does. And then, if you go back and you think about it, what's actually available to people in medicine; so we always talk about all these things, gene therapy, protein replacements, all kinds of fancy stuff that is still off in the future. But if you ask the question, can somebody get a genetic test today for Parkinson's Disease, let's say? And so, we used to do that for the genetic causes of Parkinson's, and now the rules have changed.

And so somebody can probably get it if they are Quebec resident. If their physician applies to the government, fills out all the forms, asks the appropriate bureaucrats whether or not we can send their sample to Houston, Texas and for a thousand dollars get back the results, and they might say yes or no. Somebody might lose the form. So the stuff we already know in the system is sometimes difficult to access - it depends what disease you've got.

So, David Rosenblatt runs a diagnostic lab. And if you have Huntington's diseases in your family, you want to be tested then you can go in and that's it. If you have mitochondrial disease, it's less clear where you'll to be tested. If you find me, even if you're not paying, I'll still do the test. I don't care. I'll just don't cover --

Christopher Canning: Yeah?

Dr. Shoubridge: Yeah, sure.

Christopher Canning: It's that easy to just --

Dr. Shoubridge: Yeah. I mean you still have to pay a technician to be involved in doing it. But DNA testing is not a rocket science. If I had the salaries of the few bureaucrats who run this whole system, I could set it up. It's not rocket science. And so, you could screw up but it's much more difficult to screw up with DNA than it is with enzyme.

Christopher Canning: Yeah.

Dr. Shoubridge: So for instance, the enzymes that we study, that we used to test, the ones in the oxidative phosphorylation system, they're probably -- there could be 20 labs in the world or 25 to do this kind of stuff, ballpark, not hundreds.

And at one point, somebody in Germany decided, "Let's send around some samples to all the labs, major labs in the world to do this." They couldn't do

it with human samples obviously. So they used bovine tissue. And they've got a ten-fold range in the results. And even after massaging the data for slightly different this, slightly different that, they still have got five-fold range, and that's huge.

Christopher Canning: Yeah.

Dr. Shoubridge: And so you can get -- and I heard a neurologist here talk about this the other day, you can get a positive diagnosis if you really want one from some lab.

Christopher Canning: You can find it?

Dr. Shoubridge: You can find the diagnostic lab that will give you a positive diagnosis for something. So I mean, that's I guess the basis for having the quality control in there. But all of which to say that in biochemistry, it's tricky. The proteins, they can go off. If you have a -- if it's your coffee break time and you haven't done the assay and you leave the things on your bench and you come back maybe 20 minutes later, they might be dead. So, you could get a different result, whereas DNA --

Christopher Canning: The DNA is DNA.

Dr. Shoubridge: It's DNA. And it will degrade eventually.

Christopher Canning: Yeah.

Dr. Shoubridge: But you have to be pretty brutal to do it. So, the technology is relatively straightforward. Now, there are lots of new technologies that are coming online that allow you to sequence whole exomes, whole genomes. We can sequence whole exomes for about $4000.00.

Christopher Canning: Wow!

Dr. Shoubridge: Or so. So every gene in your body that's expressed, we can know tomorrow -- not tomorrow but in the couple of weeks for 4000 bucks. Well genomes are around $10,000.00 to $15,000.00 or so. But, there's this race onto do this. I'm sure you know, for the thousand dollar genome.

Christopher Canning: Of course, yeah.

Dr. Shoubridge: Yeah. And that'll happen because the new DNA technologies -- the new sequencing technologies are extremely creative.

Christopher Canning: Yeah.

Dr. Shoubridge: I mean really, really bright guys who have these massively parallel instruments that allow you to generate terabytes of data in no time at all.

It's the analysis that's going to take the time. And how that's actually going to impact the diagnosis, I really don't know because I'm not -- if somebody comes to you and say, "I think this patient has mitochondrial disease. Could you please tell me whether or not you can do a test which would rule it out?" And you know what genes would you look for, so sometimes it's clear but most of the times it's not. If it's a textbook phenotype that we now know about from 20 years of research, we'd say, "Yeah." If somebody has a young child with cytochrome oxidase deficiency or Leigh Syndrome I'd say, it's almost certain a SURF1.

Christopher Canning: All right.

Dr. Shoubridge: We can do a quick biochemical test and prove that and then do the genetics; or just do the genetics straight away.

But if somebody comes in with a complex phenotype, looks like they have mitochondrial disease because of the metabolic profile and they have liver problem and things like that, I'd say, "Hmm, where do we even start?" There are a thousand proteins, a thousand of genes how -- it may not be quite -- that's an exaggeration in whole mitochondrion but there could be 300 or 400 things involved with the respiratory chain and we wouldn't really know which ones to start with. And so you could do this kind of massively parallel thing. But, the quality controls on those are -- it's much trickier. So for discovery, it's okay because you can go back and really prove that it's it. But if you try to rule something out or in, how do you know you didn't miss it. So if you find it, it's okay. But if you don't find it --

Christopher Canning: You don't know why you didn't find it.

Dr. Shoubridge: You don't know why you didn't find it, yeah, exactly. So, I don't know how these new things are going to impact the way we do testing. For now, I think it makes sense to do it on a smaller scale, with where we can, you know we're testing one thing and we can be sure that it's -- we can really rule it out.

Christopher Canning: Yeah.

Dr. Shoubridge: But if it becomes cheap enough, one could use it as a screen. You know, so you kind of skim the cream. If you found the positives, you go back and confirm them by the more conventional means, something independent or something orthogonal and say, "Okay, yeah we found it twice with these two different methods to do it, so we're pretty sure that's it. And, then we wouldn't have to go further." So, that's kind of where I think things might settle out if it becomes cost effective to do it that way.

Christopher Canning: Now you sound like a medical geneticist.

Dr. Shoubridge: There you go. I should have two hats.

[Laughter]

Christopher Canning: Yeah.

Dr. Shoubridge: I'm medical geneticist.

Christopher Canning: There you go.

Dr. Shoubridge: So, we have this diagnostic thing and I struggle with doing it because I'm not qualified. I mean I don't have the paper qualifications to be a medical geneticist to sign off on reports. I haven't done -- I'm not certified from the Canadian College of Medical Geneticist to be a molecular biologist. But David is, Rima is. Other people in the system are. So if you develop enough knowledge, you can -- I mean you can of course do it, and do it well. And it's not like I'm going to test for every thing in the universe. I'm going to test the things that we know about and the things that are interesting to us and for patients who come here. We're not going to do cancer genetics. That's not what we do. So, I think you can -- if you are sensible about it, you can get -- you know enough about the area. It's not like you can't figure it out.

But in the long run, it will take somebody who actually can sign off in all these things to say, "I'm satisfied with all the quality controls." And when you get set up as a diagnostic laboratory that gets certified as such, they send you blinded samples to make sure that it works. So there are lots of checks and balances once it's there. And, I think that's -- I think that's a good thing.

But, I think it's a shame to exclude the research part of it because the whole idea where we started from, the technology transfer business I thought was a really smart idea because it instantly brought -- it was instant availability, and it was free too. I mean free. Somebody was paying for some of it, but a relatively small amount of money and then there was no need to bill somebody just to try to cover somebody's salaries or technician. I mean all this is make-work scheme as far as I'm concerned because somebody has got to look at the result, look at the address, write out some invoice, send it and somebody has got to respond at the other end. All a waste of time. And that doesn't make any sense.

So, let's set up a dozen expert labs across the province and these guys will all do a muscular dystrophy, and these guys will all do pediatric biochemical, these guys will this and these guys will do that. And, we'll give them all a budget and expect them to provide good And, that's been talked about for years and years and years.

And I mean David Rosenblatt's told me, "Oh, it's going to happen. It's going to happen." And I said, yeah, but that's what you've been telling me for two decades and nothing has happened. They were –- we're still fighting in the system for a way to provide the services.

Christopher Canning: What is the system afraid of? Is it afraid that it's not going to have a direct impact on health because the diagnostics are not always reliable? Are they worried about the potential benefits, or not?

Dr. Shoubridge: I think the system is a complex organism made up by a lot of bureaucrats. And somebody, he was a marketing guy, once told me he did an analysis of the system -- medical system in Denmark and the medical system in Quebec, the populations are roughly similar. And I can't remember the exact numbering anymore, but I mean Quebec had at least twice as many people managing the system as working in the actual delivery of medical services.

So there's a huge bureaucracy in the system here I think that doesn't serve a useful purpose. So it's not like somebody logical couldn't go in there and set it up properly; I don't think anybody would deny that getting a genetic test isn't a cost-effective way to provide the diagnosis when it can be done, because it's black and white. Usually, it's black and white. There are some gray things, but mostly it's a black and white.

Christopher Canning: Meaning you can tell if someone has a disease or not?

Dr. Shoubridge: You either have it or you don't. It's a relatively easy test, relatively cheap. Technologies are similar across the board. And many, many people can do it and supervise it properly and the quality control is in easy to put in place, easy to put in place than with biochemistry, for instance.

And I don't know why it doesn't get done and I can only imagine this because that the leadership isn't there. There's nobody high enough up the food chain saying, "This is how it's going to work best." That's all I can imagine, but I'm not anywhere in that thing. I'm just at the bottom just trying to deliver.

So I go back and forth, why am I doing this? Why am I struggling to try to do this?

Christopher Canning: To keep this diagnostics afloat?

Dr. Shoubridge: To keep this afloat. And we do it. I mean we've got in to the business because I think we do research in the area. I thought you should give something back to people affected in one way or another by the disease-- we write papers that become "famous" because we solved this or that gene defect. But somebody died just to resolve that gene defect. And I think that

we owe it to those families to provide something back, to provide some kind of a service. And on a more selfish level, we could potentially get very interesting cases where we could solve new gene defects too. So they would kind of feed the research program, and if we solve the gene defect then we've done two things.

Christopher Canning: You're doing medical genetics.

Dr. Shoubridge: So to me, that works from all points of view. So on one hand, I'm a medical geneticist and on the other hand, I'm molecular biologist. You're right, yeah.

Christopher Canning: Do you still have a few more minutes?

Dr. Shoubridge: Yeah, yeah sure.

Christopher Canning: I'd like to conclude with more specific questions about the group.

What was the leadership like when Rozen was there? Was did leadership entail? And furthermore, at the symposium last November, Dr. Scriver said that the group was "grassroots"? Would you agree with that that it evolves from the bottom up, that it just became what it was but the leadership was never a top down structure?

Dr. Shoubridge: Absolutely. The leadership was more of an administrative thing. So we would have research days every year. We would have students meet monthly and we would meet as principal investigators on -- I don't think it was monthly, it was maybe in four times a year or so over pizza and beer. And people would discuss what they've found or talk about the opportunities, things like that.

So it was not top down. It never was. I think it was always grassroots. Some people would have ideas and bring them to the group. Rima never said, "Here's what we're going to do, guys. We're going to spend the money this way and that way." Everything was made as a group decision about how the -- I mean we didn't get a huge budget for this either. But, I think it was quarter million dollars split between the eight people or something like that.

Christopher Canning: On top of your already existing CIHR grant?

Dr. Shoubridge: That's true. So it was additional $30,000.00 or so. So we used it for instance for our cell culture supplies.

Christopher Canning: Yeah.

Dr. Shoubridge: And so did David do that kind of thing. So, it was like an add-on a little bit and for some of the group activities too it was used. But most of the money

went to things that supported our CIHR grants that were part of our activity in the group, but it definitely was grassroots. And I can't speak for when Charles was the head, but I mean Charles is a pretty imposing guy. But I still think he would never he would never have dictated how the things are going to work. He would like to hear from the people in the group. And I think if anybody tried that, then people would walk. They just wouldn't be interested in that.

I don't think any science -- not much good science comes from that. Curiosity driven research comes from the bottom up mostly, and that's where you find the most interesting stuff, you know. If you have a new virus that you have to conquer then you need a strong group leader and an organization top-down management. But you know we're not dealing with that kind of stuff. We're just trying to solve the genetic basis of human diseases and trying to do something about it.

Christopher Canning: So the grant was driven by this energy of strong independent programs?

Dr. Shoubridge: Yeah.

Christopher Canning: And you could come together at certain times.

Dr. Shoubridge: Yeah, absolutely. Now that's certainly from the time I was in there, that's the way it went.

Christopher Canning: Yeah. Again, I'm just curious about the group because if it's a group in a sense that is funded by the CIHR, but driven by individual research program…

Dr. Shoubridge: Right.

Christopher Canning: How did that create a dynamic of a group? And we've already kind of spoken about -- from our perspective, I find that really interesting.

Dr. Shoubridge: You know as I said before, it kind of did and it didn't. It did on some levels within the individuals in the group. But the group as an entire group was never groupie in my view. They were people who were this little part of it or that little part of it, but as a group, I would say if somebody was saying, "Let's look at the group dynamics and see if this group really function as a group. Do they all need to be together in the same room?" The answers is no. The answer is unequivocally no.

Christopher Canning: It wasn't from day one, it seems. Despite in 1972, the MRC said that all group members had to be in same physical space. They were for three years and everyone went off into their own laboratories. So the groupness was never a physical unit.

Dr. Shoubridge: No.

Christopher Canning: But it was a collaboration of ideas?

Dr. Shoubridge: See now, they I mean -- I mean the CIHR did away with groups, right? They started something called teams. So what you're describing is more of a team, right?

Christopher Canning: Yes.

Dr. Shoubridge: Where everybody -- where people are focused on solving the same problem from lots of different angles. So I mean, just to choose some example say, cystic fibrosis you know. We know what the gene defect is, but you could choose any disease and say, well we don't know what the gene defect is or even if we just discovered, we now know it, so we want to know how this thing works. We want to know about the physiology. We need somebody to make an animal model. We need somebody to make a cell model. We need somebody to make antibodies. We want to solve the three-dimensional structure of this protein, you know, that's a team.

Christopher Canning: Fantastic. One final question: In your opinion, why was the MRC group so successful for so many years?

Dr. Shoubridge: I think good people. Good leaders -- I mean the leaders as I've said we're not people who dictated what would be done. And I think that they -- the people who are in that group always manage to attract other good people to the group, I'm thinking. And as I've said before, everybody had a -- everybody who was in the group had a strong individual program before they came and they came because they've thought -- I think we all came because we wanted to share ideas, share technologies, find out what other people were doing, and be part of something which was more than just sitting in your own silo and doing your own thing. I think that -- if anything that groupiness was more of a -- social scientific thing, if you will. I mean it wasn't like we had to be together in order to be successful. I think we were successful and perhaps a little more successful by being part of the group.

Christopher Canning: Great. I think that's a good place to finish for today. Thank you very much.

Dr. Shoubridge: Thank you!

END OF INTERVIEW

Dr. Mark Trifiro, October 22, 2010

Christopher Canning: My name is Christopher Canning and I'm here with Dr. Mark Trifiro on October 22, 2010. It is my privilege to be here with you, Dr. Trifiro, to discuss two main themes: first, I would like to discuss your academic background, which, of course, contributed to the growth of medical genetics; secondly, and perhaps more importantly for this particular study, I'm interested in your involvement in the MRC/CIHR Group in Medical Genetics, which you joined in 2001 and were a member until the group funding ended in 2009. Is this correct?

Dr. Trifiro: Yes, until 2009.

Christopher Canning: Okay, we'll talk about that. First, I would like to know a little bit about your background: where were you born? Where did you grow up? What was your early schooling like?

Dr. Trifiro: Well, I was born in Montreal and my family background—we're Italian immigrants that came to Canada quite early, so my time—my parents were actually born in Montreal, but my grandparents immigrated prior to the First World War.

I grew up in a multi-ethnic community in Montreal and so my social background was a little bit different than maybe some of the established societies in the city. My parents grilled me about how important schooling was and I think that took a foothold very early on and I sort of liked school. I performed very well and my teachers had a huge impact on me and I think if it wasn't for my teachers, even as early as high school, I probably wouldn't have ended up where I am right now.

College was a little difficult, but again there—my University professors had a big impact on me and—

Christopher Canning: And where was this?

Dr. Trifiro: This was at McGill, so I finished high school in Montreal and…there were no CEGEPs [Collège d'enseignement général et professionnel] at the time. Well, the CEGEPs were introduced, but the physical buildings weren't ready. There wasn't Vanier [College] or Dawson [College], so the government introduced CEGEPs; the universities had to accommodate the CEGEPs, so I went to McGill for my CEGEP and then went to University at McGill; we really didn't move much for five years.

I got an undergraduate degree in biochemistry and I think my final three years at McGill were probably the best three years I had at school. I really

enjoyed the honors program [in] biochemistry and it was a really tough decision to decide what to do after I got my bachelor's degree and it was obviously either I do some post-graduate work towards a Masters or PhD or medical school.

I really didn't know what to prefer so I applied to both programs and I got squeezed into medical school and I was with the idea that I would've, in the end, liked to do maybe medicine and do some research.

Four years of medical school was very, very different from the undergraduate program of biochemistry. I found it really hard and a lot of memory work which I wasn't used to. And then once I finished Medical school, I applied to a residency program in Montreal.

Christopher Canning: Where was your med school? Where did you do that?

Dr. Trifiro: It was at McGill.

Christopher Canning: At McGill, okay, so you spent a lot of time there.

Dr. Trifiro: Yeah, I spent a lot of time there. And so I applied to a residency program here in Montreal. A lot of it had to do with the idea that—a closely-knit family and I really felt very uncomfortable about leaving my brother, sister, mom and dad going elsewhere. It was just very foreign for us.

Christopher Canning: It's common in Italian families, isn't it?

Dr. Trifiro: Yeah, yeah. Exactly! So I think that had a lot to do with me staying here, and during my residency I developed a very keen interest of staying in touch with basic sciences, even though I didn't do any bench work or anything like that because it is very difficult to do.

And then I decided to finally leave—well, I got married and I think that's what made me say, "Okay, you've got to get out." And I applied for a residency program in endocrinology at Harvard and I was there 1981 all the way to 1986; it was at Harvard where I got back to the basic research arena and I spent two years just doing bench work.

Christopher Canning: As part of your residency program they let you go out and do bench work?

Dr. Trifiro: As part of my residency program so that—the reason I went there is because I knew that I had a very strong basic research component. Two years of the program was doing basic research and no other program really offered that. I said, "Well, that's good opportunity to get back to see whether I like it or not." Being away from true basic sciences for four years of medical school, four years of residency—that's eight years, so things really did change a lot in eight years.

And the good thing about going back to Harvard and doing my clinical endocrine fellowship, there were the two years of basic research. [As] well, my hiatus away from basic sciences was when molecular biology was being introduced, so I missed all of that. So when I got back to the lab, I had to learn what all of this recombinant DNA technology [was] about.

Christopher Canning: So was your work at Harvard, at the time, in biochemistry or endocrinology?

Dr. Trifiro: It was in endocrinology. And those two years, I learned a lot of molecular biology and when I came back, I decided that and I did want to come back to Montreal—family reasons again. I wanted to raise my family here and not south of the border. That I probably—if I really wanted to consider doing—having some sort of career in research that I had to probably spend a little bit more time. So I did a post-doc.

So I did a post-doc at the Clinical Research Institute [at the Jewish General Hospital], so this is the institute at the corner of Pine and St. Urbain with a molecular endocrinologist for about—almost two years.

So for a long haul, after that stint, I felt that I was ready to join an academic department with the idea that the academic appointment would be basic research and some clinical work. So I joined—I had an offer here at the Jewish General Hospital in 1990-1991 and I was introduced to Dr. Pinsky who was running this molecular genetics laboratory.

Christopher Canning: I noticed that your work on androgen receptors is very similar to his.

Dr. Trifiro: Yeah, we started together. So it was a really good marriage because Len [Pinsky] was a classical geneticist who taught me quite a bit of genetics and I was sort of the young recruit who knew all of these new molecular biology techniques so we meshed very well.

Christopher Canning: Can you explain how that meshing worked?

Dr. Trifiro: Well, Dr. Pinsky was an extremely established investigator in the genetics field—extremely well recognized in Canada, across the US, in the world—had accrued—whose expertise was in androgen receptor mutations and the androgen receptor and who had this enormous data bank of skin fibroblasts from all of these individuals with androgen receptor problems; the clinical syndrome is referred to as androgen insensitivity or androgen resistance syndrome, but needed to make that jump into using your techniques to push the field forward, so I thought it was a perfect opportunity.

I had a good clinical practice in the hospital and [at] the Lady Davis Research Institute with Dr. Pinsky right next door. So I think those formative years were really—Len was really, really important in guiding me through. Having

a mentor like that really makes the beginning parts of setting up a career easier. It showed me the ropes a little bit, so I learned how to write grants, salary support and I was very lucky that things went very well.

So to summarize that point, I would say that I always had an interest in how things worked and that's [what] almost all scientists agree on, and I always had a lot of interesting people, a lot of good teachers and Len as a mentor to really get my career going. Plus I had the support from the university, which was really important.

Christopher Canning: Did you have a preference for clinical or research or did you see that it was necessary to work on the two simultaneously?

Dr. Trifiro: You know, when I say the teachers had an impact on me, what I'm referring to is them pointing out that—it's not just good enough to learn that you have to give something back to science and one way of giving back to science is that you contribute to science and the only way that you can really contribute is doing what we call research. I mean that's what brings the field forward, [and] if you could bring the field forward with some other methodology, that's okay, too. But the way I was taught was that you need to investigate to push the field forward, so I had no qualms about this idea of, "I can take care of patients, that's not a problem." Do a good job, but if I want to contribute, I need to investigate. So what we did here was we did push down the androgen receptor field forward by quite a lot, so that was a real success story. That's for sure.

I think the next big thing was when Len [Pinsky] decided to retire, which I found a little difficult because sort of the father figure was gone and a lot of things that I took for granted basically fell upon my shoulders. I had to run the lab.

Christopher Canning: Were you two sharing a lab at that point?

Dr. Trifiro: We were sharing the same lab. So—as a matter of fact, I don't know. This placed me with a longest lasting lab in CIHR history. I'd be kind of interested into figuring out—he started here in 19—

Christopher Canning: Wouldn't it have been the late 1960s?

Dr. Trifiro: Yes, the late 1960s.

Christopher Canning: This is before he started the Centre for Human Genetics.

Dr. Trifiro: Yeah, absolutely.

Christopher Canning: Yeah, wow, okay. So this would have been his space in the 1960s. In this very space?

Dr. Trifiro: Yeah, this hasn't changed.

Christopher Canning: That's neat.

Dr. Trifiro: So, I had to deal with that and there was a little bit more extra work, obviously, but we were successful in getting our series of grants and because of that, I think I was sort of—when Len [Pinsky] left, the CIHR medical genetics group and then someone else left—I was asked to join the group, I think in 2001.

Christopher Canning: I would like to come back to that and talk about that in more detail in a few minutes.

Dr. Trifiro: Sure. I think that's about it. We're now in 2010. The only other thing that really happened is I was offered Chief of Endocrinology. This is my clinical duty and I took on that position in 2007.

Christopher Canning: When did you become the director of the Lady Davis Institute?

Dr. Trifiro: When Len left, I just took that position.

Christopher Canning: So you've been the director since the mid-1990s?

Dr. Trifiro: In 1996, I believe, or 1997 when Len [Pinsky] stopped.

Christopher Canning: So at what stage during all of this growth in your investigation of basic science, in your interest in medicine, did you make the link between medicine and genetics? Was there a moment when you said, "I'm interested in the genetics aspect of medicine rather than the broader field of genetics."

Dr. Trifiro: Well, I think that—I'm not a trained geneticist, but Len [Pisnky] told me one thing and I won't forget. [He said], "you've got to go where the science brings you." So when we were studying these individuals, it was clear that the science was bringing us to genetics. We had to understand the genetics of this disorder. And that's when—the decision was that I'm going to do medicine, but if I'm going to do androgen receptor work with these families, it's genetics.

And it's been genetics ever since, but I think science now has progressed to the point where this sort of line between genetics and protein work is becoming one blur now. I think that most people are pretty comfortable [about] doing what the genetics [is] and now doing the protein work.

So the last five or six years—that's what we've been doing now. So we started off with the patients. We started off with pure genetics so then

genetics taught us how to find these mutations. What mutations were and we never knew what the mutations really did to the proteins. So in the last five or six years, that's what we've been doing. We've been now pushing the genetics and showing what this particular mutation does at the protein level.

Christopher Canning: So you're looking at a particular genetic mutation that does or does not produce this particular protein that causes these sexual malformations, is that correct?

Dr. Trifiro: Yes, exactly, and we have a much clearer idea of why these particular mutations do what they do now.

Christopher Canning: Okay and this is because of the molecular biology technology that has evolved over the last ten or 15 years?

Dr. Trifiro: Yeah, absolutely! Molecular biology has allowed us to express proteins very easily, so once you can express a protein then you could do a lot of different things with it.

Christopher Canning: Okay, I would like to talk to you specifically about how you first became involved in the Group. Obviously you're collaborating with Dr. Pinsky during the 1980s and 1990s, but at what point did someone come up to you and say, "Hey, would you be interested in coming on board?"

Dr. Trifiro: I don't know how I got introduced, but I think sort of—well, you know the genetics group at McGill's is not that big. I mean, I did—Len [Pinsky] made sure that if I was going to do this work that I would have an official position in the Department of Human Genetics, so I actually got—so I had an appointment in the Department of Medicine and an appointment with Experimental Medicine because I was doing basic research, but I also had an associated position or affiliated position in the Department of Human Genetics.

Christopher Canning: Prior to being invited into the group?

Dr. Trifiro: Prior, yes. So during those formative years, I got to know all of the group quite well, so—and they got to know what I was doing and how I was working with Len and I think they just decided at one point that maybe I should be part of their group. I think it's because our genetics work was going really well at the time.

Christopher Canning: How did your research areas overlap then? So you and Dr. Pinksy are working in one area, but how did the Group operate in terms of the science coming together?

Dr. Trifiro: Well I think—the theme in the [MRC/CIHR] genetics Group was—there was

genetics, but it was very translational. In other words, the genetics that we studied was really tied into clinical disorders. So everything that those members did had to do with some human or health disorder that was quite apparent. That was the key link in all of their work.

So Len [Pinsky] and I [fit] in to that philosophy really well because it's quite apparent that what we studied were real patients with real disorders, with real phenotypes and so did everybody else in that group.

Christopher Canning: With the hope of eventually finding some sort of treatment?

Dr. Trifiro: Yeah, therapies, basically, or if you want to identify people at risk and you do genetic testing, then you have to know—you really have to know what's going on with the genetics. So genetic testing [and] new therapies were always in the minds of all basic medical investigations.

Christopher Canning: In your own work, then, what therapies have you developed or advanced?

Dr. Trifiro: What we've done is we've pushed our fields of genetics one step; in other words, all that we've been talking about and all of our work with Len [Pinsky] was classical genetics. Mom's a carrier, she has a 50% chance of delivering this mutation, [and] so those are referred to as germline mutations. So we said, well, why don't we look at a completely different type of genetics and that's referred to as somatic genetics.

So we got interested in not [only] germline mutations of the androgen receptor, but somatic mutations of the androgen receptor; and I think that was a good topic because it's quite apparent now that somatic mutation of the androgen receptor has a huge implication in many disorders and the big, big one is in prostate cancer. So it's clear that mutations that occur during one's lifetime and referred to as somatic mutations play a very huge role in certain disorders.

Plus, the other thing is that for one lab to study both germline mutations and somatic mutation is a great scenario simply because germline mutation typically is loss of function. In other words, these individuals have their sexual maldevelopment because they lose a property. They are supposed to have a normal androgen receptor that allows them to have normal male sexual development. You take that away—

Christopher Canning: This is just caused by a mutated gene?

Dr. Trifiro: Yes, if you take that gene away, that's a loss of function and to study the structure function properties of a loss of function mutation is interesting, so you know what the mutation is and we've done all of these protein work. We know why the protein is malfunctioning.

The somatic mutation is a different kind of fish. The somatic mutations are referred to gain of function. So they work well, but they gain a new function and they gain new structure properties.

Christopher Canning: Can you give me more specific types of phenotypes that come out of this?

Dr. Trifiro: So the loss of function mutations, you introduce—well, you have a mutation in the androgen receptor, you get a defective androgen receptor. It doesn't work and it cannot work at several levels.

Christopher Canning: The androgen receptor is in the cytoplasm, right?

Dr. Trifiro: Yeah, and it binds testosterone, a male hormone and it then moves to the nucleus and it turns on a whole bunch of genes. So we found mutations at every conceivable place, so a lot of the mutations; the protein can't bind to ligand. So it's not going to go anywhere.

Christopher Canning: Does anyone know why it doesn't bind?

Dr. Trifiro: Yeah, well it's because the binding pocket for the androgen receptor is a very intricate three-dimensional structure. If a mutation is in there and affects the binding pocket's architecture, the ligand won't fit. It just doesn't bind.

So there are all of those mutations and then there are those mutations that the ligand binds perfectly well, but it doesn't go to the nucleus or it can't bind DNA; it can't bind the gene. The genes are supposed to turn on or it binds the genes, but it just doesn't have the ability to allow those genes to start being expressed.

So that's one kind of fish; the other somatic mutations have different stories. They do have missense mutations, but they're completely different. So studying the two is a really great comparison because here you have a protein that's loss of function, that has a specific biological phenotype, but has a specific protein phenotype and gain of function mutation—though a completely different thing, it also has very different structural protein phenotypes and comparing the two, you get to understand how proteins work. So, if you were interested in how proteins worked using the same protein that has a source of loss of function mutations and gain of function mutations, you learn really how proteins work, and that's what we've been able to do by having two sources of mutations, not just loss of function, but gain of function mutation.

Christopher Canning: And originally, you were doing work just on loss of function?

Dr. Trifiro: That's right.

Christopher Canning: And now you've combined the two—and was that influenced by Dr. Pinsky's work or was he—

Dr. Trifiro: Well, again, I'll come back to the statement—you go where the signs bring you and that's what the science brought us…we had to go there.

Christopher Canning: Us being your lab or us being—?

Dr. Trifiro: Us being the lab.

Christopher Canning: What was your communication like with other members of the group? At the time, you would have been working with Dr. Rozen, Dr. Gravel, Dr. McKenzie, Dr. Tennenhouse…

Dr. Trifiro: We [would] have meetings at least maybe twice, three times a year. I helped organize their post-docs meetings, so I got to know all of their post-docs and graduate students because we organized an annual meeting where our group's students would meet and present their work to the other students. So that was interesting. We were a pretty good functional group. That worked pretty well.

Christopher Canning: Did you collaborate with many of them on publications. What did collaboration mean at that time?

Dr. Trifiro: Well because we had—we're pretty competitive in each of our fields. It was sometimes a little difficult to have some sort of joint work. For some members, it was a lot easier because I think at one point, three of the members were working on folate metabolism, so right off the bat there [was] lots of collaboration.

Christopher Canning: Dr. Rozen, for example?

Dr. Trifiro: Yeah, and even Dr. McKenzie, so that was a natural. Any time there was a sort of a sex steroid angle to any of this work, yes, we would sort of get involved.

Christopher Canning: But you were the only one really working on that?

Dr. Trifiro: We were the only ones doing androgen receptor work and doing that type of stuff.

Christopher Canning: But the relationships were good with all members of the group? And was there any concern about the physical space of the group, especially because you're over here at the Lady Davis? In the early years of the group, for instance, there was a concern from the MRC that a group to be a group needed to be together and now that wasn't the case, obviously, during this time. Was there any discussion about that?

Dr. Trifiro: No because I think, in 1990 and 1995 – 1996. I would have said maybe in the 1960s and 1970s, it would have been important to be physically together, but communication has changed so dramatically and the Internet has changed everything. Documents go back and forth instantaneously and I think that, yes, it may have been a concern early on, but later on, absolutely not. It was very easy. Even to the point where Roy Gravel was part of the group living in Calgary.

Christopher Canning: He was the director for four years while he was in Calgary.

Dr. Trifiro: That's proof, I think, of the fact that you don't need to be absolutely together.

Christopher Canning: What did that mean for the leadership then? Because there was a director of the group, at the time, it would've been Rozen in 2001. Oh, pardon me, so Gravel was director in 1998, but he was in Calgary right before your time, so what did that mean for the leadership or directorship or did you get a sense that the Group was being directed by someone?

Dr. Trifiro: Well, you know, yeah. When it comes to a director, it comes to one person and whenever you comment about that leadership/directorship, it always has to be in the context of that particular individual. We're not talking about a group of people. We're talking about one guy and to me, when you're talking about one single individual, you can never generalize because each individual is very different. So we were extremely fortunate to have Roy [Gravel] even though I wasn't part of the group; I know Roy—how he works and things; [he's a] fantastic guy.

He could've been in South America and have very dramatic influence on the group. That's his personality. The way he worked, the way he communicated. That's how powerful I think someone could be as a single individual in taking leadership roles in driving things forward and that's what he did.

So Rima [Rozen], same swathe. She had that same competitiveness, same really sharp person, really bright, took over—no problem!

Christopher Canning: What do you mean by competitiveness?

Dr. Trifiro: Well, I think that if you're going to be someone who competes in CIHR [Canadian Institutes of Health Research] funding for many, many years and gets a track record going, you have to be competitive and you have to have some smarts and it's clear that those two individuals were blessed. They're the type of people that you put them—you ask more of them and they deliver more. They really rise to the occasion and they did that. No problem!

Christopher Canning: Was there some expectation in the group, created by Scriver and Fraser, who were/are extraordinarily respected scientists, that the new members should follow their trend?

Dr. Trifiro: Well, I think that the most recent members may not have felt so much of that. I mean, we still hear about them for sure, but I can tell you that's all that Len [Pinsky] talked about and Roy talked about and Dr. Rozen talked about. We would hear it from them.

Christopher Canning: Which was what?

Dr. Trifiro: Well, I think that the feeling I got [of] those two individuals was pure scientists and that's all they thought about day in and day out. That's all they worked [on] and that was their only goal in life—it was to do science and I think a little bit of that rubbed off on the next generation.

Christopher Canning: On being good scientists and doing basic research?

Dr. Trifiro: Yeah, and that you could make a difference by doing science and you could contribute by doing science.

Christopher Canning: But there was obviously an understanding that this science had to in some way or another contribute to clinical work?

Dr. Trifiro: Yeah, but their science started with patients, too.

Christopher Canning: They were geneticist-physicians, which are rare nowadays.

Dr. Trifiro: Yeah, they're rare. We still have a few. They are much rarer, yeah, but--

Christopher Canning: They were the pediatrician and geneticist.

Dr. Trifiro: Yeah, they saw the phenotypes and they said, I wonder why does this kid have this phenotype?

Christopher Canning: Right, they were looking at someone in the clinic and said "I want to understand this phenotype." Now, obviously, you're referred phenotypes from clinicians?

Dr. Trifiro: Yeah, now I think genetics is so well established and medical geneticists—adult geneticists, pediatric geneticists are a field in themselves and they're trained to do that.

Christopher Canning: I know we've discussed it a bit, but I'm still curious about your androgen receptor research. I would like to know what it has done, or hopes to do, to benefit our understanding of health. What are the potential outcomes of

your research? What do you hope to see come from your research?

Dr. Trifiro: So, to tackle sort of the loss of function problems first, so when you lose the function of the androgen receptor totally—

Christopher Canning: In the germline?

Dr. Trifiro: In the germline—that male individual, genetic male turns out to have a female phenotype.

Christopher Canning: Genetically male, female phenotype?

Dr. Trifiro: Yeah, completely female phenotype. So these individuals previously would be born, would go through life, no problems, come age 14 or 15, they won't menstruate. They wouldn't menstruate because they didn't know at the time, but part of that phenotype is that you don't have female gonads. You have male gonads.

Christopher Canning: You have testicles.

Dr. Trifiro: You have testicles, but they're hidden, but they're there and you don't have a uterus. So without a uterus, you can't menstruate. So those individuals—the diagnosis was made much later in life and there was nothing to do.

They would have a very fulfilling life though, but they would have these physical abnormalities. Okay, that's one thing.

Christopher Canning: Internal abnormalities?

Dr. Trifiro: Yes.

Christopher Canning: Externally, however?

Dr. Trifiro: Perfect. Yeah, a lot of them got married, had families—had a marriage, very successful, may adopt kids and things like that, but they couldn't have children.

And many times, probably a long, long time ago, these individuals may not have been told of these disorders as well. There is the other loss of function germline mutations where the receptor doesn't work a hundred percent, so now that's the big problem because when the children are born, they're born with maybe a mixed picture, with ambiguous genitalia that might require a lot of surgeries, psychological counseling—that is very involved.

Christopher Canning: Hard for the parents, too, obviously, who are forced to make a decision about their child's sexual identity?

Dr. Trifiro: Hard for the parents, hard for the children. Can you imagine—sexual identity is very important. If you don't know exactly what's going on—so, when the molecular genetics came, we were able to find out what the problem was and we're able to sequence the androgen receptor gene. We could tag a mutation to that particular family. For the very first time, we could say, "You're a carrier, you're not a carrier, you're a carrier, not a carrier, you are a carrier, you're getting pregnant." We could tell you whether the fetus is affected or not.

So now, we could actually manipulate the outcome. Now you're going to say, well how do you manipulate it? So okay, we're talking about maybe aborting the fetus, where it's supposed to be done very early on and that's an ethical question. We've never gotten into the ethics because the ethics has to be decided between the patient and her treating physician, so we're not the treating physicians; we just supply the team with the information that they need. I know that the team will make the proper decision, but they need that information.

So now, you could make a real impact on that disease entity in the population. And as a matter of fact, I think in 2010, it's very possible that every carrier of this androgen insensitivity syndrome is known or a vast majority is known.

Christopher Canning: And this is obviously over just the last 20 years. Neat!

Dr. Trifiro: Okay, so that has made a big impact.

Christopher Canning: No doubt, yes.

Dr. Trifiro: Albeit pretty ethical. Who is going to do what?

Christopher Canning: So this is just a single gene disorder?

Dr. Trifiro: The state of the art now is you have a carrier, we take the fetus's DNA at age eight weeks, as early as possible and we could go back and tell the family yes or no.

Christopher Canning: Okay, obviously there is no treatment in-utero for it?

Dr. Trifiro: If we're lucky, we do know that some mutations where the receptor is sort of working, but not completely, some mutations will respond if you give larger doses of male hormones.

Christopher Canning: So you inject testosterone and there is some possibility—

Dr. Trifiro: In the individual—in the young individual and you could get the kid to grow or the very young—

Christopher Canning: But it's never going to fix the mutation?

Dr. Trifiro: It will never fix the mutation. The only way to fix germline mutation is trying to avoid them to come to fruit. I mean, that's the only way. So those are the loss of function mutations.

Christopher Canning: Great! You spoke about this a little earlier, but I still find it interesting. I obtained a document in the 1980s where there was some concern about the Group's molecular biology competitiveness. And I wonder if that conversation was going on after the Scriver days when biochemistry and cytogenetics were leading the way.

Now, as you mentioned, you've seen that in the field more generally, but did you find that in the group?

Dr. Trifiro: No, there were some people in the group that haven't—that didn't sort of jump into the molecular biology world. [Scriver] was still doing biochemistry and they were rightfully—they were rightfully concerned about—because you know, MRC/CIHR and whatever you—they always—granting agencies always looked for the cutting edge. So if you're not at the cutting edge, then it makes it a little bit harder. It doesn't mean you won't get grants; it just makes it a little bit more difficult.

So of course, they were concerned. I mean, there was a real revolution over a span of, I would say, eight years.

When I was at Harvard and I was there in 1981, there was already a panic thing. And they just cloned an insulin gene. The first gene they ever cloned was in 1979, so in a span of two years—

Christopher Canning: There's suddenly a technology explosion because now you can get right down to the coding of the gene.

Dr. Trifiro: Yeah, exactly.

Christopher Canning: Was there any division between bench and clinical in the group as you were involved, or was there any discussion about the fact that you should be doing more basic research?'

Dr. Trifiro: No, I don't think so. I think everybody was convinced that the research that was going on was solid. It's just that it was still a competitive world. You still had to write competitive grants and what were the group's best chances to be successful; I think it was quite clear that they had to introduce new technology into the group.

Christopher Canning: Indeed! On one of the group's applications from the early 1990s, you said

that the group had achieved a new level of interdisciplinary scholarship in science. I'm just wondering if you could speak to this interdisciplinarity. From what a lot of people are saying, this was one of the core goals of the project?

Dr. Trifiro: Well, I don't know what they mean by interdisciplinary? You mean within the group itself?

Christopher Canning: Within the group itself. It had somatic cell genetics, biochemical and physiological genetics, molecular biology, etc.

Dr. Trifiro: Yeah, well I think it's because, I can't remember the details before—it's very possible that one or two—I don't know when Rima joined the group?

Christopher Canning: She would have joined in 1987.

Dr. Trifiro: Yeah, so was there anybody else who joined the group at that time?

Christopher Canning: New members?

Dr. Trifiro: Yeah? Because all it needs is the addition of one solid investigator to change a little bit about the look of this—

Christopher Canning: By the looks of things, I think Dr. Rozen was recruited to be the new molecular biologist.

Dr. Trifiro: Yeah, that's what I'm trying to get at. I think that's what they're referring to. The fact that getting Rima Rozen into the group at that time meant that they've reached…at least they had one person who was a new recruit with newer techniques under her belt and brought this state of the art, cutting edge stuff to the group.

Not that the other guys were slouching. Believe me, Dr. MacKenzie actually, at our day—if there is one person that had a huge impact on me, were a couple of guys. Remember, I was doing a biochemistry degree and Dr. MacKenzie was one of my tutors who taught an unbelievable class in biochemistry and they had three young individuals in that biochemistry group—me and MacKenzie and Rujinski that were outstanding individuals—totally dedicated to teaching. I'll never forget that and when I say they made a difference to me, I really mean it because I don't think without those individuals, I probably may not have decided, "Well, this is what I want to do." Just seeing them get excited about what they were doing just got me excited about—

Christopher Canning: Fantastic. A few more questions: in your opinion, what ensured the group's longevity? To this day, it was the longest running group project in Canadian history for health research—for 37 years.

Dr. Trifiro: Well, you know what, it may well be the two founders that instilled this inquisitive mind to the next generations. Starting with those two guys, two giants in the field can have a long lasting effect on two or three generation of investigators and I think that's…what rubbed off on the investigators at the time; it may have rubbed off on Len [Pinsky] and Len's sort of mannerisms rubbed off on me and I think that makes for—how long was it?

Christopher Canning: Thirty seven years.

Dr. Trifiro: Thirty seven years.

Christopher Canning: 1972 to 2009, and from what I understand, the only reason it wasn't funded is they just stopped group funding. They switched to team grants.

Dr. Trifiro: Yeah, they switched to team grants; that's right.

Christopher Canning: Yeah, which is a bit of a different structure. In your opinion, what made the group a group? The only reason I ask that question is that there are multiple ways for both the MRC and the CIHR to define what a group is. You do similar interdisciplinary work, you work together, you have meetings, but from your actual experiences, what defined the group? In other words, what was its "groupness"?

Dr. Trifiro: I think, first of all, it was the phenomenal level of the research. I mean, everybody was doing great stuff. And I think there was a really good mix between some older investigators and some newer investigators. And the central team again was genetics, but all sort of patient based. There were all of these real medical disorders. As you know, you could get a geneticist studying a gene and you never know what its clinical implications are, but I think here, it was clear that the starting point was some sort of clinical issue and that we have topnotch genetic studying this.

And I think [that] everyone has sort of respected everybody's work. Combining all of that together is what made this group a group—those three or four things and we all had a real interest in discovering new genes that were responsible for clinical phenotypes.

Christopher Canning: Do you think overall, the group was successful in that regard?

Dr. Trifiro: Yeah, sure! I mean, it could—it may well have been that the reason it happened in McGill is because McGill is a large university and has tons of people in it, so if any institution would have a long lasting, living group, it probably would be McGill because it has enough depth in their departments. We're not one—there's no single member department and they are all huge number of people. So it sort of makes sense that that would happen at McGill given the fact that we again had those two stalwart

individuals who basically started genetics in Canada. History was there [and] everything was in place.

Christopher Canning: Well put. It was just kind of lined up. And then everyone was recruited to kind of promote this and work with it?

Dr. Trifiro: Yeah and everybody made it pretty clear that when you're a part of this group, you had to show up and you had to make sure that you'd live up to the group. For sure.

Christopher Canning: And there were a few instances where some group members weren't invited back because for some reason—for a couple of reasons, they weren't funded by the MRC or they weren't publishing enough?

Dr. Trifiro: Well, more so it was MRC. I think the funding—every five years, they always say funding is going to get better and the reality is, funding was never good. Even when they created the CIHR, which was supposed to—they promised a lot of—they promised an ultimatum when the CIHR came out. They'll never be a time [again] where you have to cut grants and cut moneys to grants and it only took three years before the CIHR broke their promise and started to have competitions and salary awards and all kinds of things.

Christopher Canning: So it just made it more competitive and some people were just cut out?

Dr. Trifiro: And even to this day, I think right now, this year is going to be maybe the worst year in CIHR competition work.

Christopher Canning: Then it being difficult is because there are many applications and fewer responses?

Dr. Trifiro: Fewer responses and three to four times more applications. It's crazy.

Christopher Canning: It's like that in many areas of funding, it seems.

Dr. Trifiro: Yeah, everywhere.

Christopher Canning: A few more questions and we're almost done here. At the symposium last November, Scriver made a really interesting point and I just like you to think about it and to speak to it. He said that the group always operated as a grass roots organization, meaning that it worked from the bottom up. Was this your understanding of the history of the group and your involvement in the group?

Dr. Trifiro: Well, it's kind of hard to comment on how it started, but from Len [Pinsky], and [him] talking about the group, he would agree that that's where it started. It started from this is—it wasn't the University's initiation, so much so it is the genetics department's initiation.

Christopher Canning: In fact, they created their own genetics department!

Dr. Trifiro: Yeah, so in fact they created the department and not the other way around.

Christopher Canning: Exactly.

Dr. Trifiro: So, how the group grew and sustained were three or four individuals who had the foresight, insight and enough characters to say, "You know what, we should form a group." It wasn't the other way around. It wasn't that the department of genetics said, 'oh you know what, this is a competition for a group. Let's apply for it,' no! It was these individuals who suggested that we're going to form a group and this is the group that I want and we're going to get things going. We're going to work as a group and the group was probably formed even before they had group grant applications probably.

Christopher Canning: The first successful grant application for groups was in 1968 at the University of Montreal, actually, in the neurological sciences. So the McGill Group started right near the beginning of the group grant program.

Dr. Trifiro: So I would—from the historical—Len used to talked about the group a lot. If I took something back about that because it definitely was, it started off with the individuals getting together and not the other way around.

Christopher Canning: Neat! So where is your research headed? I'm curious about your research in prostate cancer. Do you have more recent developments in your work?

Dr. Trifiro: So this is—when we wanted to compliment our loss of function mutations, we started looking into these gain of function mutations and gain of function mutations mean that. It means that this particular mutation endows that particular protein with something new. Doing something that it's not supposed to have been doing. It doesn't necessarily mean it takes away what it does normally, but it adds to it new repertoires, so in the androgen receptor—the gain of function mutations that we saw were incredible.

So now, the androgen receptor not only binds male hormone and does all its work, but it binds several other classes of steroids. So if you're a prostate cancer cell, you now have the luxury of sustaining growth and more growth and more proliferation—

Christopher Canning: For more hormones? So there are all of these hormones out there.

Dr. Trifiro: There are tons of hormones there.

Christopher Canning: So it promotes cell growth.

Dr. Trifiro: It has a field day, basically.

Christopher Canning: Right, it has all of this energy that it can just eat up and contribute to prostate cancer cell growth?

Dr. Trifiro: Yeah, and then what's the worst part about it is even—and this was the killer in the field was that, it came at one point very popular to give anti-androgens, right? So these mutants didn't see the anti-androgen as anti-androgens. They saw them as potent androgens.

So you're giving a drug to someone thinking that you're going to block the receptor. These mutations would turn the tables on you. It would take that anti-androgen and say, 'well, I'm really happy with this.'

Christopher Canning: Do you now have recent funding to do this research?

Dr. Trifiro: Oh yeah, so we've been doing a lot of that now.

Christopher Canning: Great! That's where you see your work heading for the next little while?

Dr. Trifiro: I think so. I think that we've done our job in loss of function mutations. I don't think we could bring it much further. We find out what the problem is in loss of function, we know what the genetics is, we now have done all of this protein work. We now know why the protein doesn't work at the molecular level. There's not that much more to be done.

Christopher Canning: Where else do you go?

Dr. Trifiro: Where else do we go? So the gain of function—there we don't have the total story. We don't know all of the mutations. There is probably a whole list of mutations and what the other gain of function properties are, we still don't know. So there is still a lot of work to be done there.

Christopher Canning: Great. Well, that concludes my questions. Do you have any final thoughts?

Dr. Trifiro: No. I would like to thank, I guess, Rima who really thought about this idea. Or Roy, I can't remember whose idea this was. Actually—

Christopher Canning: To do a study of this Group?

Dr. Trifiro: To study the group. I remember, it was an interesting conversation—we have to do something, it's the end of the thing and then someone said, well maybe we should have a—I think it may have been Roy who actually thought of it. Anyway, it is a great idea. I hope that people—the University will acknowledge how much work has gone into this group—all of the individuals, massive amount of work, a lot of dedication from a lot of

people.

I would like to thank, personally, Len Pinsky for helping me. He's made a big difference and the group as well, and I think doing this is really a great idea and that people could learn from this especially where I think science is going now.

The idea of academic investigation or academia was always, since day one, built on a premise that it was the individual that had to prove his worth. But science is not going that way. Science is becoming more and more interdisciplinary that the advances in science cannot be made by one person anymore and I don't think we should judge people on their solo efforts because that's not going to push science ahead. What is going to push science ahead are teams. So funny enough, they got rid of team grants.

Christopher Canning: They got rid of group grants to institute the team grants, yeah.

Dr. Trifiro: But they're going to have reinstitute group grants because nanotechnology is now putting a lot of pressure on a lot of people. We need those people to be involved in new science and the new science is going to be big groups, big teams accomplishing big science.

Christopher Canning: Right, the more we know, the bigger it seems this collaboration demands.

Dr. Trifiro: Yeah, absolutely!

Christopher Canning: Fantastic.

Dr. Trifiro: And I want to thank you.

Christopher Canning: Thank you very much!

END OF INTERVIEW

Dr. Andrew Karaplis, November 30, 2010

Christopher Canning: My name is Christopher Canning and I'm here with Dr. Andrew Karaplis on November 30, 2010. It is my honor and privilege to be here with you, Dr. Karaplis, to discuss two main themes regarding human genetics.

First, I would like to discuss your academic background, which contributed to the growth of medical genetics in Canada. And secondly, and perhaps more importantly, I'm interested in your involvement in the MRC/CIHR group in Medical Genetics, which you joined, as I understand, in 1998, and were a member until the group disbanded in 2009.

But before we go into the group, I'd like to know a bit about you. Can you give me an overview of where you're from and where you were born, where you grew up, if you don't mind?

Dr. Karaplis: I'm 55 years old, going to be 56 next month. I was born in Athens, Greece in 1954, and my family and I immigrated to Canada in 1966. We came here by boat through the Atlantic, a 14-day trip. We arrived in Halifax on Pier 21, which is now a historical site. From there, we were put on a train and transferred to Montreal where we ended up in the 'ghetto' of lower Outremont, living with 14 other people in a small apartment. This lasted for about half a year, until we were able to rent a place of our own.

My father was a car mechanic and my mother a factory worker. Both of them continued to work until their retirement. My brother and I studied in Guy Drummond elementary school and then on to Outremont High School. I ended up going into sciences and eventually into medicine. My brother became an engineer and he's now back in Greece, retired at the age of 58. He did very well for himself.

Initially I studied physics. I went to McGill in 1972 at a time when McGill had a CEGEP, and after CEGEP I did an undergraduate degree in Honours Biochemistry, at McGill. After that, I started doing basic research in the Endocrine Unit at the Royal Victoria Hospital, directed at that time by Dr. Sam Solomon.

Christopher Canning: Okay. Before we move on to your formal training, what were the expectations you got from your parents being a first generation immigrant family?

Dr. Karaplis: Well, the expectations were based on the reasons that would force a family like ours to come to Canada. My father was 42 and my mother 38 at that time. In those days, Greece had come out of a four-year occupation and then a four-year civil war, which basically had devastated the country.

Greece needed to recover at that time. Individuals like my parents decided that such as a move would be better off for their children. Greeks in those days would immigrate to primarily four countries: Canada, USA, Australia, and South Africa.

Christopher Canning: Okay.

Dr. Karaplis: Australia was too far. South Africa was changing too fast at that time. My parents chose Canada. So, we ended up here, in Canada. The expectations were simply that the children get a good education, make something of their lives, and eventually go back to Greece. I think most of the immigrants that came here during that era had similar expectations, that eventually they will return back home. But the reality is that people just got too used to their new life, and they continued doing what they were doing. Over time, it becomes very difficult to go back.

Christopher Canning: And did you do well in school when first arrived in Montreal?

Dr. Karaplis: It was expected. I entered Grade V, I remember. In Greece, I hadn't finished Grade VI, because we left for Canada in the middle of the school year. Here they put me back one year, in Grade V, because I spoke absolutely no English or French. It's interesting, as new immigrants we didn't know the differences between the English and French communities in those days.

We just went to the nearest school that was about three blocks away from our house to register. It was a French Catholic school and a nun came down to meet us. The first question was, "Are you Catholic?" Because the answer was, "No", she said, "Well, I'm sorry, you can't come here. You have to go down to the other school where --," in those exact words, "the Jews and the Protestants and the other immigrants go."

Christopher Canning: Wow!

Dr. Karaplis: Yes. So, that's how I ended up learning English instead of French.

Christopher Canning: Right.

Dr. Karaplis: I ended up in the 'New Canadians' class where Miss Gilmore was teaching us English.

Christopher Canning: You remember that?

Dr. Karaplis: You never forget these things. No matter what you go through in life, you never forget these things. Within the first year and a half after that I won most of the academic awards at school.

Christopher Canning: Not even knowing or speaking English?

Dr. Karaplis: Barely speaking English, yes. In fact, at the end of high school, I won the Governor's Gold Medal Award.

Christopher Canning: Wow!

Dr. Karaplis: Then I went to CEGEP, but unfortunately, I didn't work so hard because of other interests I guess, being a teenager at that point.

Christopher Canning: It's kind of a good thing about the CEGEP system [Voice Overlap].

Dr. Karaplis: Yeah, it allows flexibility.

Christopher Canning: Students get to choose whatever program they want.

Dr. Karaplis: Right. Well, at that point I had no direction in my life. And you know really, as an immigrant, we did not have anyone to turn to that could give us directions as to where to go and how to proceed. And so, I ended up going into Physics. However, I didn't like it and after one semester I switched to Biological Sciences, and then into biochemistry, honours biochemistry, which I completed in 1977. Then I started in research, working at the Royal Victoria Hospital. After one year of this, I hated research.

Christopher Canning: Really?

Dr. Karaplis: After one year, yes. At that point I said, "This is not for me. I think I'm going to apply to medical school."

Christopher Canning: Okay.

Dr. Karaplis: So, I applied to medical school and got accepted. But I deferred it for one year because at that point, I was beginning to enjoy research as things started working out for me in the lab. So, I opted to get my PhD. I did two years of basic research. I got into medical school, and during medical school, on weekends and summers, I finished my research. And then, during my internal medicine residency, I wrote my thesis.

Christopher Canning: So, you're doing both simultaneously?

Dr. Karaplis: Yes, I did an MD, PhD simultaneously. In those days, McGill did not have an MD PhD program as it exists now.

Christopher Canning: And what was your PhD research on? Were you still doing biochemistry?

Dr. Karaplis: I worked with Dr. Bill Powell, whose laboratory was with Dr. Sam Solomon's group. He had just arrived from Sweden where he did his post-doc. I was his first graduate student. I worked with him for two years and continued

during the summers and weekends while I was in medical school. We were working on prostaglandins, specifically the Prostaglandin E receptors.

Christopher Canning: By this point, then, you're focusing on being a physician and being a researcher?

Dr. Karaplis: Right.

Christopher Canning: And how did that take you out of your residency, then, into your first post-doc appointment?

Dr. Karaplis: Well, I knew that I wanted to do endocrinology. I was always interested in hormone regulation. And so, I stuck with it.

Christopher Canning: Okay, that's right, yes.

Dr. Karaplis: I had to do an internal medicine residency, which I did here at the Jewish General Hospital for three years. And then, I did my endocrinology fellowship at the Royal Victoria Hospital. I think it was at that point that I made my decision as to where to go for my post-doc training. You see, our two-year endocrinology fellowship program included a year and four months of clinical training and eight months of research. The person that gave me direction was Dr. David Goltzman. One day while in clinic together, he approached me and said, "You know, there's something interesting that has come up in the calcium field," because that's his research interest. He said, "We have identified a new protein called PTH-related peptide."

Christopher Canning: I see that on your CV.

Dr. Karaplis: Yes. It was 1987-'88 when this protein was identified. It was interesting because it causes the syndrome of high calcium in patients with cancer. This protein is secreted by cancer cells inappropriately and it causes high serum calcium levels. So, Dr. Goltzman suggested that I spend those eight months of research with him and do basic research; which I took it as a challenge because what I wanted to do was learn molecular biology. In those days, molecular biology was relatively new.

Christopher Canning: This was the time molecular biology would have been in full swing?

Dr. Karaplis: I think fate is something that I do believe in. It just so happen that this was the time. It was the appropriate time. So, David Goltzman said, "I will send you to the NRC Biotechnology Research Institute. I have a collaborator there, an excellent scientist, Dr. Denis Banville. He is a great molecular biologist, and he'll teach you everything you need to know about it."

Christopher Canning: And what year this is? '87?

Dr. Karaplis: End of ’88.

Christopher Canning: So, this was a part of your fellowship in endocrinology?

Dr. Karaplis: Right. So, I ended up there. I met Denis, and over time we became very good friends. Unfortunately, Denis subsequently passed away. But he taught me everything that I knew about molecular biology, an incredibly talented scientist. I still remember my first day in his lab. He asked me to run a DNA sample on a gel. I couldn’t figure out which way the positive and the negative electrodes go, in order to run the DNA. He looked at me and said, “Oh, oh, another medical guy. I think we’re going to have trouble here.” I believe he did not think very much of medical doctors actually doing basic research.

Christopher Canning: So, there’s this pull between the clinician and the researcher?

Dr. Karaplis: Oh, it’s been always there and still is. And you know that the biggest challenge for us is to try and bridge this gap.

Christopher Canning: I would like to come back to that because I think the group tried for many years to bridge this very schism.

Dr. Karaplis: Indeed, this has been one of the biggest challenges that we have faced, and we’re still facing.

Christopher Canning: Can I come back to that?

Dr. Karaplis: Sure, absolutely. Despite my shortcomings in the lab, we actually managed to get two papers out in eight months, which was a little bit of an accomplishment, I think. After that, I believe Denis realized that perhaps there was some talent in this doc. And I think he appreciated that.

When I finally asked Dr. Goltzman as to where I should go for my post-doc he said, “Well, I think the best place for you to train is in Boston. It’s a big calcium group there, and they will teach you everything that you need to know.” So I packed my bags, took my two-year-old son Chris and my wife, and we ended up going to Boston for three years for further training.

Christopher Canning: Specifically in molecular biology?

Dr. Karaplis: Yes, exactly. They were also beginning to do that and they were very much interested.

Christopher Canning: So, this is the tail end of the biochemist turning into the molecular biologist?

Dr. Karaplis: I guess. It was indeed the core of my molecular biology training.

Christopher Canning: From my understanding, these DNA techniques were being used somewhat in the late '70's?

Dr. Karaplis: Yes, in the '70's. But the actual translation in applicability into mammalian biology took a little bit more time. Certainly, I think that it was a number of years behind because in the course of my training, I didn't get any exposure to that. To make a long story short, my family ended up in Boston. I went to the laboratory of Dr. Hank Kronenberg. Now, Hank Kronenberg is one of the brightest people I've ever met.

He can talk to you about anything and everything in science. A very brilliant man. However, it was a time that his research was going in the wrong direction. He had one NIH grant and it renewal had not been funded. He wasn't working on PTH related protein. He was working on the processing of PTH. And so, we wasted some time trying to figure out what kind of a project I was going to work on. And then there was another strike of fate, as I would call it. We were having lunch at the lab at the Massachusetts General Hospital where they televise during lunch hours, various talks that take place in other institutions. So you could sit there while having lunch, and watch without having to travel all over campus.

So, it just so happened that we were watching together a talk on adipsin, a protein involved in adipocyte differentiation given by Bruce Spiegelman who was beginning to use gene knockout technology in mice.

Christopher Canning: Can you explain that further?

Dr. Karaplis: Well, this is the technique where you can specifically destroy a gene of interest in the mouse genome, and that allows you to study what effects it has on the development of the animal.

Christopher Canning: What proteins are produced or not produced based on a knock out?

Dr. Karaplis: Yes, that is if you knock out this protein, what happens to the animal? Basically, you look at the phenotype and then you examine the underlying molecular mechanisms.

Christopher Canning: Right, got you.

Dr. Karaplis: So, I said, "Well, that's exciting. It would be great if we could do a PTH-related peptide knockout because although we know that this protein is made by cancer cells inappropriately, we have no idea as to its physiological role."

Dr Kronenberg replied, "Well, I never worked on this protein and I'm not so sure I want to get into this field," but he added, "If you're really interested, then I could find out who does these knockout mice around here and

connect you with them."

So, we ended up going to MIT at the laboratory of Richard Mulligan. In his lab he had a post-doc, Victor Tybulewicz was his name, who was actually himself using the technique of gene targeting. He was actually successful in doing so. I think he was just writing up his first paper at that point in time. However, he was having trouble accomplishing a second knockout mouse.

When Victor realized that I was a medical doctor doing research he uttered the typical comment, "What is a medical doctor like you doing here?" Initially he was very reluctant about showing me anything.

Christopher Canning: What was the fear that basic researchers have? Or maybe not a fear, but a reservation?

Dr. Karaplis: I think it's the feeling that we as clinicians do not have the training that is necessary to do solid basic research. I don't think it's a fear. I think it's, basically, the concept that you stick with what were you doing well and we'll stick with what we're doing. But I have to say that once he realized how I worked in the lab, we became good friends. It's often like that.

So, with Victor we started out setting up new approaches and techniques that would make the gene knockout procedure reproducible. This was just the beginning. For example, we didn't know what embryonic stem cells to use. We didn't know what feeders to use. We didn't know what was the best way to introduce the DNA into the embryonic stem cells. It was starting from scratch. There is no question that this was a very difficult time for my family and I. I was hardly home because of the time I was spending in the lab.

Finally, we realized that we couldn't get the necessary mutation to be transmitted through the germline because of the feeder cells we were using. So, we started developing a system where we changed the feeder cells, and things were beginning to work.

Christopher Canning: Can you explain the feeder process? If I understand it, you inject the cell with a certain mutation. It gets passed on into the germline and then you can see the phenotypic effects of that knock out?

Dr. Karaplis: Right. Basically, the embryonic stem cells that you do the knockout need to be maintained in a non-differentiated state until they are put back into the embryo. If they have already differentiated, they will never be introduced into the germ cell lineage. So, keeping the cells in a de-differentiated state was very important. The way that we were accomplishing that was by keeping them on feeder cells.

Feeder cells are just a layer of cells that secrete a protein called LIF,

Leukemia Inhibitory Factor, which keeps the cells in a de-differentiated state. Over time we recognised that this was not enough. And what we started doing was to use feeder layers made out of fibroblasts that were derived from mouse embryos.

Basically, we would take mouse embryos at 14 days post implantation, dissect them, prepare fibroblasts from them, and irradiate them in order to keep them from proliferating. But they had the capacity of actually maintaining the embryonic stem cells in the de-differentiated state. So, this was basically the big change that we did.

Christopher Canning: That's great!

Dr. Karaplis: Before this everyone was using feeder cell lines that had been propagated so many times that at the end, they themselves had differentiated.

Christopher Canning: So, the key was to keep them radiated so they didn't --

Dr. Karaplis: Yeah, exactly, so they don't proliferate but at the same time, they keep the embryonic stem cells in the de-differentiated state so that they can go into the germline lineage.

Christopher Canning: And trace it into the germline. Wow! That's very interesting.

Dr. Karaplis: Let me tell you about an incident that I haven't told too many people.

Christopher Canning: Sociologists of science like juicy stories.

Dr. Karaplis: O.K., it was at a time when we had already generated the PTH related protein knockout mice. We knew that mice missing this protein die at birth. But we couldn't figure out as to why they were dying. We knew they had very abnormal developmental features but we couldn't figure out what was the problem. It was not an easy task.

So, it was getting to be a very difficult time for me, because, although I had succeeded in obtaining the knockout animals we also needed to figure out what's wrong with them. So, therefore, writing a paper before I would leave Boston was becoming less and less of a reality for me. It was very disheartening because despite all this work and the achievements that were made, I could not reach my goal.

As I recall, it was late at night and I was waiting for one of the experiments to be completed in the lab. So, I went upstairs to the library and I sat down. Now, the Whitehead library is a very big library; many, many books. So I figured I would read something just to pass my time. I started looking through the book stacks. I walked around the isles back and forth and finally I just picked up a book – I remember it was something about human

genetics. And as I opened up the book, it was right at a chapter on human chondrodysplasias, a condition in which babies are born deformed because they have an abnormal development of the skeleton.

As I started looking at the pictures, I thought to my self, "My god, this looks exactly like what we're seeing with our mutant mice," because they had exactly the same phenotype, that is their thoracic cage was much smaller, and they had a protruding tongue because they were unable to develop the facial bones appropriately.

So, when I went back to the lab the next day, I started looking at their skeleton, and that's how we end up recognising that the absence of PTH related protein leads to an abnormal development of the skeleton.

Christopher Canning: So, this is the birth of your interest in the skeletal system?

Dr. Karaplis: Yes.

Christopher Canning: That's really fascinating. So, before that, did you consider yourself a human geneticist, or would you even consider yourself a medical geneticist?

Dr. Karaplis: No, I wasn't considering myself a geneticist. I was an endocrinologist. But it just came out of this circumstance where, basically, I realized that this is a disease that affects humans, obviously, and that this protein is likely to produce a similar form of chondrodysplasia in humans just like it did in mice. Now, at that time, most chondrodysplasias were named based on the individual that would identify it and describe it for the first time. There was very little understanding of the molecular mechanisms underlying human chondrodysplasias.

So, we finally we managed to understand that this protein is important for the development of the skeleton. And that's how we started this scientific journey, trying to explain the molecular mechanisms by which this protein regulates bone development. The next challenge however was to demonstrate that indeed this PTH related protein signaling mechanism was also involved in human disease.

Christopher Canning: Right. So, you're starting to link the mouse model?

Dr. Karaplis: To link the mouse into the human condition. So when I returned to Montreal and started my independent research career at the Lady Davis Institute for Medical Research I actively pursued this objective. It just so happened, that one day while I was searching via the internet for papers on human chondrodysplasias that have the same skeletal characteristics that our mice had, I came across one paper that actually described such a form of human chondrodysplasia, called Blomstrand's chondrodysplasia.

So, I called the author up the next day. He was in England. He said, "Well, the baby that we described in this article died four or five years ago. So, we're not sure whether we could get anything for you." Finally, he managed to get some pathology slides from the baby, and he sent them to us. And from there, we were able to do PCR amplification of genomic DNA isolated from paraffin-embedded tissue and show that an inactivating mutation in the receptor of PTH related protein was the cause of this disease. Finally, we had linked the mouse condition to human pathology. And that's how the genetics component came out.

Christopher Canning: So, that's where you became a geneticist?

Dr. Karaplis: An amateur one.

Christopher Canning: So, prior to that you're an endocrinologist?

Dr. Karaplis: Right, yeah.

Christopher Canning: Did you work on those models? You have come to this realization that this is applicable to humans?

Dr. Karaplis: Yeah, this is applicable to humans.

Christopher Canning: So, this is where you meet genetics?

Dr. Karaplis: Correct.

Christopher Canning: So, since then, have you been a geneticist?

Dr. Karaplis: Well, to some degree, perhaps.

Christopher Canning: But you're an endocrinologist?

Dr. Karaplis: Right, but I can't call myself a true geneticist. I'm looking at the genetics and molecular mechanisms of human skeletal diseases.

Christopher Canning: Okay. So, what other phenotype do you look at? So, abnormal postnatal bone development, you obviously look at?

Dr. Karaplis: Yes.

Christopher Canning: What other phenotypes do you look at?

Dr. Karaplis: Well, in the past six or seven years we have also been very much interested in the hormonal regulation phosphate homeostasis. This is a very, very exciting area that has evolved tremendously. Mutations have been described in a number of genes such as PHEX, FGF23, and DMP1 that

basically cause renal phosphate loss resulting in a variety of inherited forms of rickets.

Christopher Canning: Interesting, because Dr. Scriver was looking at rickets and vitamin D deficiency in the 1950s and '60s. So, this is another way of looking at it?

Dr. Karaplis: Yeah, absolutely. And in fact, what we're looking at right now is therapeutics; we try to marry what we do in the lab with what we do in the clinic. These patients are usually given vitamin D and phosphorus, but this therapeutic approach is associated with side effects. And at the same time, one never gets a complete restoration of the bone for reasons that are still unclear.

So, from the genetic studies we're doing with mice, we have shown that a very important component of this system is the 24-Hydroxylase enzyme in the kidney; this is an enzyme that is important in vitamin D metabolism. The active form of vitamin D is synthesised in the kidney. And this enzyme is there to regulate how much of this active form would be available for release into the circulation. So, we have shown that if you actually take mice that have the X-linked Hypophosphatemic state and knockout this enzyme, all the skeletal features of rickets are corrected.

So, we hooked up with a pharmaceutical company that makes inhibitors for this 24-Hydroxylase enzyme and with a group in France that follows a large number of children with X-linked Hypophosphatemic rickets. We aim to examine the therapeutic benefit of using 24-hydroxylase inhibitors in these patients.

Christopher Canning: Is this your first development of a therapeutic treatment?

Dr. Karaplis: Yes.

Christopher Canning: That must be pretty exciting after so many years of research.

Dr. Karaplis: For research into therapeutics, yes, absolutely. But this is, basically, the way I view my role. As we've discussed before, I think there's a huge gap between research and clinical medicine. And I find that a lot of times the two camps cannot talk to each other. They speak very different languages. And I believe that clinician scientists can bridge this gap. That is what it comes down to, trying to bridge the existing gap.

And there're very few trainees that are willing to put the effort and the time that is necessary to reach this objective. Unfortunately, our system is set up in such a way that most of our residents and fellows have absolutely no inclination for commitment to this type of career.

Christopher Canning: It seems to be in the early days in medical genetics, the 1950's, for instance,

when scientists were looking at chromosomal abnormalities and the physician and the scientist were the same person.

Dr. Karaplis: Right.

Christopher Canning: And so, do you think that we've moved quite a ways away from that, especially in a way that molecular biology is doing one thing and physicians are doing another?

Dr. Karaplis: Certainly, we have become super specialized because medicine itself has certainly expanded to such a degree that you can't keep up with everything. And obviously, when you're talking about research, it's, again, another world. So, I find myself, right now, as I am spending more and more time in clinical work that I tend to fall behind in my knowledge of basic research. This is one of the biggest problems that we run into because there's no time to do everything and do it well.

Christopher Canning: Yeah. Do you supervise grad students?

Dr. Karaplis: Yes. I do. Presently I have one student from experimental medicine who is just finishing up, and I have three research associates. These are individuals that came to my lab to do their post-docs, and they stayed with me since.

Christopher Canning: Very interesting. Well, I'd like to go into more specific questions about the group now. Your past is, actually, really interesting. I like all the serendipitous moments, which seems to be a trend in science. And science often works, contrary to what the public thinks about science being a linear programs, by chance.

Dr. Karaplis: Serendipity; I really believe in it.

Christopher Canning: So, here we are late '90's and you are invited to participate in the MRC Group. What was your knowledge of what was going on in the group and how did you first become involved?

Dr. Karaplis: I knew about the group. I knew of its existence because of Dr. Tenenhouse. Susie and I had collaborated on generating a knockout mouse of the renal sodium phosphate cotransporter.

Christopher Canning: Right. She was interested in the kidney transporter system?

Dr. Karaplis: Yes, in the renal phosphate transport system. So that's how we came together as I participated in the generation of these mice, and ended up with a publication in PNAS for all of us. Therefore, it was our common interest in phosphorus homeostasis that brought us together. And I think at that point, she wanted also to bring some additional members into the medical genetics group with similar research interests.

Christopher Canning: Which was Rosenblatt and others?

Dr. Karaplis: David [Rosenblatt] and Roy [Gravel] and Rima [Rozen] and then there was her, in a totally different area of research. And I think, by just bringing an individual that was more or less into her line of research made the group somewhat stronger. And that's when Roy asked me to give a talk at their rounds following which he asked me if I wanted to join them. So, that's how I joined the group.

Christopher Canning: Right. Dr. Gravel was the director at that time but Scriver was still loosely involved in this?

Dr. Karaplis: Very loosely involved. At that time, it was Dr. Gravel, yes.

Christopher Canning: Yeah, okay.

Dr. Karaplis: So, that's how we came to be. And from then on, it was simply keeping up with the grants. The interactions were rather limited in many respects, primarily because of location.

Christopher Canning: That was my next question: what was the location of the group during this time?

Dr. Karaplis: The location was very difficult in many respects. I was at the Lady Davis Institute, while the rest were at the Children's [Hospital]. Also, our interests were different. We had very little commonality. I had a lot of commonality with Susie but Susie retired.

Christopher Canning: She was on the 2001 application but she retired after that.

Dr. Karaplis: I believe that is correct.

Christopher Canning: So, she would've been involved from about '94, about six years?

Dr. Karaplis: After that, it was felt that they had to bring additional members in like Dr. Mark Trifiro, Eric Shoubridge, and Bob Mackenzie.

Christopher Canning: Yeah. Did you feel that you had to make these connections as being part of the group?

Dr. Karaplis: Yes.

Christopher Canning: So, what was that pressure or climate like?

Dr. Karaplis: I think the pressure was primarily on the director of the group. He/she had a very difficult job to do. First, it was to find the individuals that would fit in

the group and at the same time, make the group stronger. And they did a very good job, I have to say, over the years from that perspective. It's unfortunate that the group had to be disbanded.

Christopher Canning: Can you describe a little bit more about the space? So, where were you and where were the other folks?

Dr. Karaplis: I was here at the Lady Davis Institute. There was a time we had plans to develop a common transgenic facility, which I would be running. The idea was that if any other members wanted to generate knockout mice for their research, they will be generated here. Unfortunately, it didn't work out very well because; (a) my lack of time commitment and (b) for other political and personal reasons. So, it didn't work out very well.

So, finally that was terminated. The main facility that we all shared was the histology service that was set up at the Children's. So, occasionally, I would use it to get tissue samples processed there. But the interaction was rather limited in many other respects.

Christopher Canning: Okay. I'm going to come back to that in a second. Can you just speak a little more to what role each of the members played? What was the conversation like between members and what was each member doing? In other words, what did they do to contribute to the group as a whole?

Dr. Karaplis: I think everybody certainly had their own role and their part within the group. The interests however were somewhat diverse, I have to say. Dr. Rosenblatt, for example, was instrumental in the preservation of the tissue bank. Roy and Rima are very bright individuals who were certainly exceptionally well-organized and very good in allocating resources appropriately. So, from that perspective, they did a great job in running the group. And Susie Tenenhouse was obviously extremely knowledgeable in the field and was always very helpful. My interaction to Scriver was minimal if any. He was not around anymore.

Christopher Canning: Did you have a feeling that it was -- because until that, until the mid '90's, it was Scriver's project for many, many years. He directed it and he was obviously the founding member. Was there some sort of motion that was moving away from Scriver?

Dr. Karaplis: It's a long time ago, but from what I recall there was a bit apprehension going forward because it was unclear how successful the group was going to be in his absence.

Christopher Canning: You recall these discussions?

Dr. Karaplis: Yes.

Christopher Canning: Okay. Do you recall how the funding structure worked in putting together group applications? Do you remember or recall writing the grants? Was it the director's responsibility?

Dr. Karaplis: Yes, it was primarily the director's responsibility. What the rest of us had to do was to succeed in our own grants that formed part of the group grant. Nevertheless, there was funding that was allocated to the group as such. In part, this was used for maintenance of the tissue bank and the salary for one technician looking after it. Obviously, more senior members made these decisions and as a newcomer, I had no inclination to object.

Christopher Canning: Right, in the administration of that?

Dr. Karaplis: Yes, in the administration of that or even in the allocation of how much money would go into it.

Christopher Canning: Right. You mentioned that you had to be successful on your individual grants. And I noticed, for instance, on the '94 application, Shoubridge, Nadeau, and Malo were not successful. And I think this is a change in MRC structure where, previously, you were invited to be a part of the group as long as you got funding in the group. So, at this time you had to be successful individually in order to be included in the group?

Dr. Karaplis: Yes.

Christopher Canning: Okay, that's interesting. I'd like to come back to what you were talking about earlier. And you said, you're a physician and geneticist. In the later years, that's not necessarily the case. What were the divisions in the group specifically between the bench and the clinical? Did you have any conversation about it, you know, as you were talking about earlier that this was bit of an issue and still is in the world of research?

Dr. Karaplis: Within the group?

Christopher Canning: Within the group itself. Was there a conversation about what --?

Dr. Karaplis: No. I think that the group, from that perspective, worked very well. At that time Dr. Scriver was not around. He wasn't submitting a grant at that time. So, it was myself and Dr. Rosenblatt. There was absolutely no friction or discordance between physicians and scientists. I think our roles were very clearly dictated by the fact that we had to apply ourselves and get the grants. It was not an issue at all.

Christopher Canning: Yeah. Do you think the group succeeded in its interdisciplinary approach? It was always said that it achieved a level of interdisciplinary. And I'm just wondering from your experience and your knowledge of the group in the past and your knowledge of the group as you're a member, was there

interdisciplinary collaboration? And, in a sense, what came of that interdisciplinary work?

Dr. Karaplis: There was to some degree of collaboration but I think there is no question that there was a discordance also; different areas of research, different interests. This became quite evident when we would have our yearly meetings. So, from that perspective, I think that the coherence was not as good as one would think or one would wish that it was.

Christopher Canning: So, I've asked other members this very question. So, what made the group a group? In other words, what was its groupiness? And that's not to deny there was a group because, well, it was a group in many ways, defined by the context of its members and by the policies of the MRC and CIHR.

Dr. Karaplis: It was, indeed.

Christopher Canning: And it was funded for 37 years.

Dr. Karaplis: Yes, but I think the groupiness changed from year-to-year or at least from era-to-era. Nevertheless, from the time I was there, I don't think that there was a real group. It was just a group of very talented scientists with interest in genetic disorders. I don't know if that's what other members also said but I felt that it was a group that basically existed in the interest of looking at the genetics of human diseases, a very broad spectrum -- broad definition, I would say. I think the groupiness came from that context, from the context that we're all interested in human genetic diseases.

Christopher Canning: So, that's the umbrella trying to define the group.

Dr. Karaplis: Correct. But within the group, the interaction was limited.

Christopher Canning: So, why did the MRC and the CIHR fund the group for so long? And I'm certainly not asking that question to downplay the significance of the group. But, sociologically, it's interesting how groups were defined by policy and actual context.

Dr. Karaplis: [Laughs] No, no, I understand. I think that basically, it was the way they sold it. They sold it very well. They sold it as a very functional group. And it's not that it was dysfunctional. I think it was just that perhaps the interests were not as interwoven as one would have liked it to be, because had it been that way, I think the group would have had a lot more success.

Christopher Canning: Had it been more collaborative?

Dr. Karaplis: Absolutely. I'm totally convinced of that.

Christopher Canning: That's very interesting. So, what were the successes of the group then if

you could -- and I don't mean this in necessarily direct therapeutic benefits, but what if -- if you could look back over 37 years from what you would think of, what are the benefits of a group in medical genetics?

Dr. Karaplis: Well, I think that the initial work of Dr. Scriver cannot be surpassed. I believe this is monumental to the group. I am under the impression that the group moved away from the patient and concentrated more on basic research. And from there, the therapeutic implications of our work, although they were there and they were evident, somehow they became less prominent.

Christopher Canning: Dr Scriver was treating his patients right there in front of him.

Dr. Karaplis: Perhaps. So, I think that's where the group changed. The group moved away from the clinical arena and more into the lab.

Christopher Canning: Very interesting.

Dr. Karaplis: That's my perspective of what happened, not that either one is more important than the other.

Christopher Canning: No, of coure.

Dr. Karaplis: It's just a different approach to the same problem.

Christopher Canning: Yes.

Dr. Karaplis: And that's why you don't see as much therapeutics out of what we were doing.

Christopher Canning: I don't know a whole lot about the science of all the group members but in terms of over the last 25 years, what are the therapeutic outcomes of this basic science?

Dr. Karaplis: Not much.

Christopher Canning: And, again, basic science is great. We need basic science.

Dr. Karaplis: Of course. This is something that you're going to build on the therapeutics, but I'm not so sure how far we advanced the therapeutics.

Christopher Canning: Do you think being more collaborative in terms of medicine and basic science, do you think, as you've said, outcomes would've been different?

Dr. Karaplis: I think the outcome would have been very different, yes.

Christopher Canning: Okay. Scriver mentioned -- just a couple more of questions, are you okay

with that? Scriver mentioned at the last symposium, this is kind of related to what we're talking about. At the symposium last fall, he said the group operated as a grassroots organization, meaning that it always evolved from the bottom up. I'm wondering if you could speak to this. And I just found this really interesting as he was discussing this illustrious history of the Group, composed of respected scientists who have done amazing work. I wonder if that was your impression.

Dr. Karaplis: I'm not so sure what you refer to as grassroots. Certainly whoever was recruited, benefited the group overall. I don't know if that answers your question.

Christopher Canning: Yeah. Do you know why the group funding stopped in 2009? Why the CIHR stopped group funding?

Dr. Karaplis: I think it was a policy that the CIHR basically upheld. My personal opinion is that there was a lot of grumbling from individuals that were outside of such groups who felt that additional funds should not be allocated to members of groups who are already receiving support for a grant. Why should they have the extra money to support this sort of groupiness, which may or may not have been there to begin with? And I think that this became apparent to the CIHR. And part of the reason for the disbanding was the fact that it was the realization that perhaps there was very little benefit to be obtained by maintaining this groupiness.

Christopher Canning: Interesting. Was there a sense of elitism or just an unnecessary allocation of funds?

Dr. Karaplis: I believe that the general feeling was that the groups were elite and they should be disbanded.

Christopher Canning: And they should? And there was probably concern in other research domains that the groups are getting all the money.

Dr. Karaplis: There was a substantial amount of money that was allocated on top of what one was receiving from their own personal grant. So, it was seen perhaps as being unfair. That money could be better spent to support other researchers that needed to have their own funding, and there are some merits to that, I think.

Christopher Canning: I think they moved into the team grant, which is, as far as I understand in the policy, the team grants are specifically an interdisciplinary project. So, as opposed to the MRC group, which had different areas of science but were still group, new team grants demand a single project from different areas.

Dr. Karaplis: Therefore it has to be very well defined.

Christopher Canning: Yeah.

Dr. Karaplis: And we did not have that. I think that's part of the problem.

Christopher Canning: Interesting. Okay. Future research, what are you working on now? And you mentioned a bit earlier about how all scientists have ideas. So, what do you hope to do over the next five or ten years and what are you working on?

Dr. Karaplis: Basically on two main things. One is the therapeutics. As I've already discussed, I'm really interested in looking at the therapeutic potential of the 24-Hydroxylase inhibitors in patients with X-linked Hypophosphatemic rickets. So, this is one area that I'm certainly going to devote a lot of my time.

The second is osteoporosis. I treat a lot of patients with osteoporosis. I am the director of two outpatient clinics here that treat patients with osteoporosis. We have over 3,000 patients in our clinics.

Christopher Canning: The most common bone disease, obviously among --?

Dr. Karaplis: Metabolic bone disease.

Christopher Canning: Anyone has it over 55.

Dr. Karaplis: Potentially. And there's no question that it is a genetic disease. One of the biggest questions that had arisen in the field of osteoporosis recently pertains to one of our therapeutic modalities, which is FORTEO or PTH. PTH is the only bone anabolic agent that we have available today. It's the only agent that builds bone. The problem with this drug is it needs to be injected on a daily basis for a two-year period.

The question is how does this protein work? We don't know how it works. If you have patients that are secreting too much PTH because of parathyroid disease, they get osteoporosis. But if you administer exogenous PTH in a pulsatile fashion, not continues, but in a pulsatile fashion, to patients they actually build bone.

So, one of the outstanding questions is why this paradox exists. What we're exploring now, which is something very, very new and very exciting is the role of the clock genes in this process. All our biological systems are set to function in unison by our hypothalamus-pituitary system. For example when we see light in the morning, we get the cortisol secretion going. And we believe that what these signals do is to set peripheral tissue cells in synchrony. For example, if we take bone, we know that bone formation takes place at night while bone resorption takes place during the day. So, there has to be a switch. We are proposing that the switch is endogenous

PTH being secreted in a circadian fashion.

The concept here is that the circadian secretion of endogenous PTH is responsible for bone formation. And what we're doing by instructing the patients to inject themselves once daily is that we're reproducing that circadian rhythm. So, we are trying to understand and exploit this mechanism even further, because it will tell us why some people respond to the drug and some don't. Because if the patient injects in the morning, it's contrary to the natural timing of the secretion of the protein which normally occurs at night.

Christopher Canning: So, you have to catch it on its --?

Dr. Karaplis: Or to reproduce the endogenous pattern, by injecting it at night rather than in the day. Therefore we are trying to understand how to better improve the anabolic effects of the drug in our patients, again, bridging basic science with the clinic.

Christopher Canning: More and like potential therapeutic implications?

Dr. Karaplis: Yes.

Christopher Canning: Fantastic.

Dr. Karaplis: So, the clock genes and the circadian rhythm is something that we're exploiting right now.

Christopher Canning: Yes and linking neuroscience, too, with metabolism?

Dr. Karaplis: Absolutely.

Christopher Canning: Very interesting. And you have a grant obviously to do this within the next few years?

Dr. Karaplis: Yes, a five-year CIHR grant.

Christopher Canning: Fantastic.

Dr. Karaplis: Yes.

Christopher Canning: Well, good luck.

Dr. Karaplis: Thank you very much.

Christopher Canning: Well, that concludes my questions. I just want to thank you very much. This was a really excellent conversation.

Dr. Karaplis: Thank you. I appreciate your time.

END OF INTERVIEW

Dr. Robert MacKenzie, February 2, 2011

Christopher Canning: My name in Christopher Canning and I'm here with Dr. Robert MacKenzie on February 2, 2011. It is my great privilege to be here with you, Dr. MacKenzie, to discuss two main themes regarding human genetics.

First, I would like to discuss your academic background, which contributed to the growth of medical genetics in Canada and beyond. Secondly, and perhaps more importantly for this study, I'm interested in your involvement in the MRC/CIHR Group in Medical Genetics, which you joined, as I understand it, in 2001, and were a member until the group disbanded in 2009.

So to begin with, can you please give me an overview of where you're from, where you're born and where you grew up?

Dr. MacKenzie: Okay, that far back! I was born in Nova Scotia, got an undergraduate degree from McGill University, Macdonald Campus, and a Masters Degree from Cornell University and PhD also from Cornell University. My Masters was in Nutritional Science and my PhD was in Biochemistry. I then went to Berkeley for a post-doc with Jesse Rabinowitz. And that's what got me into the field of folate. And it was the folate connection that basically connected me to this group.

Christopher Canning: Okay, I'd like to come back to that actually in a few minutes. I have some specific questions about how you got involved in the group. I know this might be a little ways back, but I'd like to hear a little bit more about what your research at Cornell in biochemistry concerned. And did you do a post-doc after that? So let's go back a bit in terms of your academic training.

Dr. MacKenzie: Okay, my PhD at Cornell was in Biochemistry, and actually it was more of an organic chemistry project. I was interested in the fact that flavoproteins have a redox potential that varies widely depending on the particular flavoprotein. Well, riboflavin is part of both FAD and FMN. When it's combined with some proteins, the redox potential changes; it's not like the NAD and NADH couples that have a fixed redox potential. This is because the flavin is often more of a prosthetic group than a dissociable co-factor.

And so clearly the interaction of the flavin with the protein changed some of the characteristics of the flavin, and did it quite dramatically. So we were building models and trying to chemically associate and covalently link the flavin molecule to particular amino acids that you would find in proteins, and looking at these artificial redox systems, to see whether a particular amino acid could change the redox potential when in tight association with the flavin ring.

And it did to some extent; not as much as you would find in the protein itself but clearly the properties of flavin were affected even by holding this close association with certain amino acids in the protein.

So that basically got me into what I would say was a model system looking at flavoproteins. I mean, basically, it was one flavin and essentially one amino acid at a time and I thought, well I should do more protein chemistry, and looked for somebody that had a lot of protein. At that time Jesse Rabinowitz at Berkeley was working on the folate-dependent enzyme from Clostridia, and could get actually gram quanties of particular enzymes.

So I went to work with Jesse because I wanted to take my model system to a real protein and that got me into the field of protein chemistry.

Christopher Canning: Fantastic.

Dr. MacKenzie: So for my post-doc, I was working on folate-dependent enzymes with Jesse Rabinowitz. And at that point, I was able to read some literature and find that much of the folate story that was really well understood came from bacteria. And I was interested in what was going on in mammals. And many of the proteins had been only partially purified from mammals and so I was interested in pursuing some of that. And that's what I did when I came to McGill.

Christopher Canning: So if you are working on mammals at the time, what mammals in particular were you working on?

Dr. MacKenzie: I needed large amounts of tissues, so it was predominantly large animals--we were working with pig liver because we could get it at slaughter houses and we were using it in kilogram quantities trying to isolate proteins.

So pigs and basically rats to start with, because at that point, back in the '70s, what we're looking to do is identify what proteins are involved in this process. And people had detected some activities but they hadn't fully separated the proteins. And basically, I got started doing that for mammals, and we found that several of the proteins turned out to be multifunctional proteins - that is, one gene product, one polypeptide would have more than one enzyme activity. This was revolutionary at the time and people didn't really believe us at first, but the number of multifunctional proteins basically grew, and it turned out that the folate field was a good area for that because several of our proteins are multifunctional.

Christopher Canning: So does this challenge the central dogma of the single gene, one protein action?

Dr. MacKenzie: Well it's one gene; it used to be one gene, one activity. It was one gene, one

protein. But what some of these proteins were linked over time, and so often the proteins would get linked and the two activities would be expressed together, or even three activities. And so we have several examples of proteins that were multifunctional in the true sense; that is that they weren't enzyme complexes although there are a lot of those examples too.

And so my original interest was, "What's the advantage of multifunctional proteins?" Or why would nature go about putting these activities in a single polypeptide? And so we did much of our work in the early days looking at the proteins, and scratching our heads and trying to decide, well, why are these activities together? And we found a few examples, using the proper folate substrates where with consecutive enzyme activities, the intermediate product would do what we call "channel"; that is, the first enzyme would take compound A and convert it to compound B and hand it directly to the second activity, that would take B and convert it to C. And so the intermediate B never dissociated into the medium.

And so clearly, there was a kinetic advantage for these proteins to be linked. But it turned out that wasn't the answer for all of them.

Christopher Canning: Okay.

Dr. MacKenzie: And so the kinetic advantage was one explanation, but it wasn't clear in the cell why some others are multifunctional. We had one case that was trifunctional. And another one that was bifunctional but it was bifunctional only when the subunits interacted so that -- this was a funny protein. It was a tetramer of dimers. And the dimers would have one activity but when you put the dimers together to make the octamer (a tetramer of dimmers) then you would have two activities. And so it appeared that the activities then were at the two different interfaces of these subunits although all the subunits were identical.

So it was like taking two billiard balls and you put them together so that the numbers were touching, you get one activity. But if you took that pair of billiard balls and attached it to another pair of billiard balls where the numbers weren't touching, there would be another activity at that interface. So there are many ways we found that proteins were multifunctional.

Christopher Canning: Okay.

Dr. MacKenzie: And so that's really what got me started from the standpoint of protein chemistry, and with the early work that we did for several years or for many years actually involved isolation and characterization of the proteins

Christopher Canning: Sorry to interrupt, this is why you're still at Cornell?

Dr. MacKenzie: Pardon me.

Christopher Canning: This is while you're still at Cornell?

Dr. MacKenzie: No, no, no, all of this was when I came to McGill.

Christopher Canning: Okay.

Dr. MacKenzie: When I got introduced to the folate field at Berkeley working with Jesse Rabinowitz, I worked with protein from clostridia. And it got me interested in the folate field but Jesse was a bacterial person. And we worked on some proteins from bacteria; the Clostridia made huge amounts of the folate-dependent enzymes but they used them in a way that mammals did not. So they were similar activities, but with different metabolic importance. So now the question for me when I left Jesse and got my own academic position at McGill was, "What's the story in mammals?"

And so I spent a lot of years scratching through and trying to determine what the proteins were and what the properties of those proteins were. So we did a lot of protein purifications, a lot of basic protein chemistry, nothing to do with genetics.

Christopher Canning: Okay. So what year then did you end up at McGill?

Dr. MacKenzie: I went to McGill in '71.

Christopher Canning: And I guess your first appointment would have been in the Department of Biochemistry?

Dr. MacKenzie: That is correct.

Christopher Canning: Okay. And you say that you weren't actually a geneticist but you were obviously interested in --

Dr. MacKenzie: I was never a geneticist. [Laughs]

Christopher Canning: Okay. Well, that's interesting because you were involved in a group in medical genetics.

Dr. MacKenzie: That's correct.

Christopher Canning: That in itself is an interesting point. So you're doing this work on certain mammals, but did you ever have an interest in applying this to humans or understanding its application to human diseases?

Dr. MacKenzie: Well, I think everybody who worked in biochemistry, worked on model

systems because it's kind of hard to say, "Hey, can I have a kilogram of your liver." So you can't do some of that basic stuff on humans. And otherwise, what are you doing? You can't really do the basic chemistry, basic biochemistry, so you need model systems.

And I just wasn't happy to work on bacteria as the model systems. I want something closer, though the mammals are a lot harder from the standpoint that the proteins were much more difficult to purify. They had to be purified several fold more than if you did them from Clostridia -- I mean, Jesse could get pure folate enzyme with about a hundred full purification; we would have to go to 600 fold to get a pure protein from pig liver for example. Because there were so many more proteins in liver, it's much more complicated.

Christopher Canning: So most of your career was spent doing the basic biochemistry, basic science?

Dr. MacKenzie: I would say most of my career was doing the basic biochemistry because I really started out interested in protein chemistry, how proteins work, something to do with mechanism but particularly what is the advantage of the multifunctional proteins. So we ended up purifying two of these from pig liver and did a lot of work on those.

And then at some point, I forget what year that was, but we followed up on an old observation by Gray Scrimgeour had made many years ago, I would to go back to paper for the date. I think it was like, 20 -- 25 years out of date when I picked up on it. And he had mentioned that in Ehrlich ascites tumor cells (these are free living cells that grow in the peritoneal cavity of mice) he found an enzyme activity that he couldn't find in the mice, but found routinely in the Ehrlich ascites tumor cells.

So we actually thought that was an artifact probably due to the fact that you work with crude extract and you measure something that's a spectrophotometric change. You don't actually identify the product to get a change in absorbance. And so I put a summer student on it and said, "Look, let's see what you can do with this." So it turned out that we convinced ourselves that there was some activity there, and worried for a long time that that activity that we found in the Ehrlich ascites tumor cells may have been caused by some organism that was growing in the peritoneal cavity along with the Ehrlich ascites tumor cells; so that what we're measuring was really not in a mammalian enzyme but it was something that was contaminating the process.

And so that got us into looking at various cell lines that we could grow in culture, and cell lines that we could find that we knew were not contaminated. And it turned out that every cell line that we looked at had this particular enzyme activity that was an NAD-dependent,

methylenetetrahydrofolate dehydrogenase.

And so we published a paper that basically said, "Look, it is expressed in every transformed cell that we look at." And in whatever tumor cells we would get our hands on, this enzyme activity was present. So we were then convinced that it was a mammalian protein. So we set out to purify that because something was really, really strange because you couldn't find it in the cells of a mouse but you found it in that tumor cell that was growing in the mouse.

Christopher Canning: Interesting, yes.

Dr. MacKenzie: So it took a lot of purification. We had to make huge amounts of Ehrlich ascites tumor cells that we grew in lots of mice for this purpose. You would inject the tumor cells in their peritoneal cavity, wait for them to grow and then harvest them and of course you had to sacrifice the mice. And we would take huge amounts of these Ehrlich ascites tumor cells and finally ended up actually purifying the protein and showing that it was an NAD-dependent methylenetetrahydrofolate dehydrogenase, which was similar to an activity that we had found earlier as part of a trifunctional protein.

But this was not trifunctional, it was only bifunctional. And that really got us interested. And then we started to clone these things. So that point, being able to clone these proteins was possible once you had antibodies. And so we cloned the cDNA and then the process of cloning the gene and looking at some sub-cellular distribution, we discovered that this little guy, this strange NAD methylenetetrahydrofolate dehydrogenase, occurred only in the mitochondria of the cell, not in the cytoplasm as the other ones were.

Christopher Canning: I noticed some of your recent publications are on mitochondrial DNA.

Dr. MacKenzie: Yes. And so the whole story got us into the mitochondrial process because this protein was mitochondrial. And for the longest time, we weren't really sure why this protein existed in mitochondria and why it existed in transformed cells. And so what we then wanted to do to follow that up -- then I suppose that this drags me towards the genetics-- and for me, it wasn't genetics; it was to answer a biological question and that was: how important are these proteins? I mean, we know it's there. We know it's in the mitochondria but it's not in the adult mouse. So we carried out a knockout of the gene and we and found that it was embryonic lethal. So the embryos would not live beyond about 12 days or so.

Christopher Canning: Without this protein?

Dr. MacKenzie: Yes, for about 12 days roughly. And they died. And at that point, the embryos were incapable of developing red blood cells. And this protein had nothing to do with red blood cells directly. But these embryos died because

they did not develop haematopoiesis, which is the initial development of the red cells. And when that happens in the embryo, the liver is the first place where red cells are produced. And you could see in these embryos that their livers were white and in a normal embryo, the liver was bright red at this stage because they made red blood cells.

So again, we scratch our heads - why is this? And so it wasn't until we kind of realized that this protein must be doing something to support, even though it's in mitochondria, was doing something to support rapid growth because that's the only situation in which you saw it. It was in the tissue that was doing rapid growth either in the embryos or in the tumor cells.

So the rapid growth, what you do you need for rapid growth? You need purines and pyrimidines and folic acid is the co-factor that supports the one-carbon units necessary for the synthesis of the purines. So we kind of persevered and the ultimate solution was to find that this protein in fact produces a product in mitochondria that, with the help of another enzyme, can be converted into one-carbon unit that can be exported into the cytoplasm from mitochondria. And that one-carbon unit in the cytoplasm gets converted into purines.

And so in order for there to be a sufficient rate of purine synthesis for DNA and RNA synthesis, you need that process -- actually, it's the amino acid serine that is metabolized through the mitochondria, through this enzyme and ends up forming a one-carbon unit. It gets released into the cytosol and that process enables the cell to make enough one-carbon units to synthesize purines at a rate fast enough to do haematopoiesis.

So what's happening with our mice that didn't have this gene was that they couldn't make purines fast enough and so they couldn't establish -- they couldn't reach a threshold to establish-- haematopoiesis. So that in trying to understand that, was where we really came in to the group. But there was another earlier organization. That was the so-called "folate club". And several people from McGill including David Rosenblatt and Bernie Cooper and myself were all working on folate and we would meet. In fact, we started to meet shortly after I got to McGill and we kept talking about folate and B_{12}.

And so it was kind of natural from that interaction that when it came time to add people to the group, as others retired from the group, that I was interested to know what was going on. I didn't come to the point of looking at human genetics-- but actually the expression of the proteins and the role of the genes. And so at that point, I guess I became a kind of a pseudo-geneticist.

Christopher Canning: I was going to say, so obviously you're a biochemist up until this point. But by the sound of things, you were using molecular biology techniques.

Dr. MacKenzie: Well, absolutely! I went from doing organic chemistry to doing protein purification and characterization, protein chemistry to molecular biology to do the cloning and the expressions so we could do X-ray crystallography to look at the structure. We've looked at mechanisms, chemical mechanisms of some of these proteins. We've tried to explain the channeling process and we went from that to doing site-directed mutagenesis to look at properties, and from that, ultimately to cloning the genes and from that to knocking out the genes.

So I found that was really a lot of fun. But clearly you change what you do. In your career you basically adopt the technology that you need to answer the questions that you are faced with. And so I started out with linking two molecules and ended up knocking out genes in mice.

Christopher Canning: Right. Obviously, aided by the molecular biology revolution that was happening in the '70s --

Dr. MacKenzie: Absolutely. And I was very lucky that we had the people in the biochemistry department who helped with the knockouts and that was a great department to be in because it was a very, very strong department, and you could rely on a lot of people for technological help. But when it came to the point of trying to fully take advantage of what was going on with this strange NAD enzyme, I needed to know something about mitochondria and Eric Shoubridge was a mitochondrial expert from the group.

Christopher Canning: Right, of course.

Dr. MacKenzie: And so having Eric was fantastic because we could knock ideas together. We could use some of his expression vectors, and that kind of thing. David Rosenblatt and Rima Rozen of course were the folate people.

Christopher Canning: I noticed that in the early to mid-80s, you actually published a few papers with Rima Rozen.

Dr. MacKenzie: Yeah the mid-80s I think maybe one or two. But at that point, we were early in the cloning business and expression. I think at that point, it had nothing to do with this latest NAD enzyme; it was well before that. But at the same time, one of the things I needed was histology because we had to understand what was going on when we knocked out the gene. And the mice were dying in utero.

I mean, here's the biochemist throwing up his hands and saying, "What do I do now?" I mean, yes, it's important the mice died. But when do they die and what do they die of? And can you look at the pathology of this, at the embryology and the cytology and look to see what you can find. And so it was important to have that kind of expertise and that was also some

expertise that was going to be common to the group.

Christopher Canning: Right.

Dr. MacKenzie: So that was very useful when we started looking at slices of our embryos and trying to understand what was going on with them.

So again, I think I joined the group because it made sense from the standpoint of making a stronger folate group and that there would be three of us in folate rather than two. I think that I brought a strong molecular approach from the standpoint of protein structure and function to that group, looking at things differently than they would look at things, and of course they looked at the genetics differently than I did.

So it was a great way to kind of share ideas and to get ideas, and we could help each other with our projects. And sometimes, the ideas are wild and wonderful but nevertheless, there were ideas that made you think, and I think we helped each other.

Christopher Canning: To the point that you joined the group in 2001, you hadn't done a lot of work on humans. So how did you see your work specifically translating from biochemistry, molecular biological techniques, into the study of human diseases? And what specific human diseases do you think that your work contributed to or could contribute to?

Dr. MacKenzie: Yeah. I was a basic scientist and I wanted to know how things work. I didn't start out by saying, "Hey, I hope to try to look at a particular disease." I did start out by saying, "How the hell does a cell work?" And if you don't understand that, then how are you going to understand the disease? And so we were looking at things really at a molecular level. We knew that folate was very important to all mammals. You couldn't be healthy and alive without this.

And so we wanted to know how it was. I started more by looking at "how does this work" rather than saying, I'm looking at this from the standpoint of disease. Because at that point, there wasn't something that's really clear -- except for I guess -- if you're folate deficient, you had anemia and also the folate B_{12} story and some anemias. But from the standpoint of a biochemical approach, it wasn't rigorous enough for me just to look at it that way. I had to start to from the bottom up.

Some people like to start from the top down, but I find, personally, it was a bit descriptive for me. Because at that time, there really weren't the tools; there's a lot more tools now to relate lots of things to disease because now you've got the screening tools. But at the time, we didn't have those. And so now, I guess that we know that this particular NAD enzyme, which I think is probably the most metabolically important thing that we've contributed

because basically we were able to write two review articles -the final articles from my lab- putting things in perspective.

Christopher Canning: Sorry, is it your lab when you say we?

Dr. MacKenzie: My lab - my students and myself -- that these review articles basically put in perspective what this NAD enzyme is doing and its role. So the fact that it's expressed in the mitochondria of cells that are going to undergo rapid growth basically says, "There is a potential here for perhaps an anti-cancer kind of approach." But it's a tough one because you have to stop the expression of a protein you're going to try to inhibit the activity of an enzyme that is in the mitochondria. So basically, there are probably ways to do that but I had sort of come to the point of my career where I was not prepared to put in another six to ten years to try to milk that.

I had come to the right point. I thought, "Well, that was it." And I had reached this point where I thought that after 38 years of funding from Medical Research Council and the Canadian Institutes for Health Research and a few other small grants on the side it was enough. I decided that that I wasn't going to pursue it further. But it does have some potential. The problem with all of these things is that if you're successful at it, it will kill any cell that's trying to grow rapidly. So it remains to be seen whether there are ways to do this.

Certainly, in an embryogenesis system, inhibitors would be lethal to try to interfere with it. There might be ways that one might be able to do that in adult tumors but it's not clear at this point. And that would have been a complete change of direction for me.

It probably would have been a much more practical approach. But I'd gotten to that point that I just decided that I wasn't going to put in the time to pursue that. In fact, that wasn't even in the kind of science that I like, which was the hypothesis, really hypothesis-driven research and rather than the screening kind of thing and looking to see what falls out. It's powerful but to me it's not as satisfying.

Christopher Canning: I'd like to go back a bit and talk to you more specifically about your involvement in the group. I like this segue you just made leading into your involvement. But, in particular, do you recall being invited and with whom were you having conversations about that? How did they get in touch with you and say, "We would like another biochemist to work in the Group"?

Dr. MacKenzie: I don't remember the specifics but I think it was probably through Rima [Rozen] because Rima was the head of group at that time. And I'm sure that it was that she and David [Rosenblatt] probably talked it over and I don't know with anybody else in the group at that time because they were losing people, Dr. Susie Tenenhouse for example. She was retiring and the group

needed some kind of size to continue as a group.

If you lose members then you're not going to be recognized as a group if you get too small especially not with this particular one. And so, I think that I worked into the group, and we argued it from the standpoint that there were three of us in folate, that David was the MD and Rima was the molecular geneticist and I was the biochemist, and I think we argued the fact that we were complementary to each other, and that the complementarity extended to the interest of this field of folate-mediated metabolism, which is a big field and covers many, many aspects.

Christopher Canning: Great. Do you recall how the funding structure worked at that time? As I understand, you had to win your separate MRC grant and then be invited into the group; do you recall that?

Dr. MacKenzie: Oh yeah absolutely. You could not be in the group if you didn't have your MRC grant.

Christopher Canning: Okay.

Dr. MacKenzie: And if you lost your MRC grant, you are out of the group.

Christopher Canning: Right.

Dr. MacKenzie: Now, the group provided some extra funding, and in my particular case, that extra funding helped in supporting technicians and then also in particular, helped because at that point I needed histology and the group established the histology support and that meant some equipment and a histology technician.

So when I got to the point of needing to slice up my little embryos to find out what was going on, that was extremely important for me. So this was expertise that I did not have in the biochemistry department and was extremely important to making progress on my biochemical research, which of course now is leading into -- I don't know what you want to call it. I mean, it was following the biology into a bigger and bigger picture all the time.

Christopher Canning: Right. You mentioned a point just a few minutes ago, too, about how you were the basic scientist in the group. There was some conversation in the group with Dr. Rosenblatt being the MD, but were there other debates going on in the group, say through meetings or through colloquiums that you held, about this conversation between the clinical versus the basic? And the only reason I asked this is that in tracing this history, there's been an interesting conversation between basic science and its clinical application.

Dr. MacKenzie: I think that's been a large part of that group, really from its inception - basic science. But I don't think that there were as many or let's say anybody probably as hardcore a molecular basic biochemist as myself in that group. I think that Charles Scriver was a geneticist and biochemical geneticist and he certainly knew a lot about the biochemistry but he wasn't trained as a biochemist from the standpoint of molecular mechanisms and that kind of stuff.

So when you call yourself a biochemist, it's a slice of a broad spectrum. And one biochemist described to another is a completely different fish. We're not all the same. And so some biochemists were more practical people, I would say, and some of us were extremely directed to the basic. But there was that play back and forth all the time, and in fact, I used to invite Charles Scriver -- I ran the medical course -- the biochemistry course for medical students for quite a few years.

I used to invite Charles Scriver to come to talk about some of the genetic errors of metabolism. He would do PKU and that kind of stuff and it was very important. We would do some of the biochemistry and set it up and then he would come and bring patients and present the patient and review biochemistry of that patient with them, and it was terrific. The students loved it. And so, I interacted over the years with members of that group well before I was a member of the group.

Christopher Canning: And you knew, obviously, what other folks were doing throughout the years? So Scriver was a biochemist; you knew of Dr. Tenenhouse's work, as you mentioned --

Dr. MacKenzie: Yeah. Tenenhouse -- I knew Susie and she was a phosphate and bone kind of person, and this was not my interest at all. But they had several themes going in that group. So the themes over time changed. But when it came time for me to join, I think one of the things for me, you know, was that you couldn't just bring together a bunch of people and say that they've got an interest in biochemical genetics if each person was working on a different, totally unrelated project, and say well, what relates to this is genetics; it doesn't really hang.

And so I think the fact that there were three of us that could make a folate group, and then my mitochondria and Shoubridge's mitochondria cross as well, although his wasn't folate but I mean he was looking at mitochondrial defects. And in the mitochondrial genome -- wonderful scientist, Eric Shoubridge, and there was a way to link this together. He was a huge, huge help to me because of his knowledge of the mitochondria and because of the technology he had developed in the lab to deal with mitochondria in cell lines.

Christopher Canning: This is an interesting segue because my next question was related to

interdisciplinarity, and by sounds of things, at least from how you're describing this, the group achieved interdisciplinary science through making particular links under the broader umbrella of medical genetics, or finding these ways of collaborating between members. Would you agree?

Dr. MacKenzie: I think yes, that's correct. And I think sometimes in the earlier days that you could have a disparate group of biochemical genetic questions, and that worked; it was fairly broad. But times got tougher in the funding field and the concept of what constitutes a group changed. You got to the point that you had to really defend that concept of the group. There had to be some connectivity where you would say, "Well, when you put it this together, what do you get that you wouldn't have to just let these people go on their own?"

Christopher Canning: Exactly, yes.

Dr. MacKenzie: Right? And I think that that was a concept that got stronger and stronger from maybe the late 90s on, where you have to now start to defend what constitutes a group and what additional output are you going to get because you've got a group. And I think the people were starting to be a bit skeptical that people might be using these groups just to get extra funding.

Christopher Canning: That's a really interesting point because one of my concluding questions is what made this group a group? But I would like to come back to that. So do you recall conversations within your group specifically about the constitution of groups previous to the late 90s?

Dr. MacKenzie: No, I don't. I mean, when I say that, it's my own opinion. I think of it as more of an opinion because I never really thought much about the group until I was approached to join it. I knew it existed. I had interacted with Charles [Scriver]. In fact, at one point as a biochemist, I even made some compounds for Charles that he was trying on PKU children, where they were trying to decide whether the child had atypical PKU, and I was making some tetrahydrobiopterin for him.

So there was that interaction from way, way back; it's probably the '80s. So I knew about the group and from the standpoint of the folate, we had a beer club, as I mentioned earlier which was basically folate/B_{12} which Bernie Cooper started before he left McGill.

Bernie Cooper with David Rosenblatt, myself, who else? Oh, Michael Whitehead. Michael Whitehead was part of that group because he was a B_{12} scientist. So there were the B_{12} folate people; David was more B_{12}. Cooper was B_{12} and folate, and when Cooper found that I had arrived at McGill from Jesse Rabinowitz 's lab, he said, "Well, why don't we have a beer club?" And so we sat around and talked to each other and mostly a lot of us didn't know what the other guy was saying. But we had this interest in

folate and that's where I met David Rosenblatt.

Christopher Canning: In his interview, he talked about this club and how you would get French bread and beer and sit around late at night talking about folate.

Dr. MacKenzie: Yeah, absolutely.

Christopher Canning: Yeah.

Dr. MacKenzie: Absolutely. And the interesting thing was that lots of times we didn't understand what the other guy was talking about. I mean, they didn't know that much about the basic biochemistry of proteins and I didn't know that much about some of the clinical stuff that they were talking about, but a little bit of it rubbed off. And we didn't miss attending. People really wanted to go to these meetings.

So I think that Rosenblatt, Rozen and myself were part of that. And I think as time evolved, and particularly as my project changed to the point that we were doing the knockouts where we could actually say, "Hey look, if this had happened to a human - were doing it in a mouse - but if it happened to the human the same effects would be seen, right?"

So it made some sense at that point for me to be part of the group.

Christopher Canning: Great, yes.

Dr. MacKenzie: I think up to that point when I was just looking strictly at the proteins and the mechanisms, it really didn't make a lot of sense.

Christopher Canning: Right. That's great. And as a matter of fact, that sounds to me like more collaboration than some of the other members. For instance, I was talking to Mark Trifiro and Andy Karaplis and often they didn't have a lot of collaboration with other members at that time. So by being part of that folate group, you seem to have a little more collaboration with folks.

Dr. MacKenzie: You're right.

Christopher Canning: In your opinion, why was this group successful for so many years -- for 37 years?

Dr. MacKenzie: Honestly, it always boils down to people. It really boils down to people. I mean, I was Associate Dean of Research in the Faculty of Medicine for almost nine years. And the one thing that I've learned in the process was that it's all about people. You can say it's about science, but it's all about the people.

And the people just make it happen. And it seems like they were the right

people at the right time, and that the group was prepared to evolve, and I think that whoever was leading the group at that time was willing to change directions to keep the funding going.

Christopher Canning: And what directions were those?

Dr. MacKenzie: Well, I think from the direction of the evolution of science and how do we go about doing science. Science started out of individuals working in labs, you know, coming out of the dark every once in a while and publishing paper.

So there's a lot of individual effort. But for our group, you need something to build on and you can have people interested in molecular diseases, for example. So it doesn't matter whether it's bone or a hormone, an androgen problem or a folate problem or a B_{12} problem. These all have biochemical genetic questions.

And in the beginning, this was phenomenal because not a lot of people were doing it that way. And so that was unique, that process in the beginning, and I think worked very, very well. But it was really more from the observations on humans backwards.

Christopher Canning: Right.

Dr. MacKenzie: Okay, and with the molecular biology revolution you can get more information - this is basically what happened to me. You can get to the place where now you have all this new technology that you can apply to a question that you couldn't have done before. But at the same time, there was an evolution in what is the concept of a group? And just having a bunch of people together because they want to talk about particular genetic defects in a broad spectrum, at some point wasn't going to fly. You could do that but you had to have a limited number of fields. You couldn't have five or six people with five or six areas. That would be seen as five or six individuals. And I think that that by 2000, that wasn't going to fly with the funding agencies because they would say, "Where is the value added?"

Christopher Canning: So you got a sense that there was some shift in the funding agencies? That was around the same time that --

Dr. MacKenzie: Oh absolutely, absolutely.

Christopher Canning: That's the same time it switched to the CIHR?

Dr. MacKenzie: That's correct, yeah, and I was heavily involved in the early committees on establishing the CIHR.

Christopher Canning: Okay, great. Can you elaborate on what this involvement entailed?

Dr. MacKenzie: The whole concept of the CIHR was to try to bring different expertise to bear on a problem. And that meant that if you want to talk about diabetes then you should be talking about people in biochemistry that are interested in the problem of -- I don't know, say islet cell metabolism, all the way up to the physician who is treating the diabetic patient and the broader sociological impact of the disease. And rather than slicing it as a basic science, but to do it vertically and try to put things together in a vertical integration for health research.

And it was possible because we had evolved so far in our understanding that we had enough understanding, enough molecular information, enough medical information and a huge technology coming forward that we're going to be able to do that. But if you're talking about that 20 years earlier, it would not have worked particularly well.

Christopher Canning: And this conversation was happening within the funding bodies?

Dr. MacKenzie: Oh it definitely happened in the funding bodies. I mean that whole concept of going from the basic to the clinical to the social, working on a particular problem, was a fundamental concept of establishing the CIHR.

Christopher Canning: Well that's interesting because even in the early applications in the 1970's, that's what the group claimed to do, that is, to take the basic science and translate that to the patient and translate that into medical treatment.

Dr. MacKenzie: Of course, but you know what I'm saying is, what was the basic science that you were doing at that point? It was nothing like we had by the time 2000 rolled around.

Yes, that was actually true and the concept was working and I think that concept basically evolved into the CIHR. But it really depended on how much of this could you do at that time. It wasn't possible to do a whole lot compared to what we can do now with all the technology, and the fact that you can actually do molecular genetics and genomics.

Christopher Canning: Is this part of the reason why the CIHR stopped group funding in 2009 and switched to team grants? Does that have a bit to do with this shift?

Dr. MacKenzie: I think that this is true -- I'm not 100% sure because I wasn't involved in that discussion. But I think the team grants tended to be even more focused.

Christopher Canning: Okay.

Dr. MacKenzie: So I think that you might have been able to -- for example, to take out the folate group, but even as a folate group, our main interest was folate/B_{12}, might not actually mean you can consider the team grant because maybe

we should have picked folate and something like coronary artery disease and then propose a team on that.

So my feeling is that the team came along because it was going to be multi-factorial, multi-disciplinary, but even more focused than a group. Because if you look at the group, I mean the group at the end -- look at the diversity of the interest in the group at the end. And you know I think that diversity was even stronger earlier on.

Christopher Canning: It seems like, towards the later years, even though there is collaboration, the individual projects seemed a little more splintered. And that's not to say that it took away from the group, but they were just more individually focused; would you agree?

Dr. MacKenzie: Well, I think that it became clear that you had to be an individual researcher, individually funded, to be part of that group. And so therefore, you have to have a strong research project and a research program outside of the group.

Christopher Canning: Independently, yes.

Dr. MacKenzie: Independently. It means if you depended only on that group for your research, I think you would not have succeeded. They would not have funded you. The requirement was, "show me your independent research" and then -- at least at the time when I come in -- "show me your independent research and that it's high quality research and that you are adequately funded". Well, we're never adequately funded but the concept was that you have funding to do your own research. And now by joining together in this group, demonstrate to me what the value added is and what you're going to get out of this interaction.

The truth of the matter is, in my own case, if I had individually established the interactions with Eric [Shoubridge] and Rima [Rozen] and David [Rosenblatt], I probably could have done the same thing except I wouldn't have had the funding to get the histology done. So the group did bring additional funding that enabled me to do stuff that I was not able to do from my own MRC or CIHR grant.

Christopher Canning: Which seems like the very definition of what that funding should have done?

Dr. MacKenzie: Yeah, so for me, that was part of the argument of what is the value added. And not only that, but you need the people with the expertise that you were then going to use in your research.

Now these will become collaborators under your grant or something like that or if you can do it in a group, it's - from my perspective - even better.

Christopher Canning: Right. Were you involved in the conversation at the CIHR when the group stopping funded, do you know why?

Dr. MacKenzie: No. I was not.

Christopher Canning: No?

Dr. MacKenzie: I was not.

Christopher Canning: How long were you involved?

Dr. MacKenzie: Well, the CIHR never ever got enough money. The concept of the CIHR was one that required a lot more money than it ever got. And so we built this great concept but the government never really fully funded it.

And so they were always looking at ways to try to spend their money better. And I think there was always some concern that groups were not really generating sufficient value added and that maybe they weren't just targeted as the CIHR would have like to have seen.

Christopher Canning: Right.

Dr. MacKenzie: So I think that this is where I see a team in diabetes or obesity rather than a group that looked at genetic diseases of a bunch of different areas.

Christopher Canning: A few concluding questions here. I've alluded to it and you've alluded to it, but I would like you to answer: what made this group a group?

Dr. MacKenzie: I guess, for me it was a group because of really -- I don't know how to say this, and I don't want to be disparaging, but for me, it was the people in the group that directly related to me that made it a group for me.

I mean, there are other good scientists in it and you've mentioned them. But the couple of guys at the Jewish General Hospital, and they were doing some interesting work, but it did not at all relate to me and I was kind of interested to hear what they were doing and it was fun stuff. But for me, that didn't really make the group for me because I never really bought into a concept of a group being multiple areas connected by an interest in genetics. That didn't make the group for me. For me, the group was folate, B_{12} and mitochondria.

And so therefore, for me, it was Rima and David and Eric and myself. So there were probably groups within the group.

Christopher Canning: Interesting. And did space or locality of the group have anything to do with these groups within the group? Obviously you're at the Biochemistry

Department at McGill, and others are on campus or elsewhere…

Dr. MacKenzie: I was on campus at McGill. Rosenblatt is in one hospital and Rima's in the Childrens, and Eric is at the Neurological Institute. But I don't think that that for me was a problem, although we know that might be a problem for the CIHR. I think they would like to see teams working closer together, that you would be a team not only in the concept of what you're trying to do but in your physical location as well.

Christopher Canning: Well, this was a conversation right from 1972. It was actually in policy in the MRC document. The group needed to be in the same physical location. The group never did come to one physical spot but were still able to maintain funding.

Dr. MacKenzie: Yeah. But you see, I think the concept of the group was somewhat more flexible at that time. And I think what happened was that the concept of the group over time became more of a team and the team has to be working on a more specific problem.

Christopher Canning: Great. Thanks for clarifying that. Are you still doing research now? What year did you retire?

Dr. MacKenzie: Oh, I retired last May, end of last May.

Christopher Canning: Okay, congratulations.

Dr. MacKenzie: And I'm not doing research.

Christopher Canning: No? Okay. I heard from -- I forgot who this was from but I wanted to ask you. I heard you were a fantastic teacher; is this true?

Dr. MacKenzie: [laughs] I enjoyed teaching and I've got some good comments and I really did enjoy the teaching.

Christopher Canning: What did you teach, biochemistry?

Dr. MacKenzie: Biochemistry. I taught biochemistry for many years to medical students. And then after that, a basic metabolism course to the second year biological sciences students, to students in biochemistry, physiology, some biology students, anatomy and cell biology and microbiology; a lot of those students took this particular course, and basically we called it "Regulation of Metabolism".

So we taught not just about the fact that there were pathways but we tried to work on the rationale of when that pathway worked. And I love to do things like – this is the particular pathway and it works wonderfully in muscle. But what if you try to make this work in heart? Would this work?

And all of a sudden you'd realize, "My gosh! It can't work that way in heart." And then you have to figure out why it's different and how it's different, how it's regulated differently and I think the students really liked that. It made it much more functional and you built a rationale for how the system works.

Christopher Canning: Well that concludes my specific questions. Do you have any final thoughts or questions?

Dr. MacKenzie: No, not really. I enjoyed being in the group. But for me, it was actually bringing together an interaction that I already had with David and Rima. I knew about Eric when I was the Associate Dean Research. And I guess I was Associate Dean when I first joined the group. I think that the group just strengthened interactions that we might have had otherwise. In fact, it was probably more than strengthen; I think that I could manage to push some aspects of my research much better than I would ever have done on my own.

Christopher Canning: Fantastic. Thank you very much for your time.

END OF INTERVIEW

Dr. Roy Gravel, February 4, 2011

Christopher Canning: My name is Christopher Canning and I'm here with Dr. Roy Gravel on February 4, 2011. It is my honor and privilege to be here with you, Dr. Gravel, to discuss two main themes regarding human genetics.

First, I would like to discuss your academic background, which contributed to the growth of medical genetics in Canada and beyond. Secondly and perhaps more importantly for this particular study, I'm interested in your involvement in the McGill MRC/CIHR group in Medical Genetics, which you joined in 1994 and were a member until the group disbanded in 2009, and which you directed from 1994 to 2001.

But before we get into the details of the group, I would like to know a little bit about you. Can you first give me an overview of where you're from, where you were born and where you grew up?

Dr. Roy Gravel: Well, I was born in Montreal and grew up partly there. I attended McGill University as an undergraduate. I attended Yale University as a graduate student. I did a Masters at McGill as well and then I did another Masters and the PhD at Yale and a post-doctorate at Yale. I graduated with the PhD in 1972 and did the postdoctoral fellowship there until '74, and then took my first position at the Hospital for Sick Children in '74.

From there, I went to Montreal at McGill and the Montreal Children's in 1989 and joined the Research Institute there and that's when I started interacting with my colleagues at McGill in terms of genetics and such.

Christopher Canning: Fantastic. Before we get into more much detail about McGill, what sort of expectations did you have growing up in terms of academic success and maybe in science in particular from your parents?

Dr. Roy Gravel: Say that -- you better ask that again.

Christopher Canning: What sort of expectations…

Dr. Roy Gravel: What's the context?

Christopher Canning: I'm just curious about how you became interested in science from, say, high school?

Dr. Roy Gravel: Well, I was in a high school which back in those days, those were the days that a fellow by the name of Khorana, who I think was in Vancouver in those early days, was starting to break the genetic code piece by piece. And this is something I was learning about in high school on sort of a continuous basis and as new data came out, we got to hear about it. And the outcome of

that is I just had a great biology class and got to learn about genetics through that and I fell in love with the subject.

I can't think categorically that I was going to be a geneticist from that point, but I certainly was interested and as I mentioned I went to McGill for undergraduate and developed my enthusiasm for genetics throughout my undergraduate period.

So in terms of expectations, I think I knew fairly early that I wanted to go into research and genetics.

Christopher Canning: And was there a particular interest in medical genetics at that time or were you just in the Department of Biology going through sort of early courses in genetics?

Dr. Roy Gravel: I think probably the real truth is that like any uncertain undergraduate, I was going to be happy to land anywhere. And in fact, I didn't land in human genetics initially. I did my masters degree in a model organism working with Etta Käfer at McGill. That was totally outside the realm of human genetics. It was quite exciting.

I did my PhD also outside human genetics. I didn't get involved in medical genetics until I became a postdoctoral fellow.

Christopher Canning: And what was that postdoctoral research concerning? I see that you were interested in B_{12}?

Dr. Roy Gravel: Yeah, as a matter of fact, B_{12} was the center point of that, but not in the kind of history you might imagine. The work I did as a PhD and master's student was in metabolism. I worked in a fungus called Aspergillus and I studied metabolic pathways. So it was very similar to what I would eventually be involved in with human disease, but a little less exciting if you want to try to cure a fungus of a genetic disorder.

Nevertheless, that was the training I had and when I went into postdoctoral studies, I joined a lab that was just in the early days of working with tissue cultures from patients. The head of the lab was Leon Rosenberg at Yale. He was certainly one of the trailblazers in the world of characterizing inborn errors of metabolism. And the studies in those days were Vitamin B_{12} metabolism and biotin metabolism.

So this is what I worked on as a post-doc, but I didn't actually return to B_{12} until I joined the McGill Group in the '90s.

Christopher Canning: And so what were you working on in between your post-doc training and the group?

Dr. Roy Gravel: Initially, I worked on biotin metabolism, carboxylases, and this was very much on related work to B_{12}, and though I left that particular area, it was in the same general pathway of metabolism. And after a couple of years at Sick Kids in Toronto, I also switched into Tay-Sachs and Sandhoff diseases, so these are neurodegenerative diseases, and we got heavily involved in those for very many years. A lot of our major work was on those disorders with a group that I joined in Toronto.

Christopher Canning: And were you recruited to Toronto to do this work specifically?

Dr. Roy Gravel: Well, the way that life really works is you start looking for a job and hope somebody takes you. So Toronto took me rather than me feeling that I was recruited to Toronto per se, but it was a place where I had applied for a position because they were advertising back at that time.

Christopher Canning: From what I understand, Dr. Rosenblatt also worked with Leon Rosenberg in the states, is that correct?

Dr. Roy Gravel: No. You're thinking I think of Rima Rozen.

Christopher Canning: Right, Rima Rozen went to Yale to work with Rosenberg; that's right.

Dr. Roy Gravel: Yeah.

Christopher Canning: Did you know her work at the time?

Dr. Roy Gravel: Pardon me?

Christopher Canning: Did you know about what she was doing at that time? Did you have communication with her?

Dr. Roy Gravel: I think she was there after I had left, if I'm remembering correctly. What is true is apparently, she spent a summer or part of a summer in my laboratory when I was in Toronto getting exposed to some of the technology we were using. And I had the misfortune of not remembering that when I met her at McGill when I joined up there; most embarrassing.

Christopher Canning: Okay. And then, how did this eventually lead up to your first appointment at McGill? So you're in Toronto at the Sick Kids and eventually you end up at McGill in 1989, is that correct?

Roy Grovel: Yeah, Charles Scriver had sent a letter around the country. There was a recruitment going on for director of the Research Institute at the Montreal Children's. I received such a letter because back in those days it would have been an actual letter; there were no emails yet and I probably set it aside the way we want to do with those many emails. He sent the second letter saying, "You never replied to my first letter. Are you interested or not?" So

this would have been sometime later, I think. But anyway, I remember that because it was sort of like, "You're supposed to answer me," whereas I probably took it as a generic letter being sent around after all.

But that one then had me thinking about it and I guess I may have felt that it was time to do other things that go beyond the laboratory bench. So I expressed an interest and eventually got appointed to that role at McGill.

So in effect, Scriver -- you might argue that Scriver recruited me there. This is part of the Children's and it was the center of what was called MRC Group in Medical Genetics at that time. Charles was the director of the group.

Christopher Canning: And what did your directorship at the Children's Research Institute consist of at that time?

Dr. Roy Gravel: Of the institute?

Christopher Canning: Yes.

Dr. Roy Gravel: It was just that. There were 40 or 50 members of the Research Institute there and I had the administrative role of supporting the research, helping it along, conducting the program, spending the money, if you like. I feel like that the funding came to the institute to operate the research programs, so that genetics was part of that along with others.

Christopher Canning: Great. And so your early work, you were working in B_{12} metabolism and metabolism in general. In the late '80s, how did your research shift to molecular biological techniques? Were you training in Toronto in those emerging techniques from say, the late '70s through to the '80s?

Dr. Roy Gravel: Yeah. Well, let's see, probably around 1980 or so, cloning had started to become entrenched in the system. The kind of work many of us did, in terms of genetic disease in children, were not easy areas to do cloning because most of the genes were expressing what we would call housekeeping proteins and such. These are proteins that might be at very low levels in cells instead of being something very prominent whereby you could isolate lots of material easily.

So the early days of cloning, some of the more dominant sorts of stories were like going after hemoglobin, for example. Ovalbumin was a big success because a lot of that protein could be available. And the general concept of gene structures was worked out; this was all during the '70s.

So when things started to open up to make it possible to go after the kinds of genes involved in inborn errors of metabolism, we got interested at Sick Kids and the genetics group there, becoming involved in this kind of area. And so we basically dropped everything and decided to start to learn how to

do these experiments. And what was really exciting about Sick Kids from those days is it was a group that worked sort of heavily, if there's a general term to use, in somatic cell genetics. And as a group, many of the laboratories were all getting excited about learning these technologies at the same time. So we were very supportive of each other and took on different aspects of these technologies to try to perfect them and then share them with each other.

So I forget the exact year, but I remember getting a grant renewed and having -- I don't know what it was, perhaps three years ahead of me where I didn't have to worry about the grant. And pulling our lab together and saying, "Throw everything out. We're going to learn how to clone." And that would have been -- I'm not sure, 1981, '82 or something like that perhaps. And the outcome of it was, we were able to get involved in cloning genes related to genetic disease as we entered the middle '80s.

Christopher Canning: Did you get the sense that McGill, the Department of Human Genetics at McGill or folks who were researching there, were a little bit behind on those molecular techniques? And the only reason I ask that is that there was a sense in the group, in the mid-'80s, that they were lacking in the same technologies, and they weren't advancing as fast as folks at Toronto were. Did you hear about this conversation?

Dr. Roy Gravel: [Laughs] You're asking me from the other side of the fence! Well, I don't know in a formal way about how McGill was doing. What did happen when I arrived there at the end of the '80s, is the Montreal Children's I think had a homemade PCR machine as one machine in the institute at the time.

In around '87 or '88, these machines that could run PCR reactions became available and we got our first one through a donation from a family at Sick Kids and it was very instrumental in cloning genes involved in Tay-Sachs disease and so on. So this was as we moved into the later '80s.

So then in '89 when I went to Montreal, by that point, we had two or three machines in the group. I can't remember what I had -- I know I had at least one; I knew at least one or two labs that had one. People were learning the tremendous benefits of being able to do this nifty reaction. This was really early. In other words, we were not -- we didn't start late. In fact, when we got involved with PCR, the machines weren't available in Canada.

So that, when we got these first releases, various places had homemade machines, but the reagents weren't available and they weren't being released into Canada. They were being, the whole system was being beta tested at several sites in the U.S. by the company involved and we just didn't get access. And I remember when we were doing Tay-Sachs research and cloned one of the Tay-Sachs genes, the access to those reagents; we didn't have that access. And we ended up having some friends in the states

sending us the materials to do these experiments so that we could get around this sort of -- all that -- whereby these companies weren't collaborating with us or sending us the materials.

In fact, I had phoned the company involved to see if they would collaborate, so that we could get access to the reagents and their respond to us, "Send us your samples. We'll do them. We'll publish them and you can be on the paper, too."

Christopher Canning: [Laughs]

Dr. Roy Gravel: And we weren't interested in that. So it was only a couple of years later really that I showed up in Montreal and looked around and didn't see PCR machines, but I wasn't a great gap in terms of where things stood. But what we did almost immediately on arrival in Montreal is we bought a whole bunch of these PCR machines and distributed them. And we had a dozen machines distributed around the institute very quickly, so catching up certainly occurred. If there was a lag phase, it would have been maybe in the middle '80s, I suppose. But that's just because different places were starting at different times in those early years.

And in our case, for example, we got excited about getting into this stuff, but it also meant we were probably running out of ideas in the traditional methods, so we wanted the move in to these new technologies. And even for me, it's coordinated with when the grant was funded. I wouldn't have taken the risk in the year before the grant was due, say, to turn my lab upside down and start all over again.

Christopher Canning: Right. Do you think that your experience in working with the PCR machines in Toronto was part of the reason Scriver was interested in you coming to McGill?

Dr. Roy Gravel: No. I don't know why he was interested, but what I'm describing to you would not have been something he'd have been aware of it I would think. I mean, I don't know. We were cloning genes; it's possible but we never had such conversation. I think I was the guy hanging out about, but I can't say more than that.

Christopher Canning: Well, in a document I obtained from Rosenblatts' files, there was a conversation within the group in the mid-'80s where they were seeing who was doing these techniques in Canada, and your name was on this list of potential people to speak to about coming to McGill. I don't know if you knew about that.

Dr. Roy Gravel: No. The only awareness I had was getting this letter and I didn't see myself that it was sent specifically to me. I thought he was just sending the letter around the country. And I'm a geneticist, I do metabolism, I certainly knew

him. So I would have been on a list by happenstance. So I didn't take it too seriously, which is maybe why initially I didn't really respond because I didn't see myself in that kind of role and it was only after he tweaked it again, I started thinking about it. And said well, I'll visit, and then when I visited I felt -- when I was at Yale looking for a job in Canada, I wanted to come home. McGill was certainly on my mind and there wasn't anything available. But I was aware of the group there. I thought they were pretty exciting and I was actually disappointed that I didn't have access in terms of being a job applicant at the time. So to hear from Scriver was quite a compliment in those terms.

Christopher Canning: Absolutely. Before we go into specific questions about the group, I'm interested in two things. What specific -- you mentioned Tay-Sachs, but what other specific human diseases have you been looking at, say from the start of your career until where you are now in Calgary?

Dr. Roy Gravel: Say that again?

Christopher Canning: What specific diseases are you looking at now and have you looked at from the start of career from the early '70 until now?

Dr. Roy Gravel: Wow. Well, currently, I work only on B_{12}. I'm coming to the end of my career, so in the last few years, I started cutting things out so that I could focus more heavily in certain areas. So when I arrived in Calgary 10 years ago, I was working on Tay-Sachs disease, biotin, B_{12}. I think that's all. At least those are primary things and in terms of funding and such. In the middle part of the decade, say 2004 or 2005, I decided it was time to phase out Tay-Sachs disease so that I could focus on vitamin metabolism. And then a couple of years ago, I decided not to renew my biotin grant because I felt I'd be entering the last phase of my career and decided that I should try to exploit whatever research area was most exciting, well, what had the best chance to yield interesting things, and that was B_{12}. So for the past two years, I guess, I've been working exclusively on B_{12} metabolism.

Christopher Canning: So you've kind of made a full circle then back to where you started?

Dr. Roy Gravel: That part is certainly true. The reason for that might be interesting to you. The reason I went back to B_{12} wasn't because I wanted to make that circle. David Rosenblatt came to me one day and said, "You know, you are set up in Montreal, you work on B_{12}, we work on B_{12}. Join the team. Come and play." And it sounded kind of cool and so we got interested. So my return to B_{12} wasn't by intention; it was actually having these chats with David.

Christopher Canning: Okay. That's an excellent segue into my next series of questions. The first question is, can you explain the process in terms of how you first got involved with the group?

Dr. Roy Gravel: David said -- no, actually, I don't know. Somebody said, "You know, would you like to be director of the group on the next application?" What happened when I came to Montreal, I recall somebody asking me if I was interested in joining the group and I had just arrived. And at that time, I don't remember if there was a grant involved in terms of renewal or anything. But at the time I said that that wasn't a good idea, because I had just arrived; I'd never headed anything before and probably people figured that out pretty quickly. But I was now facing this institute and with a massive piece of work, certainly in the first couple of years, to learn how to do that kind of stuff and of course get my lab going and all those things.

So, at the time, I just said, "You know, this is not a good idea. I wouldn't be very much of a participant because I really hadn't the time. The reason I was there was to run the institute, so I've got to do that first and foremost." And then, couple of years later, I was asked if I was interested in joining the group and acting as the director for the next application. I suspect David was probably the guy that came to me, but I don't really know for sure, I don't remember very well. But in terms of lab, I was nearby Rima Rozen, but in terms of this kind of conversation, it very much likely would have come from David.

Christopher Canning: From speaking to other members, it seems that the group wanted to keep the directorship at the Children's Hospital. So it's not surprising that it went to you and then to Rozen, because you would have just taken over after Scriver in 1994.

Dr. Roy Gravel: Yeah. But, the mechanism was me joining the group, right? I wasn't a member prior to that point. So I joined with the idea that I was to act as the PI of the grant, which still may have been what you're describing. But I mean, there's no doubt they wanted it to stay at the Children's; I remember that. With Rima, it was a logical outcome. When I left, she had become very senior, very prominent in the field she was in and of course, as you would know, she became the director of the institute after me. She took over. She was very logical as the next head of the grant. Partly, she was at the Children's, but mostly, from my perspective at least, she was very much the right person for the role and for the reputation she developed in her research.

Christopher Canning: And what role did the other members of the group play during your time there? Can you recall? In other words, what were the different areas of research and how did you see that contributing to the group?

Dr. Roy Gravel: Well, you're asking something I have not reviewed, but we made an experiment initially. I think it was with the application that I was part of to bring in a group of people from host resistance side. Emil Skamene was already with us and we proposed to add Danielle Malo, along with Eric Shoubridge and Joe Nadeau. We wanted to expand the group in novel

directions and this was in fact an extremely good group of people.

But generally speaking, we had a diversity of science, not just scientists, but mature science in terms of the different kinds of genetic disorders that were being studied. So when you think about bone and phosphate versus the metabolism at the level of vitamin B_{12}, these are very different; they're very different in the approach.

So moving into host resistance was kind of a neat thing and Emil Skamene was essentially the leader of that group and we put all this together. I think the end result -- what I can't recall specifically is whether we survived at all. But the end result of it was they were -- we ended up splitting up because, I guess the MRC, or I think it was still MRC or CIHR didn't see that as a cohesive structure.

What we saw in it was that we had very different kinds of thinking going into the nature of genetics that we were doing; that was to our mind, quite exciting. But the key thing that's worth remembering here is that we had a core group of David [Rosenblatt] and Rima [Rozen] and ourselves studying B_{12} and folate and we were very integrated in the nature of that work. But the truth is, the group was really made up of a diversity of different kinds of areas and the large group of people that you know about reflected that, and we were just the kind of small cohort that tended to work closely together.

Christopher Canning: And that cohort being you, Rozen and Rosenblatt?

Dr. Roy Gravel: Pardon me?

Christopher Canning: That cohort being you, Rozen and Rosenblatt?

Dr. Roy Gravel: Yeah, yeah.

Christopher Canning: And what did the leadership entail? I see that -- or the directorship, you were the director for almost eight years. What did that entail as part of your role?

Dr. Roy Gravel: Gee, I don't remember. [Laughter] I mean, the most important thing I guess you could say is, the idea that a director had the responsibility to get that grant renewed and one has to think in a forward way when you're writing a grant. You use your progress as your anchor for demonstrating that you've got the ability to do these things. But what gets you funded at the end of the day is what you're going to do tomorrow.

And we would meet to discuss this, what kind of playing field are we trying to set up for the future and what will sell with the grant reviewers. And we had a really good group to think about those things because of the issues of our research programs, of course, but also training and the activities that we

held all played into this. We would get site visits as part of the review process and had to defend ourselves before other people asking us questions. So a lot of the leadership related to sustaining the group at these periods when you're writing the grant proposal, and the same applied to Rima subsequently.

Beyond that -- the in between part of it, it's really important to be talking research and thinking about it and interacting, but in an informal way, I mean nobody needed instructions, so to speak, or supervision or anything like that; that's not how it worked. So now we're talking about just doing research, focused on our own things for sure, and so again, this little group with David and Rima tended to be much more closely aligned than we would be with the other groups. But we had graduate programs together, teaching to some extent and those kinds of interactions and within the Children's Hospital itself, the institute.

So the extent to which one interacted depended on the activities we were involved with.

Christopher Canning: Right. Do you recall the physical location of the group ever being discussed? And the reason I ask that is that, from the early '70s until the '80s, there was a discussion from both the group and the MRC that everyone needed to be in the same physical location.

Dr. Roy Gravel: Yeah.

Christopher Canning: And obviously, that was never the case because, of course, you're down at the Children's, David Rosenblatt is up in the Department of Human Genetics, so everyone is kind of all over the place.

Dr. Roy Gravel: I don't remember what was the sort of test. But this issue, I do recall the issue existed. The argument that a group had to be working together in a common space, we'll call it, that is, within reach of each other, and it seemed to be an issue at the MRC level that somebody might be in another part of the campus. That was overcome, but I don't recall the circumstances. To my mind, it wasn't us. That is, we weren't the test case; it seems to me that came up independently, although I don't really know, I just don't remember. But it was by that point acceptable and that wasn't an issue. The issue that affected the host resistance group, which of course were geographically separate, they were elsewhere. But what separated them from us in the eyes of the MRC was the nature of the science. They just saw that it was quite different from what the rest of us were doing. What we saw in it was that, this was an excellent group of scientists that we wanted to interact with because they were excellent and they told some wonderful research stories that we really enjoyed.

So the scientists sometimes want to get together because they're going to

be excited about what they're doing. Not specifically because they need a technique or they're working off the same grant or something. And so we saw the MRC group as synergistic as a bunch of people thinking about their science together.

Anyway, the geography somehow was an issue. It was oddly an issue. I think in the current day and age, we would consider it a non-issue because, of course, these groups now are multi-centered over the country. When I left McGill, we had to ask permission for me to stay in the group of the CIHR. And by that point, it was no longer an issue at all. So we had permission for me to be this far away in Calgary without having an impact on the group.

Christopher Canning: That was actually my next question. How did the group look in terms of collaboration while you're in Calgary? Obviously, you were previously the director, so what --?

Dr. Roy Gravel: Say it all again. There's still break up…

Christopher Canning: You're on speaker on my cell, so it's probably a bit of an issue. Anyway, my question is that, and you sort of alluded to this is, what was it like once you moved to Calgary and what did collaboration in the group mean at the time, post-1999 when you moved off to Calgary?

Dr. Roy Gravel: Well, first of all, the principal links now were much more Rima and David and I, right? In other words, with me this far away, my interaction with other members of the group would have been considerably diminished by comparison. And that was out of the necessity of the research. The reason I had such strong links with David and Rima is we were collaborating together in various ways. So, we shared grant support, grant involvement independently of the group. We had an NIH grant, for example, that we applied for in the '90s that the three of us were all part of together. So we had a motivation beyond the group to accomplish research in this B_{12} and folate area.

So that continued into the separation to Calgary and it was fairly transparent in that sense. We could continue working together. And I still, in particular, work with David in terms of research collaboration. Less with Rima, although we had a grant together, I think, until about the same time the group ended in 2009 where we were actually formal collaborators.

So, the link -- the relationship that I had with the group after coming to Calgary was manifest by virtue of the collaborative research we were doing in other contexts. I mean it was the same context that's originally existed in the group, but what I mean by that is we had specific research funding that went outside the group and directly on operations in our folate and B_{12} work. The group, you maybe aware, evolved from a group that was funded to do the operations of research, core facilities, training programs, all of this

other stuff in the way it was originally formulated in the '70s. But eventually the CIHR, the MRC, changed the mandate of groups to be more core grants rather than operational grants, and people were expected to have their own independent grants to run their research programs.

So after I came to Calgary, my access to the group was in "my share of core functions", which was awkward because for example, if the group had a core function related to animal facilities, well my facilities would be in Calgary, not in Montreal. So that was solved by providing me with some research funds to displace what I would otherwise have been benefiting from in Montreal. And in particular, it supported my animal work, which was related to B_{12}.

So the nature of the group changed in that respect to not having a such an integrated research interaction because the MRC or the CIHR later actually changed that for us by having a requirement for independent grants.

Christopher Canning: And I was just talking to Dr. MacKenzie the other day who was on the committees during the change over from the MRC to CIHR in 2000 and he stated the same thing. And it is great you mentioned that because that's one thing we're investigating: the change in funding structure, which happened around the same time the MRC switched to the CIHR in about 2000, where individual members needed to hold their grants first and then apply to be included in the group. Is that what you're saying?

Dr. Roy Gravel: Yeah, that's what they did. And the reason for it I remember fairly well, the problem that one has and you could sort of see this. You form a group and you've got let's say, 10 members in it, and you make an application for a renewal and you have a diversity of talent. So some of the talent is exceptional and some of the talent is not so exceptional in the eyes of other regular competitions. In other words, if all those people went in as individuals, would they all get grants?

Christopher Kenning: Okay.

Dr. Roy Gravel: And just on a probability basis, the answer is no because CIHR in those days was funding at, I don't know, 30% to 40% success rates, and a lot of people with perfectly wonderful research programs weren't getting funded because there just wasn't enough money to go around to permit that. But the groups where immune from that; if a group got funded, everybody got funded. Boy, that did not make the people outside groups very happy.

So there was a fair amount of turmoil over these kinds of issues as money became scarcer during the '90s. The CIHR was formed to try to create new ways of raising funds and justifying the existence of such an agency to parliament to try to command descent budgets. But the reality from the investigator point of view was things at the funding level didn't get a whole

lot better. Structurally, the CIHR is a better organization and money has certainly increased over the years. But, if you match it up to the inflation in science and everything else, you probably won't get people saying that the CIHR is really well funded.

So, in the '90s, when all these sorts of things were happening, the groups really had special status being, in a sense, immune from some other rougher parts of competing for research support. So it was solved in the way Bob MacKenzie had said to you, that the decision was made that individual members of groups, and there were quite a few groups out there, would have to obtain their own independent funding, be reviewed through the regular system, and survive it in order to be retained within a group.

And I think that diminished the groups, but probably it was a fairer system. It diminished the groups because our group working together to become funded is also working intellectually. I mean, one of the more creative times you might say that people will have is when they're trying to get that grant renewed because we're really thinking forward.

And then, you suddenly lose the importance of it if you have to apply independently for a grant; what you're discussing now at the group level is a core grant or how to get the core renewed, not how to develop research programs that will excite the reviewers.

Christopher Canning: How did you know about these discussions in the '90s, then? Were you involved in committees on the MRC or the CIHR?

Dr. Roy Gravel: No, no. We were all gripping! [laughs]

Christopher Canning: [laughs].

Dr. Roy Gravel: So people talked in this way. I think it was just the regular scuttlebutt out there. In fact, I was not involved at all at the CIHR level in those days. So I think this was a general conversation and the other thing that existed in those days were the genetic diseases networks, Networks of Centers of Excellence programs, and there were similar complaints about those programs that they had special status and so on.

So, the turmoil of the day of the individual researcher versus groups, groups became much more prominent through that period or maybe in the '80s until the '90s than they had been beforehand and so produced these kinds of debates. Nowadays, research is widely recognized as being very difficult on the individual basis and there are a lot of structures for groups to work together, so we passed that. But, that period was the period when the discussion had to be out there where people were discussing the best way to get research done and to acknowledge the quality of individuals.

Christopher Canning: Right. That's excellent. Thank you for mentioning that because that's one of the things that we're definitely interested in, this sort of change in the funding structure. And that's actually the most comprehensive description we've heard of it. So, thanks for that.

More specific questions about the group, how are you doing for time? About another 20 minutes, half hour, are you good with that?

Dr. Roy Gravel: Yeah, I'm okay.

Christopher Canning: Okay good.

Were there divisions in the group, as far as you could tell, between basic science or the bench and clinical work and what sort of discussions were happening throughout maybe -- even your time as a geneticist, but more specifically during your time in the group. What is this discussion happening throughout sort of your work in medical genetics?

Dr. Roy Gravel: If I'm understanding the question, you're just asking where we fit in to basic versus clinical?

Christopher Kenning: Yeah, and what conversations were happening in human genetics about this conversation between bench and clinical work.

Dr. Roy Gravel: Well, maybe I can comment on that in a more -- my own career sense and personal sense and it even continues to this day as an issue.

Well, this sort of gives you the origin of it: I'm studying metabolism in a fungus, and of course, there's nobody to cure, and I switched to human cells in my post-doc days, so I did B_{12} metabolism and there is somebody to cure. But it's all metabolism. I'm studying genes -- well, in those days, genes hadn't been quite invented yet. So the concept was genetic diseases, but studying them at a level of metabolic blocks and proteins and things.

And, from the point of view of doing it in a fungus versus doing it in a human cell, I mean the methods are obviously different just because of the organisms involved, but the intellectual thinking about it is very, very different. When I was studying fungus, I was perfectly excited about doing metabolic disorders in fungi where of course what that really meant was I made mutants and then I tried to figure out what I made.

When you make the transition to human cells, at least for me, and to patients behind those human cell cultures as you know with genetic disease, it was a night and day change as you might imagine, and I became very much more involved at the medical level. As a post-doc, I was able to go on rounds, see patients who had these disorders. I took a very active role in a program that was essentially designed to train post-docs to understand the

relevance of what they were doing to the patient population. So this is very, very effective and very exciting and this was all Leon Rosenberg doing this.

So, first of all, I developed the appreciation that my role was to understand genes and proteins and mutations and all this stuff in the context of the patient. I was still a guy at the laboratory bench, not in the clinic; I'm not an MD and didn't participate that way. But when I went to Toronto, I went on rounds, I participated in rounds with people dealing with metabolic diseases and continued in the sort of thing I had been trained in and found that very exciting.

So for me, the relevance was the clinical applications, but I didn't participate directly in delivering it, but I participated in trying to understand it. So seeing humans, human subjects, patients, was part of my early years. That dissipated over time. I became much more involved at the bench, but I've always studied genetic disease. I've never studied any science outside the fact that it was involving diseases in humans. I've switched organisms when it was appropriate to have model systems to study those things. So I studied in mice and I studied in C. elegans, which is a small worm and I do that now by the way.

So in Montreal, Montreal as seen even from Toronto, it had the reputation of being the place where metabolism was the center of the universe. I mean I wasn't in a place in Toronto where metabolic disease was the name of the game. Toronto was the center for somatic cell genetics and by the nature of that field by the way, it had a lot to do with why it could jump into the cloning game a little earlier because the tools were more suited. But Montreal, through Scriver and Fraser before that, they were seen as truly the place you go to do metabolism in patients.

And my early interest in that place was because of people like Scriver, I mean as an undergraduate I never had a major course with them, but I was certainly attending lectures and stuff with Fraser or Scriver or other people presenting that work and me getting very excited about it. But it was always oriented towards the patient.

So in the group, it was a mixed bag. I had evolved into a person who dealt at the bench, but I was trying to clone genes involved in genetic diseases in children. But other people in the group, certainly Scriver and Rosenblatt and such, they were delivering medical care to those varied patients and it was at a different level. And I think that continuum from guys like me at the bench to what people did in terms of seeing patients is what kept the sense of why we're doing that stuff there. I've never thought of my science as being independent of the application to the patient. So that stays to this day, but it was very much the nature of the game in Montreal.

Christopher Canning: So you've always had this sort of translational orientation to your bench

work?

Dr. Roy Gravel: Yes, but never delivering it, right? I'm the guy in the backroom solving a problem if I can so that somebody else can deliver it.

Christopher Canning: Well, it's interesting -- sorry to interrupt. It's interesting that you don't have an MD and yet you were still included to go on rounds at the Sick Kids, which -- that's actually the first I've heard of it as a scientist being included in these clinical environments.

Dr. Roy Gravel: Yeah. Well, there was a fellow there, Andrew Sass-Kortsak. He studied disorders related to liver, Wilson Disease as an example. And, I don't know how that came to him, but he became a kind of mentor to me and he's a guy who hauled me off to rounds and of course since I'd participated that way in the States, I found that very exciting. But, maybe all they were doing was tolerating me, but I really got to learn a lot through that process.

Christopher Canning: Shifting gears a little bit, and this is a broad question and I don't know how much you want to speak to it, but in your opinion, why was the MRC/CIHR group so successful for so many years?

Dr. Roy Gravel: Charlie Scriver.

Christopher Canning: Can you elaborate on that?

Dr. Roy Gravel: Yeah. I think Scriver had a sense of where we were going. In other words, we weren't always caught in the present. The way to think about research activity is that you need a dynamic component to it to sell it. If I'm writing a grant proposal, the goal is to show some great progress, show some wonderful experimental design that I can answer questions for the future and so on. But that doesn't mean the reader will be very excited about it. The excitement is no different than if you're reading a novel. I mean you can take a novel and not be able to put it down or you can take a novel and not get past the first page. So there's an excitement, a passion to what you're reading to sustain the interest. When you write a grant proposal, one of the things you really have to think about is having the reader – the guy that's reviewing it, be excited by what you're doing.

Well, Scriver -- I don't know, he just made this world that we were in, in terms of his group or -- I don't mean this on one-on-one basis, I didn't necessarily see him. We were in different buildings at the Children's. I just mean that he had an aura about what we were doing that was very special and made it very exciting.

Christopher Canning: Even after he left the group in the '90s?

Dr. Roy Gravel: He didn't leave. [Laughs]

Christopher Canning: Well, I guess he was still around. I guess he stopped participating in the group as a member, but…

Dr. Roy Gravel: Charles was there right through to my departure anyway.

Christopher Canning: Okay, which was in 1999?

Dr. Roy Gravel: Yeah. The other thing is I trained with a guy, Leon Rosenberg as I mentioned, who had a very major role in establishing the science of inborn errors of metabolism, and he was very successful at it. Charles was very much exactly that as well and I saw them in similar fashion with respect to that. I can only put a handful of people in that category.

Christopher Canning: So you would say that Scriver created a sort of spirit or aura around the group that ensured its longevity?

Dr. Roy Gravel: Yeah. I mean, I think so. That's a tough one to say because on a day-to-day basis, that's not -- you couldn't really say it that way. I think that he had the communication ability and the passion associated with it that was contagious and certainly affected guys like me, and from that point of view, yes. But it wasn't that he said something to me or we would have a research conversation or something like that. There was nothing going on that was any different than any other everybody is busy sort of stuff. It's just that he really did command a -- he was -- the only way you can describe it is that he was the center of the universe for metabolism in this country and it was great to be in the same place to do work.

Christopher Canning: Fantastic. At the symposium last November, Scriver mentioned that the group always operated as a grassroots organization, as a grassroots group, meaning it worked from the bottom up. As a sociologist of science, I found that to be a really interesting comment and I'm just wondering if you can speak to that. Do you feel that the group operated from this more organic grassroots way as opposed to being say directed from above?

Dr. Roy Gravel: Yeah. That's another way of promoting anarchy. [Laughter] He didn't tell us what to do or where we were going or any of those things. I think the idea which is certainly, very, very true in science, you can't tell people what to do for the research. What you can do is encourage them and that's what Charles did. So the grassroots was the decision-making process, the discussions which we turned on, the whole kind of thing was up to you. Everybody did their own thing.

So we therefore generated the interactions, we talked to each other in a chaotic sort of way, which is to say that the group did not define our behavior; that is -- he wasn't -- to the extent that he was in charge of the group, he didn't tell us how to behave and what direction we were going to

take in the science or any of those things.

And earlier when you were asking me what the role was that I had in terms of the group, I had a hard time answering it outside the grant comments because there was no directing the group in any way. And I never thought of it in terms of having a policy of grassroots as our structure, but I guess you could say that. It's just that it just moved along according to its own random motion. It's important to think about that because these days, we get so much top down direction from our universities, from the government, from the people who are funding us about what we should be doing and how we should be doing it, why we should be doing it and so on and so forth. I think it undermines the potential for successful science.

And, in particular, when universities or governments tell us what research they will support, "We want research in this, we want research in that," you count papers or you count successes in various ways. We've reached this kind of quantitative approach to evaluation through annual reports, all those sort of stuff. I watched it happening here and it certainly happens elsewhere that I think it takes away the opportunity for people to be creative because they're out there doing their share of counting beans. None of that existed through back then. I don't want to make the CIHR group sound like something special in this way. It was just the normal behavior and these weren't the issues.

I would not have expected to get a knock at my door from Charles who would say, "You hadn't published a paper in the last six months. Maybe you should do something about that." That's not how science succeeds. It's the encouragement.

Christopher Canning: So in that sense, the group operated exactly the way he said it did in this grassroots, organic way.

Dr. Roy Gravel: Yeah. Except giving it a label, it's probably the wrong thing to do.

Christopher Canning: Right. Fair enough.

Dr. Roy Gravel: The group just simply did their own thing and as a result of that, we had the fortune to survive for such a long time.

Christopher Canning: I'm going to ask you what might be a funny questions following from that then: what made the group a group? What was its groupness?

Dr. Roy Gravel: Boy, I tell you, at every grant review, certainly to the extent that I was aware in the couple that I was involved with, that was always a question. And it's addressed at two levels, right? The first is the one where you don't have a formula involved: why are you a group, why we feel like being a group, or we have an opportunity to do something better as a group than we do

individually. That part of it is just the opportunistic side. The other side is the reviewers are looking at us as a group and saying, "Okay, where's the groupiness here? What are you doing to be a group?" And I think that's how we lost the Skamene arm of the group because [the MRC] couldn't fathom that.

But what I know from some the people I work with is you're influenced by your environment totally, and what I mean by that is by landing in Montreal and having Rima Rozen down the hall or David Rosenblatt there, I ended up in B_{12} metabolism. I wouldn't have otherwise. I got involved with making mouse models because [Jaquetta] Trasler, who actually became head of the institute after Rima, because Trasler was a couple of doors down and was a mouse person and I got to learn about mice.

I came to Calgary and the guy next door was a microscopist and I got heavily involved using microscopes. You see what I'm getting at?

Christopher Canning: Absolutely.

Dr. Roy Gravel: The nature of the group, the happenstance of interactions that occur, and the group acting like glue to make that easier to come by because we were grouped together, therefore, we talk to each other. But, the real story behind interactions in science is who you bump into. And my research, I have to tell you, has been very, very directed by who my neighbors were, getting excited about different things that other people are doing and why not do that myself.

Christopher Canning: I can say the same thing from my field in sociology showing up the different places, people have different ideas. We have the same shift, so I think that's great, yeah. What do you think are some of the major breakthroughs or advances in medical genetics offered up by the group throughout its time? Or in other words, where are we headed now based on the research that everyone has done, which has been obviously superb in many ways. Where are we headed in terms of medical advances in human genetics?

Dr. Roy Gravel: Well, I think that the field moves faster than the individual, so though this has been a highly productive group it is only part of a much bigger effort. It has made a contribution to the field that by the effort of some of the people involved has been very profound. And also, what I see by the nature, the nature of the contributions by some individuals -- I'm thinking of guys like Fraser and Scriver in particular -- go beyond the experiment, go into the world of what genetics is all about towards us as people. They've had a much bigger contribution, in other words, broader contribution than just in the laboratory.

And of course treating patients; I mean, treating patients with genetic disease is a tough one because you get a constitutional problem, that isn't a

broken arm that you can mend. And, what we've seen over the years, certainly in the time that I've been involved in genetics, is surprisingly the capacity to treat patients with genetic diseases has really evolved.

So having said that, what I'm describing is having a bunch of scientists with some specialty who have contributed in a specific way very successfully over long careers in their particular fields. And it's fair to say that some of that has been synergistic and the group, through the existence of the group, has made the science go better. But I'm more inclined at least for me to think that the existence of the group has given direction to the science. Certainly, in my case, that might not have been what always occurred. So our depth of interest in B_{12} has come from my interaction with Rima and David.

So having said that, where is all of this going? I think that's the broader issue. The breakthroughs in technology and in terms of the science that occurred, the human genome project, these are the very big things that have occurred that have turned this whole science upside down and are changing the way we think about it, they're changing the health delivery side of it very, very rapidly. No individual group or scientist can take the credit for that; that's a whole field that has done that.

Christopher Canning: Great. How much longer do you have left in your career?

Dr. Roy Gravel: [Laughs] I'm being asked that all the time.

Christopher Canning: [Laughs]

Dr. Roy Gravel: This year I turn 65.

Christopher Canning: Okay.

Dr. Roy Gravel: So a couple of days ago, I received an envelope from the government that looked like it was from the taxman, but it was from something called Services and I'm going, "What the hell." And I opened it up and it was advising me that I was now eligible to start my pension. [Laughter] So that's a little on the premature side. And, I have a couple of research grants operating right now. One ends next year and the other one ends in 2014, so I tell my employers here that somewhere in that frame of time, I'll probably sail into the sunset, but it's an indeterminate thing. But yeah, I've got a couple of years left in me.

What I am doing is I've made a shift in my research. I've got to tell you the one other thing that makes science really exciting is that it's sort of like forever playtime and the real challenge to scientists is the question or trying to solve a puzzle. And then, you don't stay at the same puzzle forever. You change what you're doing, you change the way you're doing it and the beauty of what I'm involved in is the technology that has evolved so

dramatically over my career means that there's never been a lull at all. I mean, there's always something new to learn to try a new way to do stuff and the same applies to the research domain. We've cloned a number genes and in different fields and it's been the challenge of the puzzle.

So when I told you that I decided to focus on the B_{12}, it's partly because as I said, I'm ending my career. But I wanted to focus on B_{12} because I wanted to find that next level that I could go to. I'd love to say because I'm trying to make my contribution to science, but the real truth is, it's just a blast to do it. And I also mentioned to you that my neighbors affect me. Well, in this place, I've got a whole bunch of neighbors who work in model organisms: fruit flies, zebrafish and C. elegans and it turns out that when we were cloning B_{12} genes, we found that C. elegans that I mentioned is a nematode, it's a microscopic worm. They have a human B_{12} pathway. They have genes that by sequence are homologous to the human genes.

Christopher Canning: Wow, interesting.

Dr. Roy Gravel: And they have virtually every one of the B_{12} genes, all but one that we know about. And one of my great curiosities is, are there any more genes involved in B_{12} metabolism that we've missed? Because in the period of the group and research and the interaction and so on, we've been able to see every gene identified in humans. Well, sorry, I shouldn't say it that way. Every category of disease related to cellular B_{12} metabolism identified in humans, the genes now have been identified. David Rosenblatt has been a piece of every one of those clonings of the genes, for example. And so, my curiosity was, "Well, okay, we've run out of patients, so how do we find out if there's more genes involved? What do we do? I mean where do we go for that?"

And because we saw that C. elegans had all of this human pathway and we can squish and make extracts out of C. elegans in ways we can't even imagine being able to do with human cells and so on. We had the bright idea to go after more genes in C. elegans. So my last grant, the one that's going to run to 2014, had a great emphasis on use of C. elegans as the model organism to solve B_{12} metabolism. So we've been growing C. elegans for the last couple of years and have some hands-on novel aspects to the pathway through that.

So it means the research has evolved yet one more step and I really want to get through that project before I retire. So I'm going to hang around until we beat up C. elegans sufficiently to yield all the secrets.

Christopher Canning: That sounds great. So new novel pathways in the metabolism or new genes that might contribute to the understanding of B_{12}?

Dr. Roy Gravel: Well, in other words, their missing parts. These are the genes to identify in

the end, defining the metabolism of vitamin B_{12}, that is, how we process the B_{12} to make it a useful cofactor in us. The interesting thing about vitamins and certainly about B_{12} is it's not useful to you if you just swallow it. It doesn't act in the form that you're ingesting in terms of its activity. In fact, it's got to be metabolized and converted to different forms and delivered to different places and there are many, many genes involved in that.

Christopher Canning: I see.

Dr. Roy Gravel: And so, the issue is for humans, I mean for my interest in the pathway and for David's is to figure out all the steps involved. And the patients that have been catalogued into these categories that I referred to, they're called complementation groups and David had been the major player in that. These complementation groups, in each case, yielded the gene. A category of patients was defined by the fact that they all had mutations in the same gene.

And so, about eight genes were identified through this and still more are coming. And in our case, we look at the gaps in the pathway where we haven't got a gene identified, but we might predict there would be one and we don't have patients to be able to help us decipher it. So we're saying, "Well, how can we find these?" So we decided to go to C. elegans as a place where we could disrupt genes and do experiments to try to figure out what these additional genes might be.

So we're just looking for the missing genes in the pathway that have yet to be identified, in finding them to then use DNA sequences to identify their equivalent partners in human cells and then we would be back in the human and identify those roles.

Christopher Canning: Fantastic. Okay, that concludes my questions for today. Thank you very much for your time, Dr. Gravel.

END OF INTERVIEW

Dr. H. Susie Tenenhouse, February 8, 2011

Christopher Canning: My name is Christopher Canning and I'm here with Dr. Susie Tenenhouse on February 8, 2011. It is my honor to be here with you, Dr. Tenenhouse, to discuss two themes regarding human genetics. First, I would like to discuss your academic background, which contributed to the growth of medical genetics in Canada and beyond. And secondly and perhaps more importantly, I'm interested in your involvement in the MRC/CIHR Group in Medical Genetics, which you joined as a post-doc in 1972, as a PI in 1981, and were a member until 2004, making you one of the longest standing members of the group during its 37 years.

But before we get into the more specific questions about the group, I would like to know a little bit about you. To begin with, can you give an overview of where you're from, where you were born and where you grew up?

Susie Tenenhouse: I was born in Montreal, Quebec, went to Strathcona Academy, and completed my B.Sc. in honors Biochemistry in 1961 and M.Sc. in Biochemistry in 1963 at McGill University. I should mention that after my B.Sc. I was accepted to McGill Medical School. However, I chose to enroll in the M.Sc program instead because I married Alan Tenenhouse in 1961 and thought that a research career would be more flexible and compatible with married life. Our first daughter Lee was born in 1962.

: After my Master's Degree, which dealt with the active allergenic component in green coffee beans under the supervision of Dr. Alec Sehon, I moved with my husband first to the Madison, Wisconsin and then to Philadelphia, Pennsylvania where Alan pursued post-doctoral training with Dr. Howard Rasmussen. (In 1965 we followed Dr. Rasmussen to the the University of Pennsylvania where he became Chairman of the Department of Biochemistry.)

At the University of Wisconsin I was a research assistant in Dr. Harold Deutch's immunochemistry lab for two years. In Philadelphia I was a research assistant in the immunochemistry laboratory of Dr. Fred Karush. I gave birth to a second daughter Ruth in Philadelphia in 1965.

Christopher Canning: Great, yes, I see on your CV, this would've been 1963 to 1968.

Susie Tenenhouse: When we moved to the United States, we obtained green cards, i.e. we had immigrant status. We thought that if the opportunity presented itself, Alan would accept a position there. But it turned out that because of the Vietnam War and the fact that he had an MD degree, Alan was drafted into the US military. We were not aware that as immigrants we had the privilege to serve the country.

At that point we left the USA. The University of Pennsylvania had lawyers on site who were able to help people like my husband leave the country legally. Alan was fortunate to obtain a position as Assistant Professor in the Department of Pharmacology at McGill University. It was at that point that I decided to pursue a PhD degree at McGill. So, in the fall of 1968, my daughters registered for nursery school and grade one, respectively, and I for a PhD program in the Department of Biochemistry.

I did my PhD with Dr. Murray Fraser on the characterization of ribonuclease activities of two novel Neurospera Crassa nucleases, one with exonuclease activity and the other with endonuclease activity. These enzymes were of great importance in determining the primary and secondary structures of DNA and RNA in the days when molecular biology was in its infancy. I therefore gained knowledge in a new area of research and completed my degree in 1972.

When I was considering my postdoctoral training, I was eager to get into an area that was more clinically relevant. I also had to stay in Montreal. Dr. Scriver's group in Biochemical Genetics looked extremely interesting to me. After meeting with Dr. Scriver, I was accepted as a post doc in his lab and arrived there in September 1972 with my own MRC post-doctoral fellowship.

Christopher Canning: I'm just going to step back of it. What got you interested in the medical part of genetics, then, if you were coming from chemistry and biochemistry? What was your initial interest in applying genetics to medicine?

Susie Tenenhouse: Although Dr. Scriver's team worked in genetics, they were using biochemical approaches to answer their research questions. I was therefore going to be using technology that I was familiar with to work on and solve clinically relevant problems, which were of great interest me.

When I arrived in 1972, the Scriver lab was situated on the second floor at the Montreal Children's Hospital. The lab was extremely crowded but the people working there were very stimulating, cooperative and friendly. Drs. Peter Hechtman and Renny Gold, principal investigators in the MRC Genetics Group, also worked in the same lab. Dr. Clarke Fraser, who spent some of his time in the hospital, was not far away. So that was my introduction to the group.

Dr. Scriver, who was my supervisor, put me on a research project that was of great interest to him. He had been managing many patients with an inherited form of rickets called X-linked hypophosphatemia (XLH). These patients had rachitic bone disease even though their nutrition was perfectly normal. Moreover, the disorder ran in families and was found to be X-linked. But the nature of the defect in XLH was not known. Clinical studies by

Scriver revealed that XLH patients had reduced levels of Pi in their blood and excessive amounts of phoshpate in their urine, suggesting that they had a specific defect in renal phosphate reabsorption. In other words XLH patients had insufficient circulating phosphate concentrations for normal bone formation. On the basis of these findings it was hypothesized that XLH was a genetic disorder in phosphate transport.

My first project was to determine whether phosphate transport was impaired in red blood cells (RBC) from these patients. The reason why we chose RBC as our model was that these cells were easily accessible from the patients as well as from control subjects. We found that RBC from the patients behaved similarly to those of normal subjects, indicating that the genetic defect was not expressed (present) in RBC. I don't know how much detail you would like in this regard.

Christopher Canning: Well, to be honest, I actually really love the detail and you can speak as for as long as you want. Also, interestingly enough, I recently spoke with Dr. Gold and he passes on his best to you, by the way.

Susie Tenenhouse: I got to know Dr. Renny Gold at the same time that I was pursuing the XLH project and had the opportunity to chat and eventually collaborate with him on a project in mice with an inherited disorder of keratin (proteins in skin and hair) metabolism. The mice, depicted Naked, were unable to produce a normal coat (fur), suggesting an abnormality in keratin biosynthesis. The study with Dr. Gold proved to be very interesting and productive and led to a few publications.

Christopher Canning: Can I just interject right there and say I had a question here saying that Dr. Gold said that, "You are a fantastic experimentalist."

Susie Tenenhouse: Oh that's very nice to hear!

Christopher Canning: And I just want to know, from your perspective, what he meant by that. He suggested, within this collaboration between you two, that he added a bit of a theoretical side to your savvy experimentalist side. Would that be accurate?

Susie Tenenhouse: That would be because he was brilliant mathematically and I had the technical expertise to generate the data. He worked out a method to estimate the composition of keratin proteins in Naked mice and normal littermates. Our data revealed that the mutants had a significant defect in the synthesis of a family of keratin proteins, known as high glycine and high tyrosine proteins. So it turned out to be a good collaboration; he had expertise in one area and I in another.

To follow up on the XLH project, Dr. Scriver learned that Dr. Eva Eicher, a mouse geneticist at the Jackson Laboratory in Bar Harbor, Maine, had

discovered a mutant mouse strain designated Hyp, that exhibited all the clinical features of XLH in humans. Interestingly, the mutation in the mice was also on the X-chromosome, suggesting that Hyp mice were a perfect model to elucidate the underlying biochemical and molecular basis of the human disease XLH.

Are you familiar with the Jackson Laboratory?

Christopher Canning: I didn't hear anything about it, so if you can speak to that that would be great.

Susie Tenenhouse: The Jackson Laboratory is a world renowned research institution and is a valuable resource of mutant mouse strains which serve as valuable models to study and better understand human genetic disorders.

Christopher Canning: So this is the work on renal transport systems, right? In the kidney, this is what you spent the majority of your career working on?

Susie Tenenhouse: That's right. I switched experimental models and proceeded to set up a Hyp mouse-breeding colony at the Montreal Children's Hospital to determine the nature and site of the phosphate transport defect in the kidney in the mutant strain. Hyp mice served me very well until my retirement and much of my research over the years dealt with elucidating the mechanisms for the abnormalities in renal phosphate transport and vitamin D metabolism in Hyp/XLH.

My group showed that:
- Hyp mice have a specific phosphate transport defect in the brush border membrane of the proximal tubule, the major site of phosphate reabsorption.
- Hyp mice also have defect in the renal activation of vitamin D and in addition exhibit increased degradation of the active form of vitamin D (1,25-dihydroxyvitamin D).
- The gene encoding the major phosphate transporter in the kidney does not map to the X-chromosome of mouse and humans and therefore is not the gene that is mutated in Hyp/XLH.
- Hyp mice have a large deletion in the PHEX gene. (This gene is also mutated in XLH patients and maps to the X-chromosome.)
- The PHEX gene is expressed in bone and not in the kidney. However, we still do not understand precisely what PHEX is doing in vivo.

We also established a PHEX mutation database, which is available on line. I'm sure that you're fully aware of the benefits of such databases from the work of Dr. Scriver.

Christopher Canning: And how did this research translate into broader questions of human health?

Susie Tenenhouse: It is important to understand the underlying mechanisms of a disease process before one can devise an effective treatment strategy. In the case of XLH, the treatment involves oral phosphate supplementation and the active form of vitamin D (1,25-dihydroxyvitamin D). This regimen is not ideal, difficult to manage and requires continuous monitoring. We hope that future studies of PHEX function will lead to the identification of novel targets for the development of drugs that will be effective in the treatment of XLH and other hypophosphatemic disorders.

Christopher Canning: Right. So you're working on this in post-doc with Dr. Scriver, and this would have been around the same time efforts were being made to introduce vitamin D into milk. So did your research contribute to the basic science work and the political efforts to eventually apply these studies to human health?

Susie Tenenhouse: Actually, much of the work that I described above was done after my postdoctoral fellowship and significantly later than the introduction of vitamin D in milk in Quebec. I should also point out that the vitamin D metabolite added to milk is not the active form of vitamin D. Rather it has to be modified in vivo, first in the liver to 25-hydroxyvitamin D and then in the kidney to 1,25-dihydroxyvitamin D to acquire biological activity.

While the addition of vitamin D to milk was a huge benefit to the population at large, especially to people in northern climates and to patients with nutritional rickets, this intervention was of no benefit to patients with XLH and other forms of inherited rickets.

After my postdoctoral fellowship, I had the opportunity and good fortune to continue my research in Dr. Scriver's lab as a research associate. It proved to be an excellent arrangement for me and it was only later on, when I felt more comfortable with my commitments at home, raising a family, that I was able to branch out on my own.

Christopher Canning: I did notice that didn't join the group until 1981, so there is this nine-year gap between you being a post-doc, a research associate and a member of the group and eventually a tenured professor.

Susie Tenenhouse: Yes. In 1981, I got a tenure-track appointment in the Dept of Pediatrics. Prior to that, I was a non-tenured assistant professor and a research associate. During this time I successfully competed for salary awards from McGill University (Harry Bagley and Fraser Monat).

Christopher Canning: I have another question related to that, and it came up in my interview with Dr. Gold, because I know that you two were working closely together during that time. Dr. Gold suggested that there was some dispute about getting tenure within the group, that he was also looking for a tenured position and that there were conversations between you and Dr. Scriver, and Dr. Gold

and Dr. Scriver, about getting more of a protected tenured position as opposed to just being under the umbrella of the group and Dr. Scriver's research. Can you speak to that?

Susie Tenenhouse: Right. I can only speak for myself here. When I made the decision to apply for my first grant, within the MRC Group, and set up my own research program, I wanted some commitment from the Department of Pediatrics. So it was an issue for me as well as for Dr. Gold. Eventually, with the help of Dr. Scriver, and because I was productive in research and had competed successfully for salary awards, I was finally granted a Tenure Track appointment as Assistant Professor in the Department of Pediatrics.

Christopher Canning: And that was in 1981 you said?

Susie Tenenhouse: Yes.

Christopher Canning: And it's interesting that you would have been appointed to the Department of Pediatrics not having a medical degree. So you're a biochemist, at that time, being hired into a pediatrics department.

Susie Tenenhouse: To my knowledge, there was a significant number of basic scientists, i.e., PhDs, with tenure track appointments in clinical departments at that time. So, there was a precedent for that at McGill and Dr. Scriver had a lot of clout in the Department of Pediatrics.

Christopher Canning: Right. And what was your knowledge of the group's activities before being invited to participate in '81? So obviously you're involved with Scriver's work in particular, but what about the other members at that time, Dr. Fraser, Dr. Hechtman and Dr. Rosenblatt?

Susie Tenenhouse: I was very familiar with the research programs of the MRC group members at Montreal Children's Hospital, namely, Drs. Scriver, Hecthman and Gold. A highlight for me were our group research seminars where faculty, graduate students, research assistants, clinical fellows, etc. got together for either clinical or basic science research presentations and discussion. And there was a great camaraderie.

Obviously, we didn't see the people who were not at the Montreal Children's Hospital campus as often, namely Drs. David Rosenblatt, Leonard Pinsky and Clarke Fraser. But we had a very good relationship with them as well. There was lot of exchange.

In the later years of the MRC Group, there were very productive collaborations between members of the group including Drs. Rima Rozen, Roy Gravel and David Rosenblatt who worked in similar areas.

Christopher Canning: That was the folate group?

Susie Tenenhouse: Yes. They were all at the same institution, and had similar interests. This led to a productive research program and to many important publications. But for those of us without collaborations within the Group, productive collaborations with scientists outside the university and outside the country were developed. Over the years, I did have many productive collaborations and opportunities.

It was only at the very end of my time in the group that a new person was brought in, Dr. Andy Karaplis, with interests in my research area. You spoke to him?

Christopher Canning: I did, yes.

Susie Tenenhouse: Dr. Karaplis worked in the area of bone and mineral metabolism. He had a lot of experience in molecular biology and we did collaborate together on the production of a knockout mouse where we inactivated the major phosphate transporter in the kidney. This allowed us to investigate the role of this phosphate transporter in vivo and to compare the knockout phenotype with that of the Hyp mouse model. This brought a whole new dimension to my research and it was really rewarding to collaborate with a member of the group.

Christopher Canning: And so obviously this knockout technique was obviously aided by molecular biological techniques, which developed in the 70s and into the 80s. So did you learn new molecular biology techniques after your work in biochemistry?

Susie Tenenhouse: Absolutely. In this business, you must continually retool; it involves continuous learning. If you weren't applying molecular biological methods in the field of genetics, you were no longer competitive for research funding. And for that molecular biology expertise, I am very grateful to Dr. Roy Gravel, who became director of the group as well as scientific director of the McGill University - Montreal Children's Hospital Research Institute sometime in the 1990s. He encouraged us all to gain molecular biology skills and was very helpful in this regard.

Another important contribution by Dr. Gravel was the introduction of an internal grant review process. Each PI applying for external funding was required to submit his/her grant for review by an internal committee before it was sent out to a granting agency. This proved to be a very useful learning experience in grantsmanship and led to a significant improvement in our funding our record.

In my case, I was fortunate to obtain continuous MRC/CIHR research funding from 1981 to 2004. Over the years I also had funding from other sources, such as the Kidney Foundation of Canada, the Quebec Government

and the Pharmaceutical industry.

Christopher Canning: Right, I'd like to step back a bit about something you said about the competitiveness of the group related to molecular biology. According to some documents I obtained, there were some disputes in the group in the mid 80s to late 80s, around '85 to '87, in regards to the group's direction and competitiveness, especially in the area of molecular biology. So this was right before the time that Roy Gravel joined the group, and from what I understand, him and Rima Rozen were trained and recruited specifically to contribute this to the group.

So can you speak to this conversion and this conversation in the 80s, because you were involved for so many years, about the shift to be more competitive in this molecular biology shift?

Susie Tenenhouse: I can't remember being involved in any formal discussions about becoming more competitive and going more molecular but it seemed to me that to answer some of the research questions that we had, it was the only way to go. And that's why Dr. Scriver was trying to recruit in that area. He recruited Ken Morgan, who wasn't a PI in the group but was a geneticist with statistical skills required to identify disease-related genes in pedigrees with inherited disorders. He also recruited Dr. Golder Wilson, a clinical geneticist from United States who didn't stay very long and Dr. Rima Rozen who obtained training in molecular biology during her post-doc in the US.

Christopher Canning: I think it's when she went to Yale and did her post-doc training.

Susie Tenenhouse: That's correct. And then Roy Gravel was recruited. So I definitely agree that it was an issue to remain competitive; we had to retool.

Christopher Canning: To remain competitive in the area of human genetics, correct?

Susie Tenenhouse: Yes this technology was necessary to answer the questions that we were asking about the types of mutations causing genetic disorders, their localization on the genome, their mechanism of action, etc.

Christopher Canning: And do you think the group achieved that after this shift in the 80s from what you saw?

Susie Tenenhouse: Definitely. Rima Rozen and Roy Gravel were very productive investigators and made significant contributions to their field. And then with the new members of the group, such as Drs. Mark Trifiro, Eric Shoubridge, Andy Karaplis, the expertise in molecular biology reached a peak. All were a tremendous resource and helpful to others.

Christopher Canning: Yes. Shifting gears a little bit, what was the space like during your time in the group? In other words, where was the group located and how did the

concept of the physicality of the group play in to the role every one had in the group?

Susie Tenenhouse: Space is always a big issue and was especially so at the outset of the MRC group. When I first arrived in 1972 as a post-doc, the lab was extremely crowded and I had neither a desk nor a bench of my own. The situation significantly improved in the mid 70s when we moved to the A-wing of the hospital where we acquired the entire seventh floor and everyone had sufficient space to do their work.

Christopher Canning: Right.

Susie Tenenhouse: There is always competition for space.

Christopher Canning: And what sort of facilities? You mentioned that these facilities were eventually added. What was added after the tight space of the early years?

Christopher Canning: Most of the equipment we required was on site and the working environment was a lot more comfortable. Everybody had their own desk and bench space. In addition, the mouse facilities in the basement of the hospital were significantly improved - more space and personnel to monitor and care for the breeding colonies.

In the early 90s, my group moved to Place Toulon, an office building on St. Catherine St just 2 blocks away from the Montreal Children's Hospital. The hospital Research Institute had rented several floors in this building to increase their research space. Both Drs. Rozen and Gravel, as well as several other hospital investigators, had set up their laboratories in this facility. There was a lot of common equipment, secretarial support, a small library and conference room, and what was critical for me, more animal space.

Over the years the rules and regulations governing the experimental use of animals and the requirements for animal facilities became a lot more stringent. Compliance with these regulations was mandatory and justification for the number of animals housed by each investigator was necessary. So, the improvements in our animal facilities at both the Montreal Children's Hospital and Place Toulon were very timely and made life a lot easier for investigators.

Christopher Canning: There was a letter sent out to the group that I actually got from David Rosenblatt about the group being competitive in regards to space, because the MRC at the time was pushing to centralize the group in a single site. Do you remember this discussion that everyone needed to come to a single site?

Susie Tenenhouse: I only have a faint recollection and can't really speak to that.

Christopher Canning: Okay.

Susie Tenenhouse: I was never really involved in making that type of decision.

Christopher Canning: Okay.

Susie Tenenhouse: I could discuss my own feelings about the space -- the space issues at the time. But usually I was quite content with what I had.

Christopher Canning: Right. But it didn't seem like an issue to you that group members were located at different locations?

Susie Tenenhouse: At other sites?

Christopher Canning: Yes.

Susie Tenenhouse: But even early on we had Pinsky, Rosenblatt and Fraser at other sites.

Christopher Canning: Yes, and Pinsky was a member until 1990. So obviously around this time certain members are being recruited and certain members are sticking around but people are in different locations. And the only reason I ask that is that it's interesting how the group defined itself. In other words, is the centrality necessary for the workings of a group in medical genetics?

Susie Tenenhouse: I don't think so because you can accomplish a lot of work with other investigators even if they are at a different site. Of course it's a lot nicer to have your group together.

Christopher Canning: Yes.

Susie Tenenhouse: But that was of course impossible.

Christopher Canning: Okay.

Susie Tenenhouse: And so I think we did well with what we had.

Christopher Canning: Do you recall what the leadership was like in the early days? So the director of the group, so early it was Dr. Scriver and then obviously it shifted to Roy Gravel and Rima Rozen. So what was the role of the director of a group of this sort?

Susie Tenenhouse: When Dr. Scriver was director of the group, the group was much smaller. He ran the group very well. We did a lot of things together, from eating lunch together in the cafeteria, to attending seminars together and participating at national and international meetings together. We were a much more unified entity in those days. But when more people joined the group and their areas were a little different, it was no longer that way. I found that Roy

Gravel had a very good rapport with everyone in the group and was a very good director and as was Rima Rozen when she took over. I can't really say much more about that.

Christopher Canning: Okay, that's fine. Do you recall how the funding structure of the group worked? In other words, applying for individual funding and being included in the group funding, do you recall?

Susie Tenenhouse: I didn't pay too much attention to the administration of the group budget. We had Fran Langdon in the Department of Human Genetics and, prior to that in the Center of Human Genetics, whose responsibility was to handle the budget. She was extremely helpful and a wonderful person to deal with. I myself was never too involved. And it's been a long time so I don't recall those details.

Christopher Canning: That's absolutely fine. How about I move to some more general questions about the group then? As I mentioned, you're the 14th member I've interviewed. And throughout all the discussions that I've had, we have talked about the bench versus the clinical. And I'm wondering if you can speak to what the group dynamics were like in terms of either being a bench basic scientist or being a clinician and how the group worked around these divisions or, in a sense, if they were divisions at all?

Susie Tenenhouse: When I came as a post doc, I was very interested in the clinical discussions. As I mentioned earlier, the group met on a regular basis to discuss either the basic science or the clinical aspects of our work. I thought that was a very good idea. But in the end, the clinical aspects were secondary; in reality we were a basic science group. Some of the clinicians within the group did have clinical responsibilities but that was independent of their research program. And to the best of my recollection, patient issues were rarely discussed with the basic scientists.

Christopher Canning: Right.

Susie Tenenhouse: Both Scriver and Rosenblatt are clinicians, and Pinsky, Fraser, Karaplis, Trifiro as well. They had their clinical interests, which often set the stage for their basic research program.

Christopher Canning: Right.

Susie Tenenhouse: That's how I viewed the situation.

Christopher Canning: So you were never yourself involved closely in patient diagnoses and care but your research in some way or another contributed to that?

Susie Tenenhouse: Although my research did not involve patient diagnosis and care, I was interested in hearing about it. I think it's important to have the whole

picture. And I found that over time, there was less emphasis on the clinical research side.

Christopher Canning: Do you think the group achieved this, what you called the "whole picture?"

Susie Tenenhouse: I can only speak for myself when I say that the non-clinicians in the group were not up on the whole clinical picture.

Christopher Canning: Okay. On one of the group applications, it says that the group had achieved a level of interdisciplinarity. And I'm just wondering if you can speak to this. Do you think that the group overall, bringing together all the areas of somatic cell genetics, cytogenetics, biochemistry, molecular biology, do you think this brought together what we would consider an interdisciplinary group?

Susie Tenenhouse: The group was somewhat interdisciplinary and that can be a very positive thing. But on the other hand, if you have more people working in one discipline, you might be more productive. It just depends on how you want to run things. We did have a lot of different projects going on but also there were little groups within the group that were highly productive because of their common interests, such as the folate group.

Christopher Canning: Right. And again, who were you involved with specifically again?

Susie Tenenhouse: I worked with Dr. Karaplis on one project only. I would have liked more involvement with him, but it didn't work out. He was very competitive, and actually competing with me. We all have these issues with competitors who don't want to reveal the whole story. I know it sounds awful but that is the reality.

Christopher Canning: I see. Can you elaborate?

Susie Tenenhouse: When Dr. Karaplis joined the MRC Group, he had been working with investigators in the Calcium Lab, headed by Dr. David Goltzman for many years. That group was/is very well known in bone and mineral metabolism and disorders thereof and they were very molecular as well. Although I approached them to collaborate with me, it didn't work out. As a result, all my collaborators were from other universities and I had very productive collaborations over the years.

Christopher Canning: So you collaborated with more outside folks than you did with people within this group?

Susie Tenenhouse: Yes. Initially, I worked with Dr. Scriver but he was my post-doctoral supervisor. In the years after my post-doc, we did do some interesting work together. But once I went out on my own, it was critical for me to establish my own identity and independence, both of which were necessary to

successfully compete for MRC funding. So sometimes you're damned if you do, damned if you do. So it's just the way the funding agencies view you. You have to be independent of other groups, of other people, other investigators. But now more and more people are looking for collaborative groups and bringing in people with all kinds of expertise, such as statisticians, epidemiologists, clinicians, and basic scientists.

Christopher Canning: I agree and that seems to be an interdisciplinary focus on a particular problem and everyone shares an interest in that single problem, is that correct?

Susie Tenenhouse: Exactly.

Christopher Canning: So the difference between that, the way groups are oriented now, and the way the McGill group was oriented is that everyone in your group was focused on so many different topics?

Susie Tenenhouse: Yes, many different projects in many different areas. So it was very different then.

Christopher Canning: So then you can you speak to a broader question of, okay, what made this group a group? How did collaboration or anything else define what this MRC/CIHR group was?

Susie Tenenhouse: I think the major factor that led to the Group's success was Dr. Scriver's leadership abilities. He is a very charismatic person, intelligent, articulate and had the skills necessary to put it together, pull in together and sell it to the MRC. The PIs were all accomplished and productive in their respective fields of interest and surprisingly, collaboration was only evident with three PIs working on folate research.

Christopher Canning: And it seems like you're saying that there were little groups within the group.

Susie Tenenhouse: Yes, one primarily.

Christopher Canning: And those people would collaborate with one another but it was rare, like you say as opposed to groups now, there wasn't a big group collaboration.

Susie Tenenhouse: As I said earlier, this is in contrast to "groups" or teams today that consist of people with training and skills in very different disciplines, e.g., clinicians, basic scientists, epidemiologists, statisticians. Our group didn't have that type of composition.

Christopher Canning: So then what contributed to the group's longevity, do you think, from 1972 to 2009, which is the longest funded group project in Canadian history in Canadian health research?

Susie Tenenhouse: I would say that Dr. Scriver had a lot to do with the Group's longevity. He has a lot of credibility and expertise. He did a great job marketing the Group's accomplishments and he's very talented when it comes to talking to politicians and makes a very good impression. I think it was because of him that we were able to continue on as a group for so many years.

In addition, his work on The Metabolic and Molecular Basis of Inherited Disease, and then making it available on line, and his contributions and dedication to field of genetics had some impact. Finally, the successes of each member of the group in their areas of research was also important.

Christopher Canning: So in some respects, it was largely political, that you had someone who was very talented at holding the group together, lobbying for funding and maintaining the structure, however you want to define that structure, and called it a group.

Susie Tenenhouse: David Rosenblatt was also very eager to keep the group together and to work within a framework of the group. So he continued the push for the group. Dr. Gravel did much of the same.

Christopher Canning: Yes. But you said the framework of the group, but interestingly, how do we define that framework as a group? Sorry to keep pressing on this question, but how do we define the framework of the group?

Susie Tenenhouse: Well, it is a puzzle to me. It was just a group of people working in the field of Genetics who got together for funding purposes. I think it is kind of artificial. We believed that it was very advantageous to be part of the group because in addition to research funding, we received funding for facilities and equipment. In addition, it included salaries for the PIs and trainees. I think that's all I can say about that. It just happened and we were successful at maintaining it.

Christopher Canning: Yes. By the looks of things and speaking to other members, that seems to be the consensus. Everyone contributed to their areas of science and called it a group and had the success of the funding, and that the funding offered them the opportunity to do their individual research.

Susie Tenenhouse: Right. And as I said above, up until 1996, all PI salaries were covered by the group grant. This was a tremendous benefit for the university departments in which we had appointments. My salary as a PI was covered by the group grant from 1981 to 1996.

Christopher Canning: Wow. So obviously, the department loved you because you're bringing in your own salary.

Susie Tenenhouse: Exactly. I should mention that many of us PIs were supplemented to some

extent by McGill, but I can't really speak to that.

Christopher Canning: Right. Do you recall in around 2000 when the MRC shifted to the CIHR, that members had to secure their own funding before being invited into the group? So this, again, is part of the shift, a member couldn't be funded by the group but had to secure their own funding individually. Do you recall that?

Susie Tenenhouse: I think it was always the case that the research proposal of each PI, new or continuing, was assessed independently and acceptance to the group was based on that assessment as well as the fit of the individual in the group.

Christopher Canning: Yeah or any member who wanted to be part of the group had to secure their own CIHR grant and then also had to be accepted for inclusion in the group.

Susie Tenenhouse: Yes, I suppose that's correct. I know that if you did not get your funding in the group grant, you couldn't be a member in the group.

Christopher Canning: Right. Okay. In your opinion, what are some of the major scientific or clinical advances in genetics influenced by the work of the group?

Susie Tenenhouse: I think that the MRC Group's most important clinical contribution in genetics is Charles Scriver's work in newborn screening and testing for carrier status in families at risk for genetic diseases. The identification of mutations in these families and the ability to offer prenatal diagnosis is also very important. In this regard, Dr. Hechtman made significant contributions for his work on Tay Sachs disease.

Unfortunately the immediate benefits of basic research are not apparent until much later. In other words, knowing which gene has the mutation does not always lead to an effective treatment. A good example that does not relate to the MRC group is cystic fibrosis, a common genetic disease. While the gene for cystic fibrosis was identified in the late 80s, a cure for this devastating disorder had not been forthcoming. It appears that more information about the how the gene product behaves in vivo is necessary to identify new drug targets and develop novel therapies.

In this regard the Genome Project itself has been a disappointment. Many people are of the opinion that the project hasn't been worth the investment. According to Drs. Francis Collins and Eric Landers, more work and time are necessary to reap the benefits of this enormously expensive and labour intensive project.

Christopher Canning: And what's your position on that?

Susie Tenenhouse: I think the Genome Project is very important but it's going to take more

time for the data generated to be useful in predicting predisposition to disease. Things are a little more complicated than originally expected. Many of the association studies to identify genetic risk are not reliable and the interpretation of these data will require more knowledge. So it's going to take a lot longer but at the end of the day, I think it will be of enormous benefit.

Christopher Canning: You think human genetics will eventually yield for things like cystic fibrosis, or other more therapeutic outcomes?

Susie Tenenhouse: Yes, we are told that someday everyone will carry a little card in their wallet, like a bank card, that will provide a readout of their genetic status and genetic predisposition to disease. But we're not quite there yet.

What was the consensus by other PIs about the contributions of the group?

Christopher Canning: You're asking me what the consensus is?

Susie Tenenhouse: Yes, from the other PIs.

Christopher Canning: Well, actually I think it would be a very similar story to what you've said. Most everyone speaks to the early development of Scriver's work in vitamin D metabolism and inborn errors of metabolism. And in the history of Canadian genetics research, this is a major breakthrough and contribution, undeniably. And I think a lot of other folks just say that a lot of this is still in development.

Susie Tenenhouse: That's right.

Christopher Canning: Like you say, this basic science doesn't necessarily yield therapeutic effects immediately.

Susie Tenenhouse: I agree.

Christopher Canning: Yeah.

Susie Tenenhouse: As I mentioned above, I saw Drs. Francis Collins and Eric Landers interviewed on TV and they were being asked very tough questions about the genome project. How come we don't have more answers yet? It just takes time; it's very complex.

Christopher Canning: Yeah and it seems like the more geneticists know, the more complex it becomes, which makes it harder to explain.

Susie Tenenhouse: Yes but eventually, we'll know it.

Christopher Canning: Yes.

Susie Tenenhouse: Maybe not in my time but in the future we will.

Christopher Canning: Do you keep up with current studies? Obviously you're retired now, but do you still do research? Do you still read in the area of genetics or you're just relaxing in Arizona?

Susie Tenenhouse: I am relaxing in Arizona during the winter months but I also do keep up a little bit. For a while, I was reviewing many manuscripts for journals and things of that nature but then I felt I couldn't really do a good job of it. It is necessary to keep up with the scientific literature in order to make a judgement on the originality and validity of the work described in submitted manuscripts.

I do go on to PubMed every now and then but I spend most of my time reading in other areas, which I never had time to do before retirement.

Christopher Canning: So you've moved out of the kidney, so to speak, into other areas?

Susie Tenenhouse: [laughs] Right, but I do like to hear about it every now and then.

Christopher Canning: So what are your plans for the next while?

Susie Tenenhouse: We're just hoping to keep healthy and spend our winters here and continue to read widely, travel and hike; we like that, and do all the things we never had time for. And of course, we enjoy our grandchildren, two in Toronto and three in the Boston area. I keep in very close touch with my mother in Montreal who's going to be 100 in April. We speak everyday and I see her fairly often. She's doing amazingly well for someone her age and we look forward to celebrating this important milestone with her.

Christopher Canning: That is very exciting.

Susie Tenenhouse: I just spoke to my Mom today and she's just horrified at the idea of turning a 100! I said, "You should be proud of it." And she said, "I don't feel a 100." And she said "I hope you have my genes". I said, "I hope so too." [Laughter]

Christopher Canning: Fantastic. And your husband was a medical doctor, right? So he's retired now as well?

Susie Tenenhouse: Alan (MD, PhD) retired from his position at McGill where he headed the Division of Bone Metabolism. In 1993, he set up a large epidemiological study called the Canadian Multicentre Osteoporosis Study (CaMos). The study is following a random cohort of Canadian men and women, age 16 and older, to assess bone health and fracture rates. In many respects the study is unique and one of the more important epidemiological studies worldwide. CaMos is still in progress and renewal funding from CIHR was

recently acquired. Alan still participates in CaMos conference calls with the centre directors and is very proud of the study's productivity. He also enjoys travel, hiking and reading.

Christopher Canning: Fair enough.

Susie Tenenhouse: Everybody I speak has their own take on getting old and what they want to do with their lives at this stage of the game..

Christopher Canning: Yes. Well, now you should enjoy this time and like you say, do things that you didn't have time to do.

Susie Tenenhouse: Before retirement, reading novels or other texts that were unrelated to my work always made me feel guilty. I knew that perusing the scientific literature would be far more productive. Now I'm making up for lost time. Both Alan and I now have Kindles and we love the idea of having an unlimited number of books at our fingertips. It's just great!

Christopher Canning: So now you can just sit in the sunshine and read your Kindle.

Susie Tenenhouse: That's right.

Christopher Canning: One final question. Do you still have contact with any of the group members?

Susie Tenenhouse: Very occasionally, perhaps on a yearly basis. I try to keep up with the progress of their careers.

Christopher Canning: Yeah. Well, as I said, Dr. Gold sends his best. He spoke very highly of you especially regarding your work in the lab.

Susie Tenenhouse: I truly enjoyed the MRC/CIHR Group research retrospective in November 2009. It was wonderful to see all the people that were involved with this group over years.

Christopher Canning: Yeah, and that was a really great day.

Susie Tenenhouse: I wish you much success with your project and look forward to reading your publications.

Christopher Canning: Thank you! I'm just going to turn off the recorder now that we're done. Thank you very much for your time, Dr. Tenenhouse.

END OF INTERVIEW

Dr F. Clarke Fraser, le 3 novembre 2009

Christopher Canning : Nous sommes le 3 novembre 2009. Ici Christopher Canning en compagnie du Dr F. Clarke Fraser du Département de génétique humaine. Docteur Fraser, je suis très honoré de pouvoir m'entretenir avec vous de deux grands sujets qui touchent la génétique humaine. J'aimerais d'abord que nous parlions de votre parcours universitaire qui, bien sûr, a grandement contribué à l'avancement de la médecine génétique au Canada et ailleurs dans le monde. Ensuite – et surtout, pour les besoins de notre étude – je m'intéresse à votre participation au groupe sur la médecine génétique des IRSC[1], anciennement le CRM[2]. Vous l'avez formé en 1972 avec le Dr Scriver, il est demeuré en activité jusqu'en septembre dernier et a également été dirigé par Roy Gravel et Rima Rozen. Comme vous le savez, j'ai pour mission de raconter l'histoire de chacun de ses membres. Mais parlons d'abord de vos origines, si vous le voulez bien. D'où venez-vous?

Dr Clarke Fraser : Je suis né à Norwich, au Connecticut.

Christopher Canning : En quelle année?

Dr Clarke Fraser : En 1920. J'y ai vécu neuf mois. Mon père travaillait là-bas. Mes racines sont canadiennes, mais je suis né là-bas un peu par accident.

Christopher Canning : Après ces neuf mois, où votre famille s'est-elle installée?

Dr Clarke Fraser : Mon père a travaillé un certain temps à Saint John, ensuite à Montréal, puis il a finalement été délégué commercial du Canada, avec une première affectation à Dublin. Puis – je devais avoir autour de sept ans à l'époque – il a été muté en Jamaïque, où nous avons passé dix ans. J'ai fréquenté une très bonne école publique, le Collège Munro. J'y ai reçu une très bonne instruction de base, je crois. Après mon secondaire, j'ai été admis au programme préparatoire de médecine de l'Université Acadia, et j'étais suffisamment avancé pour qu'ils m'envoient directement en deuxième année.

Christopher Canning : Vous êtes passé directement du secondaire à la deuxième année d'université?

Dr Clarke Fraser : Oui.

Christopher Canning : En quoi étudiez-vous, puisque vous n'aviez pas fait de biologie au secondaire?

Dr Clarke Fraser : Je faisais le programme préparatoire de médecine et j'étudiais en biologie.

Christopher Canning : Je vois. Aviez-vous des frères et sœurs?

Dr Clarke Fraser : Oui, une sœur : Mary. Malheureusement, elle est morte assez jeune de ce qu'on appelait alors la « maladie de Pick », une démence présénile précoce.

Christopher Canning : Ah, et si je puis me permettre, c'était en quelle année exactement?

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[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

Dr Clarke Fraser : Voyons voir… Elle devait avoir 35 ans et elle était née en 1922, donc ça veut dire 1957, n'est-ce pas?

Christopher Canning : Pouvez-vous me parler un peu de vos parents? Quel genre de parents étaient-ils?

Dr Clarke Fraser : Ma mère était une personne chaleureuse, pleine de vie et avait une très belle voix. Elle était diplômée de l'Université Mount Allison en chant et était contralto. C'était une femme dynamique et affable, certes, mais elle était autoritaire de nature. Sans recourir à la fessée ni à quelque punition corporelle que ce soit, elle nous apprenait à distinguer le bien du mal et savait se faire obéir. Quant à mon père, c'était un homme doux et discret qui avait un bon sens de l'humour; il adorait la poésie et ne se lassait pas d'en réciter. Ces deux-là s'adoraient, c'était évident; jamais ils ne se parlaient en élevant le ton, et je pense que je leur ressemble sur ce point. Lorsque j'ai été en âge de jouer, mon père m'emmenait au golf; j'étais très attaché à lui. Quoi d'autre?

Christopher Canning : Étaient-ils exigeants avec vous en ce qui a trait aux études?

Dr Clarke Fraser : Jamais ils ne m'ont mis les points sur les i et les barres sur les t, mais je pense qu'ils donnaient l'exemple, tout simplement. Ils m'envoyaient dans une bonne école, et je suis certain qu'ils s'attendaient à ce que j'obtienne de bons résultats. Inutile de me faire un dessin : je comprenais le message.

Christopher Canning : Qu'est-ce qui vous a motivé alors à aller en médecine?

Dr Clarke Fraser : Eh bien, il y avait oncle Lew, un oncle par alliance. Lew Lovett était le médecin type de l'époque : il se déplaçait dans sa voiture attelée à un cheval et pratiquait des appendicectomies sur les tables de cuisine. J'avais beaucoup d'admiration pour lui, et c'est probablement l'une des raisons qui m'ont incité à étudier la médecine. Ça, et le désir d'aider mon prochain. Je suis donc allé à l'Université Acadia. En biologie 1, il y avait deux exposés magistraux sur la génétique présentés par Muriel Roscoe, qui, en passant, a été plus tard doyenne des femmes à McGill, mais à l'époque enseignait la biologie. Pour moi, c'est là que le déclic s'est fait. J'ai tout de suite su que c'était ce que je voulais faire.

Christopher Canning : Quel âge aviez-vous?

Dr Clarke Fraser : Dix-sept ans. Alors, au lieu d'aller en médecine, j'ai fait une demande à McGill. Je voulais faire des études supérieures au Département de génétique qui, à mon grand étonnement, était prêt à m'accueillir pour autant que je décroche une bourse. Et encore une fois à mon grand étonnement, le NMRC m'a octroyé cette bourse. Si je me souviens bien, c'était 600 $, une somme rondelette à l'époque.

Je suis donc allé au tout nouveau Département de génétique, qui existait alors depuis quelques années à peine. Apparemment, il trouve son origine dans la botanique et la zoologie. D'après ce qu'on raconte, l'Université n'arrivait pas à arrêter son choix sur un professeur de génétique. Un professeur de botanique, Leonard Huskins, a offert ses services. Il s'est adressé à la Fondation

Rockefeller et a obtenu une subvention pour fonder le Département de génétique. Lors de mon arrivée, le Département n'avait que trois ou quatre ans d'existence.

Christopher Canning : Était-ce essentiellement un département de phytogénétique?

Dr Clarke Fraser : Il y avait le trille, en raison de ses chromosomes volumineux, et le blé, parce qu'ils étudiaient la génétique de la rouille du blé, je crois. Mais il y avait aussi des drosophiles et des souris, et j'ai su en entrant dans la pièce des souris que c'était ce que je voulais faire, parce que c'était ce qui se rapprochait le plus de la médecine. Mais je n'ai pas pu le faire la première année, parce qu'il y avait déjà là deux étudiants, et la pièce ne pouvait pas en accueillir davantage. Je me suis donc rabattu sur les drosophiles – les mouches à fruit – et j'ai mené une étude avec Arthur Steinberg, qui venait tout juste d'arriver au Département. Ce fut probablement un mal pour un bien, parce que nous pouvions faire des analyses génétiques très rigoureuses. C'est comme ça que j'ai obtenu ma maîtrise. L'année suivante, j'ai eu ma place dans la pièce des souris, et c'est comme ça que j'ai décroché mon doctorat.

Christopher Canning : Pouvez-vous m'expliquer brièvement le sujet de votre doctorat?

Dr Clarke Fraser : Plusieurs souris perdaient leurs poils en raison d'une mutation. L'une était surnommée « souris glabre » (*hairless*) et l'autre, « souris rhino », parce qu'elle avait la peau plissée. J'ai réalisé une étude histologique et tenté d'élucider le mécanisme d'action du gène. J'ai pratiqué des greffes cutanées pour voir si un agent pouvait passer de la peau saine au greffon de peau glabre et y faire pousser des poils. Je pense que mon doctorat repose sur deux hypothèses erronées. Des poils ont effectivement poussé à la jonction de la peau et du greffon, et j'ai utilisé des couleurs différentes pour pouvoir déterminer avec certitude de quel côté poussait chaque poil. Mais en fait, je pense qu'il y avait du tissu cicatriciel le long des greffons, et c'est pour ça que les poils restaient à l'intérieur. Puis je me suis dit que comme la vitamine A était efficace dans certaines kératoses humaines, je pourrais en faire l'essai chez les souris rhino. Je leur en ai donc administré en grande quantité, et leur peau plissée s'est transformée en un revêtement cutané bien lisse. Mais quand j'y repense aujourd'hui, j'ai l'impression que c'est parce que c'était toxique.

Christopher Canning : La vitamine lissait la peau des petits de ces souris?

Dr Clarke Fraser : Non, mais la peau des souris elles-mêmes, oui.

Christopher Canning : Quelle a été l'influence d'Arthur Steinberg sur vos travaux à l'époque? Vous a-t-il encouragé à rester pour faire votre doctorat? Avez-vous fait votre doctorat avec lui?

Dr Clarke Fraser : Oui. La bonne entente n'a pas été immédiate, parce qu'il me trouvait paresseux, et le premier… J'espère que je ne me perds pas trop dans les détails.

Christopher Canning : Non, non, je veux connaître tous les détails.

Dr Clarke Fraser : Nous étudions l'effet d'inversions chromosomiques sur l'enjambement dans le chromosome X.

Christopher Canning : C'était votre première publication?

Dr Clarke Fraser : Oui. Et personne ne comprenait ce qui se passait. Nous avons donc eu recours à des inversions de différentes longueurs et à divers points de cassure pour tenter d'élucider le mystère. Ma première série d'expériences a donné des résultats complètement loufoques, et Arthur Steinberg pensait que je bousillais quelque chose, alors il… la fois suivante, nous avons mené la même expérience en parallèle et obtenu les mêmes résultats tordus. Figurez-vous donc qu'il y avait une inversion dans le matériel témoin : c'est ce qui faisait dérailler le processus. Bref, quand il me voyait rater mon coup, il n'était pas particulièrement impressionné; mais nous avons fini par être sur la même longueur d'onde et, en définitive, il a eu une très bonne influence sur moi en raison notamment de sa rigueur.

Christopher Canning : Avez-vous collaboré de nouveau après cet épisode?

Dr Clarke Fraser : Non. Dès la fin de ma thèse, je me suis joint à l'armée de l'air, parce que nous étions encore en guerre.

Christopher Canning : Ce serait en 1943?

Dr Clarke Fraser : Peut-être en 1945.

Christopher Canning : D'accord.

Dr Clarke Fraser : Oui, c'était plus tôt que ça; en 1943, je crois, parce que je suis revenu à l'école de médecine en 1946.

Christopher Canning : Oui, c'était probablement en 1942 ou en 1943.

Dr Clarke Fraser : Le major-général McNaughton, alors président du CNRC[3], avait recommandé aux étudiants de poursuivre leurs études au lieu de s'enrôler, parce que le Canada avait besoin de scientifiques pour l'effort de guerre. Je suis donc resté pour terminer ma thèse, mais après, je me suis enrôlé et j'ai passé trois années entières dans l'armée de l'air; lorsque j'ai été libéré du service militaire, j'ai pu utiliser mon allocation d'ancien combattant pour faire ma médecine. Voilà, c'est comme ça que ça s'est passé.

Christopher Canning : Donc, avez-vous terminé votre doctorat après votre service militaire ou juste avant?

Dr Clarke Fraser : En fait, j'ai remis ma thèse. Je l'ai remise avant de partir, mais la soutenance – c'était un rituel, je crois – a eu lieu après ma sortie de l'armée, puis je suis entré tout de suite à l'école de médecine.

Christopher Canning : Dans vos mémoires, vous dites que vous avez eu envie de décrocher quelques fois pendant vos études de médecine. Pouvez-vous nous expliquer pourquoi?

Dr Clarke Fraser : Mon idée en me dirigeant en médecine, c'était d'aller chercher uniquement ce

[3] Conseil national de recherches du Canada

dont j'avais besoin pour faire de la génétique, alors disons que mes résultats n'étaient pas trop bons. La première année, j'ai échoué au cours d'anatomie et j'ai dû faire un examen de reprise. En troisième année, j'ai échoué aux cours d'obstétrique, de pathologie générale et de pathologie des maladies spécifiques, surtout parce que je n'étais pas attentif; je n'aimais pas le « par cœur », comme l'anatomie… et la pathologie des maladies particulières, un cours dans lequel il fallait apprendre un tas de choses disparates, qui n'obéissaient à aucune logique; je n'étais pas bon là-dedans. En obstétrique, l'insolence était sans doute responsable de mon échec. Voyez-vous, à l'examen oral, le professeur me dit : « Vous avez devant vous une dame mal en point, en proie à de dangereux vomissements; que faites-vous? » Alors, moi, j'y vais de quelques suggestions, par exemple des biscuits soda et des choses du genre, et il me répond : « Bon, d'accord, mais elle vomit encore », alors je propose quelques autres interventions, puis il me dit « vous voyez bien, docteur, elle continue de vomir, alors, que faites-vous? ». Et moi de répondre : « Je nettoie le dégât, Monsieur ».

Christopher Canning : Et vous n'avez pas réussi à obtenir la note de passage avec ça? [rires]

Dr Clarke Fraser : Non, et je ne m'explique pas pourquoi. [rires]

Christopher Canning : Donc ça n'a pas été un long fleuve tranquille, mais vous vous en êtes sorti.

Dr Clarke Fraser : Oui. Mais je dois dire qu'à ce moment-là, j'ai touché le fond du baril et envisagé de tirer un trait sur cette aventure. J'ai écrit à quelques personnes, et leurs réponses m'ont beaucoup encouragé; je pense notamment à Jim Neel, l'un des premiers spécialistes en génétique médicale, que je connaissais déjà plutôt bien, et à J.S.L. Browne, un biochimiste – ou endocrinologue, je crois – hors pair, qui faisait partie de ma confrérie et que je connaissais aussi très bien. En gros, sa lettre disait : « Voyons, ne fais pas l'idiot ». J'ai donc pris une année sabbatique pour faire le point, puis j'ai fait ma dernière année en me concentrant sur la médecine plutôt que sur la génétique, et les résultats ont été pas mal plus concluants. Pendant mon stage en pédiatrie, j'ai fait la connaissance d'Alton Goldbloom, qui enseignait la pédiatrie; je me suis présenté et je lui ai parlé de mes projets. C'était l'une des rares personnes qui mesurait le potentiel de la génétique en médecine, en pédiatrie surtout, alors c'est lui qui a fait le nécessaire pour que j'aille à l'Hôpital [de Montréal] pour enfants; à l'époque, on pouvait remplacer un stage par une année de recherche. Alan Ross a sauté sur l'occasion; il était le successeur d'Alton Goldbloom et a été une autre personne très importante dans ma vie. Il s'est organisé pour que je puisse prendre cette année de soi-disant recherche pour mettre sur pied la division de génétique humaine et médicale à l'Hôpital pour enfants.

Christopher Canning : Justement, j'allais vous demander pourquoi vous aviez choisi l'Hôpital de Montréal pour enfants. Pour travailler avec ces gens-là?

Dr Clarke Fraser : Voilà! Déjà, McGill était un choix logique pour l'établissement d'une division de génétique, mais la présence de ces deux grands visionnaires a été le facteur déterminant.

Christopher Canning : Savez-vous si d'autres établissements canadiens ou nord-américains faisaient

de même, c'est-à-dire fusionnaient la pédiatrie et la génétique humaine? Était-ce dans l'air du temps?

Dr Clarke Fraser : Non, pas vraiment. Il y avait Norma Ford Walker à Toronto, mais elle avait un doctorat en zoologie; elle travaillait à l'Hôpital pour enfants, où elle faisait de la consultation génétique, étudiait le syndrome de Down et utilisait la dermatoglyphie, mais je ne pense pas qu'il y ait eu de service constitué en bonne et due forme avant un certain temps. À l'époque, il n'y avait personne au Canada qui avait à la fois un diplôme en médecine et un Ph. D.

Christopher Canning : J'aimerais, si vous le voulez bien, que vous me donniez des précisions sur un passage fort intéressant de vos mémoires qui a retenu mon attention : vous étiez à l'Hôpital pour enfants, vous aviez mis sur pied l'unité de génétique médicale, votre intérêt pour le sujet se précisait et vous étiez à l'affût de patients intéressants du point de vue génétique. Qu'entendez-vous par là exactement? « Intéressants du point de vue génétique », ça voulait dire quoi concrètement à la fin des années 1940?

Dr Clarke Fraser : Je me promenais d'un service à l'autre et je posais des questions aux résidents sur les antécédents familiaux et des trucs du genre, et je les incitais à aborder la question de la consanguinité lors de la prise des antécédents. Je me souviens de plusieurs cas qui, je crois, ont marqué leur imagination. Je pense notamment à une jeune femme venue consulter en raison d'un abdomen aigu – c'est-à-dire des douleurs abdominales; personne ne savait d'où venaient ses douleurs. J'ai noté ses antécédents familiaux et remarqué qu'il y avait dans sa famille de grands buveurs; non pas des alcooliques, mais des buveurs d'eau. Ils buvaient d'énormes quantités d'eau et urinaient abondamment. Elle m'a raconté que son grand-père, notamment, déposait un seau d'eau à côté de son lit tous les soirs et le reprenait de l'autre côté du lit le matin. Finalement, il se trouve que la consommation de ces énormes quantités d'eau faisait enfler son foie, d'où ses douleurs; je pense que le diagnostic a quelque peu impressionné l'équipe. Il y avait aussi ce garçon qui présentait une hémorragie intestinale dont ils n'arrivaient pas à trouver la cause malgré tous les tests qu'ils lui faisaient passer. En relevant les antécédents familiaux, j'ai découvert que le père avait des saignements de nez. Finalement, ils étaient aux prises avec ce qu'on appelle une « télangiectasie hémorragique héréditaire », une faiblesse des vaisseaux sanguins; comme les capillaires sont parfois fragiles, ils se rompent en cas d'agression, quelquefois dans le nez et quelquefois dans le tube digestif, et c'était la cause de l'hémorragie du petit garçon. C'est ce que je voulais dire par « patients intéressants du point de vue génétique », je crois.

Christopher Canning : Alors, à l'époque, le diagnostic génétique passait de toute évidence par la prise des antécédents familiaux.

Dr Clarke Fraser : Exactement.

Christopher Canning : Et, bien entendu, ce n'est que lors de l'entrée en scène des spécialistes en recherche moléculaire que la collaboration a débuté, qu'on s'est demandé quels étaient les mécanismes moléculaires à l'origine de ces maladies génétiques.

Dr Clarke Fraser : Oui, à une étape avancée du stade biochimique. Les tournées et les études de

cas en groupe me laissaient un peu sur ma faim : on pouvait dire tel patient a une maladie récessive et il y a une chance sur quatre qu'un autre membre de la fratrie soit touché, mais ça s'arrêtait là. Si seulement on savait ce que fait le gène, on pourrait peut-être remédier à la situation. Alors, quand Charles Scriver est arrivé dans le décor, mes prières ont été exaucées. Je l'ai accueilli à bras ouverts, parce que…

Christopher Canning : … il était le biochimiste que vous appeliez de tous vos vœux?

Dr Clarke Fraser : Il s'employait à déterminer les effets des gènes et à trouver des façons de les contrer, notamment dans la phénylcétonurie et plusieurs autres maladies sur lesquelles il travaillait.

Christopher Canning : J'aimerais qu'on revienne sur le Dr Scriver tout à l'heure, parce que nous allons bientôt parler de la formation du groupe, en 1972. Mais revenons un peu en arrière… La collaboration entre l'équipe de l'Hôpital pour enfants et du Département [de génétique] à l'Université était-elle bonne? Les relations étaient-elles amicales? Ça se passait comment à l'époque?

Dr Clarke Fraser : Il y avait une certaine ambivalence. Wallace Boyes, le directeur du Département de génétique, était favorable à la création de cette division à l'Hôpital pour enfants, parce qu'il la considérait comme un laboratoire où je pourrais voir des patients et accueillir des étudiants aux cycles supérieurs. Le Département y gagnait en prestige, c'était avantageux sur le plan financier, mais d'un autre côté, il craignait que la génétique humaine prenne le pas sur la génétique fondamentale, alors il était, comment dire… protecteur?

Christopher Canning : Il y avait une petite guerre de territoire, non? Le diriez-vous comme ça?

Dr Clarke Fraser : Le mot « guerre » est peut-être un peu fort, mais effectivement, si je disais « Il serait temps d'offrir un cours de génétique humaine », on me répondait « Mais pourquoi donc? Vous n'avez qu'à glisser des exemples de génétique humaine dans le cours de génétique générale ». Eh bien, non, ça ne suffisait pas. La génétique humaine avait progressé à un point tel qu'elle avait un corpus et des caractéristiques bien à elle. Ça m'a donc pris pas mal de temps à mettre ce cours sur les rails. Après, j'avais besoin de personnel, et ça, c'était menaçant. Alors, oui, il y avait de la concurrence. Finalement, le principal James[4] a réglé le problème en créant le secteur de la génétique humaine. Il relevait de trois doyens – médecine, sciences et – quel était le troisième, déjà? – études supérieures. Bref, c'était un monstre tricéphale qui cadrait parfaitement avec mon bagage en tératologie et dont, disons-le franchement, aucune des équipes ne se souciait vraiment, mais…

Christopher Canning : De votre travail en tératologie?

Dr Clarke Fraser : Oui, ou du secteur lui-même. Je n'avais pas à consulter le doyen très souvent. Son budget était indépendant de celui du Département de génétique, alors je pouvais embaucher du personnel et faire mes propres demandes de subvention sans passer par Wallace Boyes. Par contre, l'enseignement et la formation relevaient encore du Département, ce qui me convenait très bien,

[4] Frank Cyril James

parce que j'avais le sentiment que nous n'étions pas encore mûrs pour l'école de médecine; nous devions encore rester ancrés dans la génétique fondamentale. Bref, c'était un très bon compromis qui a fonctionné à merveille.

Christopher Canning : À quel moment, alors, avez-vous proposé une collaboration à l'école de médecine?

Dr Clarke Fraser : Le doyen de la Faculté de médecine était l'un des trois doyens dont relevait le secteur de la génétique humaine. La responsabilité de ce secteur lui incombait donc en partie. À vrai dire, je ne me rappelle pas avoir jamais… c'est arrivé beaucoup plus tard; je pense que par la suite, on a recommandé aux départements de génétique, de zoologie et de botanique de renoncer à leur identité propre pour former le Département de biologie. Des comités, des analystes indépendants, etc. ont jugé que c'était une bonne chose, et c'était probablement le cas, mais pour moi, ça voulait dire renoncer à mon secteur de génétique humaine et me joindre au Département de biologie. Ce n'est que beaucoup, beaucoup plus tard que nous avons commencé à faire pression pour la création d'un département distinct au sein de l'école de médecine. Leonard Pinsky, qui dirigeait le Centre de génétique humaine de la Faculté de médecine en 1979, a officiellement amorcé le maillage avec la médecine, et ces liens se sont resserrés peu à peu pour donner naissance au Département de génétique humaine, en 1993.

Christopher Canning : Je pense que Leonard Pinsky a créé le Département en 1979, et le groupe a été formé en 1972, alors c'était peu de temps après.

Dr Clarke Fraser : Pardon, vous alliez dire quelque chose.

Christopher Canning : Il n'y a pas de mal; continuez, je vous en prie.

Dr Clarke Fraser : J'en suis venu à connaître très bien le CRM, et j'ai été président du comité de génétique de cet organisme pendant sept ans, puis j'ai siégé à plusieurs autres comités. Alors, je connaissais ce groupe, et je pense que c'était réciproque. Je dois dire que ces gens m'ont très bien traité, et je suis sûr… enfin, lorsque je demandais du financement, je leur disais : « Voilà ce que j'ai fait jusqu'à maintenant. Je ne peux pas vous dire exactement ce que je ferai l'an prochain, parce que ça dépend de ce qui se présentera à l'hôpital, mais je m'attends à faire ceci et cela ». Ça leur suffisait, et ils continuaient à me financer. Jamais on ne verrait quelque chose comme ça aujourd'hui, j'en suis certain.

Christopher Canning : Ça se passait pendant vos premières années de recherche subventionnée, donc tout de suite après l'obtention de votre diplôme et le début de votre pratique?

Dr Clarke Fraser : Ils ont fait ça pendant quelques années. Au début, j'ai reçu de l'argent de la Fondation Rockefeller; cet organisme a donc doublement influencé la génétique à McGill. Mais l'essentiel des fonds provenait de… j'avais une subvention du CRM pour mes travaux en génétique humaine et une du Conseil national de recherches pour la tératologie; mais au bout d'un moment, ils ont réduit cette subvention à un point tel que j'avais à peine assez d'argent pour fonctionner. Je leur ai demandé plusieurs fois pourquoi ils me coupaient les vivres, et ils ont fini par admettre que selon eux, je touchais tellement d'argent

du CRM que je n'avais pas besoin de leur aide. J'ai donc mis fin à ma collaboration avec le CNR[5] et j'ai mis toute la gomme sur mes travaux avec le CRM, en tératologie.

Christopher Canning : La tératologie relevait du CRM?

Dr Clarke Fraser : Après que le CRN m'eut coupé les vivres, oui.

Christopher Canning : Je vois. En consultant vos publications et vos mémoires, j'ai constaté que les bases de la consultation génétique – qui allait prendre une énorme place dans votre travail – ont été mises en place essentiellement pendant les années 1950, est-ce exact?

Dr Clarke Fraser : Oui, oui.

Christopher Canning : Alors, j'aurais deux choses à vous demander, si vous le permettez. Dans un premier temps, j'aimerais que vous nous parliez de votre conception de la consultation génétique, et dans un deuxième temps, que vous expliquiez, pour ceux qui n'en auraient jamais entendu parler, la nature et l'origine de cette activité.

Dr Clarke Fraser : Bon. À mes débuts, la consultation génétique incombait surtout à des généticiens qui n'avaient pas de formation en médecine. Le médecin téléphonait pour dire : « J'ai une patiente atteinte d'hémophilie, et elle a un frère hémophile. Quel est le risque qu'un de ses enfants soit hémophile? » À l'époque, il n'y avait pas de test génétique. Il fallait être capable de prédire le risque à partir des modèles mendéliens. Le généticien évaluait le risque à, disons, un sur quatre, un sur douze et demi, 12,5 %, etc., et c'est ce que le médecin disait à son patient ou à sa patiente. Ensuite, par exemple, la patiente devait déterminer si le risque était assez grand et la maladie, assez grave, pour qu'elle mette fin à sa grossesse si elle était enceinte ou décide de ne pas avoir d'enfant; à l'époque, les gens étaient placés devant ce genre d'alternative. Quand je suis arrivé, c'est comme ça que les choses se passaient, et j'ai pu… d'abord, j'ai pu recueillir plus de données – des données plus précises – sur le risque de réapparition. Et j'ai aussi commencé à parler aux parents, à aller au-delà de ces simples questions pour plonger dans… j'ai publié un article intitulé « Genetic Counseling – The Darker Side », si je ne m'abuse.

Christopher Canning : Je me souviens d'avoir vu ça, oui.

Dr Clarke Fraser : C'est un constat – l'un des premiers constats – sur la complexité de la consultation génétique. Ça ne se résume pas à « oh, le risque est de un sur quatre, alors voyez ce que vous pouvez faire avec ça ». Je me suis rendu compte à quel point deux patients pouvaient percevoir différemment la gravité d'une maladie. Certains considèrent le bec-de-lièvre comme quelque chose de terrible qui est source de culpabilité, alors que d'autres l'acceptent très bien… même une chose comme la polydactylie, c'est-à-dire la présence de doigts supplémentaires. Certains considèrent cela comme la pire des calamités, alors que d'autres trouvent ça anodin. Les gens n'ont donc pas tous la même perception de la gravité, et il en va de même pour les risques. Si je dis : « les

[5] Conseil national de recherches

chances qu'un de vos enfants ait votre bec-de-lièvre sont de cinq pour cent », certains vont répondre « c'est sûr que ça va tomber sur moi », alors que d'autres vont dire « il y a donc 95 % de chances que ça ne se reproduise pas; génial, c'est beaucoup mieux que ce que nous pensions ». Voilà comment un simple risque statistique se décline dans toute une gamme de nuances suivant la perception qu'on a du problème et des solutions possibles. À mes débuts, la contraception était illégale au Québec.

Christopher Canning : Tout comme l'avortement?

Dr Clarke Fraser : Ah oui, l'avortement, ça va de soi, mais même la contraception était illégale. Pour se faire avorter, la femme, ou plutôt son obstétricien, devait en faire la demande, et c'est un comité qui déterminait si la maladie était assez grave et le risque, assez élevé; je devais envoyer des lettres à ce comité pour me prononcer sur ces questions.

Christopher Canning : En votre qualité de spécialiste en génétique ou parce que vous n'étiez pas obstétricien?

Dr Clarke Fraser : À titre de généticien. C'est moi qui savais quel était le risque. C'est comme ça qu'on fonctionnait. Peu à peu, avec la Révolution tranquille, l'avortement est devenu beaucoup plus accessible, mais il reste qu'un avortement, c'est un acte lourd de conséquences, et avant cela, il y avait… Je pense avoir évoqué une femme qui avait trois fils hémophiles; elle a voulu faire une demande d'avortement et un jour, elle s'est présentée, enceinte, chez son obstétricien et s'est mise à saigner dans son bureau. Plutôt que de laisser la nature suivre son cours, il a hospitalisé d'urgence la patiente et a jugulé l'hémorragie pour qu'elle puisse mener sa grossesse à terme, si bien qu'elle a donné naissance à un autre fils hémophile. Ce n'est vraiment pas simple. Est-ce logique de faire ça?

Christopher Canning : Effectivement, c'est assez ordinaire. Alors, dans un sens, vous avez aussi dû jouer les psychologues. C'est curieux… en ce milieu du XXe siècle, la consultation, la psychologie et la génétique médicale baignent dans une sorte de flou.

Dr Clarke Fraser : Vous avez absolument raison, et d'ailleurs, je ne me sentais pas du tout à la hauteur. Une formation en psychologie aurait été bien utile, mais j'ai dû improviser et consulter tantôt des psychologues, tantôt des psychiatres et…

Christopher Canning : Oui. Vous avez collaboré avec Abby Lippman pendant un temps, non?

Dr Clarke Fraser : Oui.

Christopher Canning : Vous a-t-elle aidé à préciser votre pensée sur le sujet?

Dr Clarke Fraser : Oui, elle a été géniale. Elle a publié avec moi trois articles qui ont fait école en consultation génétique, et elle assistait à mes rencontres habituellement avec les mères, parfois avec les parents, et enregistrait tout; après, elle les réécoutait et en tirait des thèmes. Elle a consigné dans des articles ce dont je vous parlais tout à l'heure, c'est-à-dire la diversité des perceptions et des réactions en matière de risque et de gravité.

Christopher Canning : Dans un autre ordre d'idées, il y a un thème qui revient constamment dans vos écrits, et c'est l'interaction entre le gène et le milieu.

Dr Clarke Fraser : Oui.

Christopher Canning : Et vous parlez même d'épigénétique, ce qui est intéressant étant donné que le terme a été créé en 1942…

Dr Clarke Fraser : Par…?

Christopher Canning : Par Waddington.

Dr Clarke Fraser : Ah oui, Waddington, c'est ça.

Christopher Canning : Donc, vous en parlez dans un article qui date de 1946, soit peu après la création du terme. Vous faites de la consultation génétique, mais vous savez, surtout en raison de vos travaux en tératologie et en cytogénétique, qu'il y a une interaction entre les facteurs du milieu et les gènes.

Dr Clarke Fraser : C'est exact.

Christopher Canning : Puis-je vous poser quelques questions sur vos recherches dans ce domaine? Que faisiez-vous pour comprendre l'interaction entre les deux?

Dr Clarke Fraser : On entre ici dans mes travaux de tératologie, puisque la tératologie est l'étude des anomalies congénitales, plus précisément de leurs causes et de leurs mécanismes. À l'époque, quand je suis arrivé à l'Hôpital [de Montréal] pour enfants, j'avais encore la salle des souris au Département de génétique. Il y avait un plasticien, Hamilton Baxter – « Happy Baxter » pour les intimes – qui était tout un numéro; il me donnait accès à des familles où il y avait des becs-de-lièvre pour que je puisse évaluer les risques de réapparition du problème. Un jour, il est arrivé avec de la cortisone; à l'époque, c'était tout nouveau, et on ignorait à peu près tout de ce médicament, sauf que c'était un corticostéroïde efficace dans l'arthrite. Alors, Hamilton Baxter a dit : « Il y a dans le jeune embryon un centre organisateur… un agent qui provoque la formation du tube neural à partir de l'ectoderme. Eh bien, c'est un corticostéroïde et le centre organisateur est aussi un corticostéroïde (ce qui s'est révélé faux), mais peut-être qu'en introduisant ce corticostéroïde dans l'embryon, on ferait dérailler le processus et on provoquerait une anomalie du tube neural chez l'embryon. Je trouvais ça un peu fou, mais je me suis dit essayons, on verra bien. J'ai donc injecté de la cortisone à quelques femelles gravides au labo en fixant pas mal au hasard la posologie et la durée du traitement, et, surprise, certains des embryons se sont retrouvés non pas avec une anomalie du tube neural, mais bien avec une fente palatine. Alors…

Christopher Canning : C'était une surprise totale? Vous ne vous attendiez pas à ça du tout?

Dr Clarke Fraser : Oui, c'était la première fois qu'on montrait l'effet tératogène d'un médicament chez des animaux de laboratoire. Évidemment, ça a causé tout un émoi, et bien sûr on s'est demandé si ça pouvait se produire chez l'être humain. Mais tout compte fait, la cortisone n'est pas très tératogène pour l'humain. Il y a des risques, mais ils sont minimes. Cela dit, j'ai constaté que la sensibilité variait

selon la souche murine; ainsi, la fréquence était élevée chez la souris AJAX, très sensible au médicament, alors qu'elle était très faible chez la C57 – l'autre souche –, très résistante. C'est donc ça, l'interaction entre les gènes et le milieu. Et c'est alors qu'un de mes étudiants, Bruce Walker, a décidé d'approfondir la question et a montré que pour que le palais se ferme, les bourgeons palatins devaient passer de leur position verticale, de part et d'autre de la langue, à la position horizontale et, pour ce faire, s'élever, pousser la langue pour l'écarter et se rejoindre sur la ligne médiane. Or, ce processus survenait beaucoup plus tard chez les souris AJAX que chez les C57. J'ai donc pensé que, passé un certain point, la tête grossissait tellement que lors de leur élévation, les bourgeons palatins étaient trop éloignés pour se rejoindre et que passé ce seuil, il y avait malformation; chez la souris AJAX, l'élévation des bourgeons palatins est beaucoup plus proche de ce point, normalement, sans… ça n'a rien à voir avec la sensibilité à la cortisone : ces souris sont plus exposées à la malformation en raison tout simplement du déroulement de leur développement.

Christopher Canning : Les gènes et leur milieu, bien sûr. Génial. Est-ce que tout ça est lié au terme « hétérogénéité génétique », que vous avez créé? Vous dites que vous avez utilisé le terme pour la première fois en recherche sur la génétique; que vouliez-vous dire par là, et comment en êtes-vous venu à le mettre en opposition avec de simples maladies mendéliennes?

Dr Clarke Fraser : À vrai dire, ce n'est pas vraiment simple et il n'y a pas d'opposition; c'est seulement que deux gènes différents peuvent être à l'origine d'un même phénotype, en l'occurrence de la même maladie. Et c'est logique, puisque la plupart de ces maladies génétiques résultent du blocage d'une chaîne de réactions biochimiques. Si la chaîne est bloquée, on n'obtient pas le produit final, ce qui provoque la maladie. Alors, que la chaîne soit bloquée au point A chez un animal – ou une personne – et au point C chez un autre, la maladie sera la même, puisque dans un cas comme dans l'autre, on n'aura pas obtenu le produit final de la séquence. Malgré tout, génétiquement, ce n'est pas la même maladie : nous sommes en présence de deux gènes différents à l'origine de la même maladie ou du même caractère.

Christopher Canning : Ou du phénotype, oui.

Dr Clarke Fraser : C'était donc un fait connu depuis longtemps. J'ai simplement forgé un terme. Je n'ai rien ajouté de fondamental au savoir existant.

Christopher Canning : Y avait-il à l'époque un autre mouvement qui prônait la fusion de la tératologie et de la génétique? Y avait-il la tératologie d'un côté et la génétique de l'autre, ou la tératogénétique a-t-elle au fond toujours existé? À quel moment la symbiose a-t-elle débuté?

Dr Clarke Fraser : La tératologie existait déjà à mes débuts; elle était portée principalement par Joe Warkany, à Cincinnati, qui avait montré qu'une déficience en vitamine B pouvait – à un niveau bien précis – provoquer des malformations chez le rat. Par ailleurs, on venait de constater que la rubéole causait de la surdité, des malformations cardiaques et des cataractes, et je pourrais vous donner un tas d'autres exemples; en revanche, jusqu'à mon arrivée, personne n'avait mis en lumière l'origine génétique de la sensibilité. Je n'ai forgé le terme

« tératogénétique » que beaucoup plus tard, je crois, mais c'est à ce moment que la génétique a fait son entrée en tératologie.

Christopher Canning : Vous êtes pour ainsi dire la première personne à avoir travaillé sur le bec-de-lièvre, non?

Dr Clarke Fraser : La fente palatine, en fait. Quoiqu'on pourrait inclure le bec-de-lièvre aussi. L'aspirine provoque le bec-de-lièvre chez la souris.

Christopher Canning : L'aspirine, ah oui?

Dr Clarke Fraser : Oui.

Christopher Canning : Prise en trop grande quantité?

Dr Clarke Fraser : Oui.

Christopher Canning : Est-ce la même chose chez l'humain?

Dr Clarke Fraser : Non, du moins pas à des doses non toxiques.

Christopher Canning : D'accord. C'est quelque chose que j'ignorais.

Dr Clarke Fraser : Eh bien, c'était… mais je m'écarte encore une fois du sujet.

Christopher Canning : Il n'y a pas de mal.

Dr Clarke Fraser : J'ai fait un exposé – je ne me rappelle plus où, peut-être à Cincinnati – devant des journalistes. La presse avait été invitée à une grande réunion d'information sur la tératologie, où j'ai fait un exposé sur les médicaments tératogènes, les malformations d'origine médicamenteuse; j'ai terminé ma présentation en disant qu'une femme ne devrait prendre un médicament que si elle en avait vraiment besoin, puisqu'on ne savait jamais…

Christopher Canning : Quels pourraient être ses effets indésirables, bien sûr.

Dr Clarke Fraser : … et quelqu'un a dit : « Est-ce vrai également pour l'aspirine? » Ce à quoi j'ai répondu : « Eh bien, je suppose que oui. » Le lendemain, on pouvait lire à la une des journaux, d'un bout à l'autre du pays : « L'aspirine provoque des déficiences congénitales ».

Christopher Canning : [rires] « Un médecin affirme que l'aspirine cause des déficiences congénitales. »

Dr Clarke Fraser : Bon, « un médecin affirme » n'était peut-être pas toujours là. Mais, oh, mon ami Joe Warkany m'en voulait au possible. J'y suis donc retourné et j'ai demandé à ma collègue, Daphne Trasler, d'administrer de l'aspirine à des souris… qui se sont retrouvées avec de superbes becs-de-lièvre. C'est ce qui m'avait fait soupçonner l'aspirine dès le départ.

Christopher Canning : Et vous avez ensuite réussi à localiser le gène lié au bec-de-lièvre?

Dr Clarke Fraser : Moi, non, mais certains de mes étudiants aux cycles supérieurs ont localisé une partie des gènes. Car ce n'est pas un seul, mais bien plusieurs gènes, et je pense qu'ils sont encore loin de les avoir trouvés tous.

Christopher Canning : Mais c'est ce qui a fait germer l'idée d'une sensibilité génétique à l'aspirine?

Dr Clarke Fraser : Oui.

Christopher Canning : Et, bien sûr, cela a influencé vos propres travaux dans d'autres domaines, comme la fente palatine?

Dr Clarke Fraser : Je ne suis pas certain qu'on puisse parler d'influence; ça en faisait partie.

Christopher Canning : Je vois. C'est également à cette époque qu'est apparu dans vos publications le modèle multifactoriel à seuil. Et selon vous, c'est là que se situe le point de jonction entre la tératologie et la génétique dans vos travaux. Nous avons effleuré le sujet, mais que voulez-vous dire exactement par « des gènes bien définis ont un rôle à jouer dans le modèle multifactoriel »?

Dr Clarke Fraser : J'ai dit ça, moi?

Christopher Canning : Oui, je vous cite textuellement.

Dr Clarke Fraser : Je vous ai parlé de la fente palatine provoquée par la cortisone, de la répartition de la prédisposition et du seuil. Nous avons pu cerner plusieurs facteurs qui modifient la position de la répartition, c'est-à-dire le moment où s'élèvent les bourgeons palatins. Ces bourgeons possèdent une force intrinsèque qui leur permet de venir à bout de la résistance de la langue et de l'écarter du chemin pour s'élever; c'est, véritablement, une lutte sans merci. Il y a donc la force des bourgeons palatins, et nous pensons que les mucopolysaccharides, qui confèrent aux bourgeons leur souplesse, pourraient y être pour quelque chose. Chose certaine, la cortisone a fait diminuer les mucopolysaccharides, alors c'est une explication raisonnable. Puis il y a la résistance de la langue. Par exemple, il existe un gène qui réduit à néant la musculature de la langue. Or, en présence de cette masse difforme et inerte, les bourgeons palatins ne s'élèvent pas. Divers facteurs entrent donc en ligne de compte : la force des bourgeons, la résistance de la langue et le seuil. Si la tête est trop large, les bourgeons doivent s'élever plus tôt pour réussir à fusionner. Il y a aussi la largeur des bourgeons : s'ils sont trop étroits, ils doivent fusionner plus tôt. Donc, les facteurs sont nombreux, et chacun subit l'influence de gènes. On peut donc dire sans se tromper que des dizaines, voire des centaines, de gènes déterminent le moment de l'élévation des bourgeons palatins et influent sur le risque qu'ils ne s'élèvent pas à temps pour fusionner, et le cas échéant…

Christopher Canning : … il se forme une fente.

Dr Clarke Fraser : Voilà. Et ce principe s'applique à un tas d'autres… à la plupart des maladies familiales qui ont un seuil, je pense. Je ne saurais dire avec certitude si la schizophrénie, par exemple, a un seuil, mais enfin, la plupart des maladies familiales. La quasi-totalité des troubles familiaux qui ne sont pas des maladies monogéniques pures et simples entre dans cette catégorie. Et maintenant, les chercheurs s'intéressent à ce qu'on appelle les « maladies complexes »,

recherchent les gènes sous-jacents. Je leur ai dit il y a bien des années que chacun de ces gènes allait avoir un effet minime. Si le gène avait un effet marqué, nous serions en présence d'une maladie mendélienne. Alors, tous les gènes qu'ils recherchent ont des effets minimes, et il y en a des centaines. Un individu peut avoir six gènes qui provoquent une lente élévation et se retrouver avec une fente palatine, et un autre peut avoir six autres gènes qui, eux aussi, provoquent une lente élévation. Il se peut que certains gènes soient les mêmes – il peut y avoir chevauchement – mais il demeure que chaque individu possède un ensemble de gènes distinct, qui lui est propre, mais se retrouve avec la même fente palatine. Comme vous le voyez, c'est très complexe.

Christopher Canning : Sur des chromosomes différents?

Dr Clarke Fraser : Ça se pourrait fort bien, oui; probablement, en fait.

Christopher Canning : Parlant de complexité, quelle est la complexité du développement?

Dr Clarke Fraser : Il y en a qui commencent à se rendre compte, à leur grand étonnement, qu'il est très difficile de trouver des gènes qui modifient la prédisposition; c'est pour ça que leur quête n'est pas très fructueuse.

Christopher Canning : C'est intéressant, parce que vous avez parlé d'épigénétique tout à l'heure; or, à mon avis, cette compréhension de la complexité, c'est la direction que prend la recherche en épigénétique actuellement.

Dr Clarke Fraser : Elle va vers…

Christopher Canning : … la complexité. Quels sont les interactions génétiques complexes et le milieu qui contribuent à l'apparition de la maladie?

Dr Clarke Fraser : Oui, alors on complexifie une réalité déjà complexe.

Christopher Canning : Oui, ce qui interpelle les généticiens encore à la recherche d'un seul gène.

Dr Clarke Fraser : Oui.

Christopher Canning : Vous dites que la question se posait déjà il y a cinquante ans.

Dr Clarke Fraser : Oui, elle se posait. Mais à l'époque, on n'avait vraiment pas les outils moléculaires nécessaires pour y répondre.

Christopher Canning : Je vois, très intéressant.

Dr Clarke Fraser : Aujourd'hui, on a les outils nécessaires pour trouver ces gènes, mais on ne les trouve pas, probablement parce que dans une famille, c'est tel ensemble de gènes et dans l'autre, c'est tel autre ensemble. Et même au sein d'une famille, les six ou sept gènes en cause exercent chacun un effet minime. Or, il est très difficile de trouver un gène dont l'effet est minime.

Christopher Canning : D'accord. Êtes-vous encore d'attaque ou si vous aimeriez faire une courte pause avant que je passe aux questions sur le groupe? Nous pouvons nous arrêter cinq minutes, le temps d'aller chercher un verre d'eau, puis reprendre

la conversation; nous en avons pour une autre demi-heure à peu près. Ça vous convient?

Dr Clarke Fraser : Oui, ça me convient.

Christopher Canning : Parfait.

Dr Clarke Fraser : Vous dites que j'ai utilisé le terme il y a des années au sens où Waddington l'entendait, mais je ne pense pas qu'il était au courant de cette inactivation des gènes dans les ovaires, mais pas dans les testicules… ce genre de choses.

Christopher Canning : Les groupes méthyles, et…

Dr Clarke Fraser : Oui, et la transmission à la génération suivante. C'est tellement récent… ça date d'au plus dix ans, non?

Christopher Canning : Dix ans, oui. Le plus fascinant dans tout cela, c'est la transmission des caractères de génération en génération, sans modification de l'ADN. C'est presque lamarckien. C'est ce… on dit que c'est un retour aux caractères acquis de Lamarck.

Dr Clarke Fraser : Pour ma part, j'ignore comment Lamarck pourrait y voir une « orientation sélective ». Je ne vois pas cela en épigénétique. Il n'y a pas de réorientation ciblée, par exemple la girafe qui se retrouve avec un long cou parce qu'elle s'étire.

Christopher Canning : D'accord, c'est le hasard qui décide, dans un sens, ce n'est pas ciblé; je comprends.

Dr Clarke Fraser : Donc, ce n'est pas lamarckien.

Christopher Canning : Oui, évidemment, vous le savez beaucoup mieux que moi; je suis encore un néophyte en la matière.

Dr Clarke Fraser : Puis il y a la variation du nombre de copies, quelque chose de tout nouveau… une autre source de variation génétique.

Christopher Canning : Comment dites-vous?

Dr Clarke Fraser : La variation du nombre de copies.

Christopher Canning : Je n'ai jamais entendu parler de ça.

Dr Clarke Fraser : Ça va venir.

Christopher Canning : D'accord.

Dr Clarke Fraser : C'est une toute nouvelle source de variation génétique, quelque chose de totalement inattendu. Je suis allé à un congrès de la Fondation Gairdner à Halifax, où j'ai assisté à un exposé – de Scherer je crois, de Toronto – sur la question. Faites une recherche sur « variation du nombre de copies ».

Christopher Canning : D'accord. La dernière partie de l'entrevue est moins longue que la première et porte sur les origines du groupe du CRM. On m'a demandé de faire des entrevues avec les treize membres qui, à un moment ou à un autre, ont reçu du financement et fait de la recherche dans ce groupe. J'ai apporté une liste que nous pourrons parcourir ensemble dans un moment. Pour l'instant, j'aimerais que vous me parliez de l'importance de votre rencontre avec le Dr Scriver et de votre relation avec lui. Quelle a été son influence sur votre travail et la nature de votre collaboration à cette époque?

Dr Clarke Fraser : Eh bien, comme je vous l'ai dit, j'étais bien content de le voir là, parce que sa présence nous a ouvert un tout nouveau champ de recherche; [notre rencontre] a ouvert la possibilité de présenter certaines de ces maladies, ou au moins de les traiter intelligemment. Cela dit, nous n'avons pas beaucoup collaboré. Nous travaillions en parallèle, et je dois avouer que je n'en connais probablement pas autant que je devrais en biochimie génétique, parce que dès que quelque chose du genre se présentait, j'envoyais ça au laboratoire de [Charles] Scriver pour qu'il s'en occupe. Alors, je pense que c'est la bonne entente qui décrit le mieux notre relation; nous n'étions pas en compétition et nous ne marchions pas sur nos plates-bandes respectives. Nos rapports ont toujours été on ne peut plus cordiaux, et si nous n'étions pas en concurrence, c'est sans doute parce que nous travaillions dans des domaines différents.

Christopher Canning : Comment vos travaux l'ont-ils influencé, à votre avis? Vous avez mentionné qu'il vous voyait un peu comme un père; selon vous, qu'est-il allé chercher dans vos travaux en génétique et en médecine?

Dr Clarke Fraser : Je l'ignore.

Christopher Canning : Je devrai lui poser la question.

Dr Clarke Fraser : Oui. Il semble m'avoir en haute estime, et c'est réciproque, mais je ne vois pas… il n'avait pas besoin d'aller chercher quoi que ce soit dans les travaux des autres.

Christopher Canning : Je vois. À votre avis, y avait-il d'autres endroits au Canada où cliniciens et biochimistes collaboraient ainsi? Avez-vous eu le sentiment que, du moins dans les années 1950, il y a eu une amorce de collaboration entre fondamentalistes et cliniciens?

Dr Clarke Fraser : Oh oui, un climat de collaboration s'installait. C'est en grande partie la phénylcétonurie qui a ouvert le bal, je pense. Nous avions là une maladie génétique que nous pouvions traiter; ce n'était pas rien, et cette maladie-là a fait beaucoup de bien à l'image de la génétique médicale. Je ne me souviens pas si quelqu'un à Toronto s'est penché sur ce dossier à l'époque. Chose certaine, le germe de la collaboration était bel et bien là.

Christopher Canning : Vous souvenez-vous la première fois où vous avez vu l'appel de propositions du CRM pour cette subvention de groupe, et vous rappelez-vous avoir dit au Dr Scriver qu'il ne fallait pas laisser passer ça, que vous deviez former un groupe?

Dr Clarke Fraser : Non. Mes souvenirs ne sont pas très clairs. J'avais des problèmes personnels

à l'époque et, comme je l'ai dit tout à l'heure, je travaillais de près avec le CRM et je passais pas mal de temps à Ottawa, alors ils me connaissaient. Selon moi, l'idée des subventions de groupe, c'était essentiellement d'offrir une stabilité financière à des gens qui travaillaient dans tel ou tel domaine : au lieu de devoir faire des demandes de subventions tous les deux ou trois ans, les chercheurs avaient l'esprit tranquille pendant cinq ans et pouvaient planifier en conséquence. La règle, c'était que chaque membre du groupe devait d'abord aller chercher une subvention à titre individuel, puis on procédait ensuite à une mise en commun. Il y avait un groupe de génétique, un groupe de physiologie, un groupe de biochimie, etc., et notre groupe à nous. Je ne sais pas si nous avons soumis une demande en bonne et due forme; c'est peut-être même Malcolm Brown qui a proposé que nous formions un groupe; je n'arrive pas à m'en souvenir.

Christopher Canning : Une partie de mon travail consiste à réunir d'anciens documents, et le Dr Rosenblatt m'a donné la plupart des demandes. Je peux donc vous confirmer qu'il y a une demande datée de 1972; si les fonds sont arrivés cette année-là, j'imagine qu'elle a été soumise en 1971.

Dr Clarke Fraser : Ah, voilà. Mais par qui est-elle signée?

Christopher Canning : Je ne l'ai pas encore vue. Tous les documents sont dans une boîte; je ne les ai pas encore parcourus.

Dr Clarke Fraser : Mmm.

Christopher Canning : C'est un autre volet du projet : réunir le plus de documentation possible pour en faire don à la Bibliothèque Osler et immortaliser ce groupe important, actif pendant si longtemps. Mon autre question est la suivante : est-ce que les projets ou les divers champs de recherche à la base du groupe – cytogénétique, biologie moléculaire, biochimie, pédiatrie – se sont présentés naturellement ou ont été triés sur le volet? Vous êtes-vous dit « voilà le genre de groupe que nous devons former » ou plutôt « il y a ce chercheur-là et ce médecin-là qui pourraient travailler ensemble »?

Dr Clarke Fraser : Je ne me rappelle pas avoir dit « c'est comme ça que nous allons procéder ». La biochimie génétique s'imposait tout naturellement, puis… la cytogénétique, qui allait de soi. Il ne s'agissait pas de dire « nous devons aller chercher ça pour former un groupe ». La génétique moléculaire n'existait même pas à l'époque si je ne m'abuse, n'est-ce pas? Oui, alors non, ça s'est fait tout naturellement; les gens s'aimaient bien et avaient envie de travailler ensemble.

Christopher Canning : Vous souvenez-vous des réunions du groupe? Vous réunissiez-vous lorsque vous travailliez à ces projets et à ces demandes de subvention?

Dr Clarke Fraser : Je ne m'en rappelle pas. Charles [Scriver] pourra vous renseigner à ce sujet.

Christopher Canning : D'accord, j'en saurai sans doute plus au fil des entrevues. Dans une de vos publications, vous soulignez que la mise sur pied du Département de génétique humaine en 1979, par Leonard Pinsky, est en partie attribuable au travail acharné de ce groupe. Quels sont les protagonistes dans ce dossier, vous en rappelez-vous? Quels facteurs, au sein du groupe précisément, militaient en

faveur de la création d'un département de génétique humaine?

Dr Clarke Fraser : Je n'en sais rien. Déjà à l'époque, par son corpus, la génétique humaine était une entité à part entière, distincte en quelque sorte de la génétique fondamentale, et logiquement beaucoup plus près de la médecine que de la biologie. Je dois vous avouer que j'ai toujours fui comme la peste les tâches administratives et que je n'avais pas envie de prendre cette responsabilité. En quelle année le Centre de génétique humaine a-t-il été formé, en 1972?

Christopher Canning : Non, en 1979. Et d'après ce que je peux voir jusqu'à maintenant – vous êtes la première personne que j'interviewe – le Dr Scriver et vous avez organisé et supervisé cette entité ensemble, un peu comme des codirecteurs, jusqu'à ce que Leonard Pinsky, probablement, reprenne le flambeau en 1979.

Dr Clarke Fraser : Oui, c'est ça, je crois.

Christopher Canning : D'après vos souvenirs, c'est bien comme cela que ça s'est passé? Je vérifierai au fil de l'étude. Dans l'ensemble, quelle était la dynamique du groupe?

Dr Clarke Fraser : La dynamique du groupe? Je ne suis pas très ferré en psychologie.

Christopher Canning : [rires] Eh bien, il faut être un peu psychologue pour faire de la consultation génétique, non?

Dr Clarke Fraser : Ou plutôt sociologue, peut-être. Je me souviens de réunions du groupe, probablement au Département de génétique humaine. Je ne me souviens d'aucun conflit, à vrai dire. Les gens se respectaient et s'aimaient bien, nous faisions notre planification de façon très amicale. J'étais bien content d'avoir réussi à persuader Leonard [Pinsky] d'accepter la responsabilité, parce que moi, je n'en voulais pas.

Christopher Canning : Au début des années 1980, vous vous êtes installé à Terre-Neuve, n'est-ce pas?

Dr Clarke Fraser : Exact. J'étais à trois ans de la retraite, la routine commençait à me peser un peu, j'étais surmené et je croulais sous les demandes de consultation génétique; des familles revenaient me consulter, bref, j'étais débordé. Des gens désiraient établir un service de génétique à Terre-Neuve; ils m'ont d'abord demandé de faire partie du comité de recrutement du directeur, puis un jour, ils m'ont appelé pour me proposer de me retirer du comité et de poser ma candidature au poste. Je me suis dit que ça pourrait être bien de changer d'air pour finir ça en beauté, alors j'y suis allé et j'ai adoré ça. Nous avons eu beaucoup de plaisir, nous avons rencontré des gens de bonne volonté et essuyé quelques vents contraires; finalement, je n'ai pas mis le service sur les rails, mais je pense avoir très bien préparé le terrain pour mon successeur, et aujourd'hui, ils ont un bon service. Ils ne m'ont pas parlé du statut de professeur émérite ou de ce que je ferais passé l'âge de la retraite. Je pense que c'est Charles [Scriver] qui a convaincu McGill de m'offrir un poste de professeur émérite, que j'ai accepté avec gratitude, et je suis revenu en… 1985, peut-être?

Christopher Canning : 1985, oui, c'est ce qui est indiqué sur votre C. V.

Dr Clarke Fraser : J'ai donc pu continuer à enseigner et à faire un peu de recherche à l'Hôpital [de Montréal] pour enfants, et j'ai eu quatorze autres belles années.

Christopher Canning : Comme professeur émérite, ici même à Montréal. Puis vous avez pris votre retraite dans votre maison de Nouvelle-Écosse.

Dr Clarke Fraser : C'est bien cela.

Christopher Canning : Pouvez-vous me parler un peu de cette maison?

Dr Clarke Fraser : Je pense que vous avez une photo.

Christopher Canning : Dans vos mémoires, oui.

Dr Clarke Fraser : C'est une belle vieille maison que mon grand-père a achetée en 1898, je pense, alors que je n'étais encore qu'un jeune enfant. Elle surplombait la rivière, et j'y ai vécu beaucoup de moments heureux quand j'étais enfant. Ma femme, qui était généticienne, a un jour voulu devenir avocate; après l'école de droit, elle a fait son stage à Digby, parce qu'elle aimait la Nouvelle-Écosse. Bear River est tout près de Digby, alors elle habitait la maison et faisait la navette matin et soir. Elle a consacré un temps fou à la remise en état de la maison, qui n'avait fait l'objet d'aucuns travaux pendant peut-être cinquante ans. Elle a arraché trois ou quatre épaisseurs de papier peint et a reconfiguré une partie de la maison pour la moderniser, en particulier la cuisine. Elle a fait un superbe travail, et au fond, c'est elle qui… elle disait qu'elle se sentait davantage chez elle dans cette maison que dans sa propre maison à Winnipeg… non, à Edmonton. Alors, grâce à elle, je n'ai eu aucun mal à retourner m'installer là-bas.

Christopher Canning : Et vous y êtes depuis votre départ de McGill?

Dr Clarke Fraser : Depuis 1999, oui.

Christopher Canning : 1999. Et vous lisez et écrivez encore; vous avez publié pas mal de choses depuis.

Dr Clarke Fraser : Oui, je publie encore. J'entretiens mes relations dans le milieu de la recherche. Je ne sais pas ce que je ferais sans Internet. J'écris aussi beaucoup de critiques de livres. Je dirige la revue de livres de l'*American Journal of Medical Genetics*, ce qui me donne une excuse pour appeler de vieux amis. J'ai fait un truc sur l'agent orange il y a quelques années.

Christopher Canning : Ah oui? Et n'avez-vous pas écrit aussi un petit guide sur la génétique, une sorte d'initiation à la génétique fondamentale?

Dr Clarke Fraser : Vous parlez du livre sur la généalogie?

Christopher Canning : Oui.

Dr Clarke Fraser : Il renferme effectivement une introduction à la génétique, mais il s'adresse d'abord et avant tout aux généalogistes, qui, pour la plupart, ne semblent pas s'intéresser du tout à la génétique. Vous savez, ils ne consignent pas les

choses importantes, par exemple la cause de la mort ou les maladies dont souffrait le défunt. Je voulais les encourager à commencer à le faire. Mais le livre renferme aussi beaucoup d'informations habituellement difficiles à obtenir pour le profane, par exemple sur la transmission des maladies familiales, sur les conséquences d'avoir un proche parent atteint de telle ou telle maladie, vous voyez, quels sont les risques d'en être atteint et comment faire pour s'en protéger. Ce n'est pas un gros vendeur. Je l'ai écrit pour informer les gens, et il semble que ce ne soit pas très populaire, mais c'est un bon livre.

Christopher Canning : D'accord, je vais jeter un coup d'œil à ça. Où s'en va la recherche en génétique à votre avis?

Dr Clarke Fraser : La génétique?

Christopher Canning : La génétique et la médecine; la génétique médicale. C'est une vaste question, je sais, mais étant donné votre apport important à ce domaine, j'aimerais savoir où nous en serons, selon vous, dans dix ou vingt ans.

Dr Clarke Fraser : Bon, alors, j'imagine que la plupart des gens voient la génétique médicale là où il y a… à long terme, nous recevrons tous à la naissance une puce qui renfermera l'ensemble de nos prédispositions génétiques, des médicaments auxquels nous sommes sensibles, etc., et le médecin pourra s'y reporter lors de la prescription d'un médicament. Ça arrivera peut-être un jour, mais je pense que ce sera beaucoup plus long que certains le croient, parce que ça pose de nombreux problèmes éthiques et pratiques, et la thérapie génique progresse beaucoup plus lentement qu'on le croyait au départ. Je vois très peu de maladies pour lesquelles on aura un jour un traitement génétique, et ce n'est pas demain la veille.

Christopher Canning : Vraiment. Ils devront se heurter à un mur, selon vous?

Dr Clarke Fraser : Je le répète, faire entrer un gène quelque part, s'assurer qu'il y reste et qu'il ne provoque pas de cancer dans la cellule pose tellement de difficultés pratiques… les choses sont loin d'aller comme sur des roulettes dans ce domaine. On devra s'armer de patience, mais j'imagine qu'on arrivera un jour à traiter au moins quelques-unes de ces maladies en changeant le gène défectueux plutôt qu'en traitant ses conséquences.

Christopher Canning : Je vois. On parle donc de diagnostic et de traitement prénatals.

Dr Clarke Fraser : De diagnostic préimplantatoire… c'est déjà une réalité, en fait. Non, je pense à des interventions postnatales. Je pense qu'un jour, on pourrait trouver le gène à l'origine de la dystrophie rétinienne, qui touche beaucoup de personnes âgées. Selon moi, c'est l'un des problèmes qu'on pourrait parvenir à traiter par voie génétique.

Christopher Canning : Ah, d'accord.

Dr Clarke Fraser : La fibrose kystique n'est pas… ils pensaient que ça irait tout seul, mais c'est loin d'être le cas. Ils ont tenté de traiter un type d'hémophilie par voie génétique, mais des lymphomes sont apparus chez plusieurs patients. Donc, ça avance à pas de tortue, mais on va y arriver.

Christopher Canning : La recherche sur le cancer… à votre avis, la génétique médicale progresse-t-elle sur ce front?

Dr Clarke Fraser : De ce côté, les résultats sont encourageants. Je lisais dernièrement qu'ils arrivent maintenant à observer les gènes d'un cancer donné. Le cancer résulte habituellement de la mutation somatique de trois ou quatre gènes et non d'un seul gène. L'existence des nombreux mécanismes de régulation de la division cellulaire est utile, puisque si l'un d'eux lâche, plusieurs autres pourront prendre le relais; mais à un moment donné, ils lâchent tous et la cellule peut se multiplier sans contrainte. Aujourd'hui, on peut déterminer quels gènes ont subi une mutation dans un cancer donné, ce qui permet de choisir un traitement beaucoup mieux adapté.

Christopher Canning : Vous avez commencé à publier des articles sur la schizophrénie et les anomalies du tube neural; votre publication la plus récente remonte à 2005. Puis-je vous demander sur quoi portera votre prochain article? Sur quoi travaillez-vous?

Dr Clarke Fraser : Lors d'un congrès sur les anomalies du tube neural auquel j'ai assisté, à Burlington, une personne a souligné que l'anencéphalie était plus fréquente chez les filles; il a aussi été question d'un groupe d'anencéphales où les filles étaient plus nombreuses non seulement chez les sujets anencéphales, mais également chez leurs frères et sœurs sains, ce qui était pour le moins curieux. Et là, j'ai pensé qu'il y avait peut-être un sous-groupe d'anencéphalie liée à un seul gène, qui serait mortel pour les garçons, mais provoquerait une anencéphalie chez une minorité de sujets hétérozygotes – les femmes porteuses; et si on y pense, ça pourrait fonctionner : il y aurait 25 % de garçons non touchés et donc absents du groupe, ce qui laisse un excès de filles. C'est une explication qui se tient. En ce moment, je fouille dans les vieux dossiers du Département de génétique de l'Hôpital [de Montréal] pour enfants pour voir si ça s'applique dans nos familles. Le cas échéant, nous pourrions faire d'autres analyses pour confirmer ou infirmer ce mécanisme. Peut-être pourrait-on ensuite cibler ce sous-groupe et trouver le gène, qui serait un gène important. J'ai aussi accepté un autre mandat… il y a une sorte d'encyclopédie, je pense, la « Lincoln Reference Library », et on m'a demandé de mettre à jour la partie sur la génétique. Je vais m'attaquer à ce mandat très bientôt.

Christopher Canning : « Lincoln Reference », vous dites?

Dr Clarke Fraser : Lincoln Reference.

Christopher Canning : C'est un genre de base de données scientifique?

Dr Clarke Fraser : C'est cela, mais davantage une bibliothèque de référence générale.

Christopher Canning : Je vois. Voilà, c'est ce qui conclut notre entrevue. Un grand merci à vous, docteur Fraser.

FIN DE L'ENTRETIEN

Dr David Rosenblatt, le 1er décembre 2009

Christopher Canning : Nous sommes le 1er décembre 2009. Ici Christopher Canning en compagnie du Dr David Rosenblatt du Département de génétique humaine. Docteur Rosenblatt, je suis très honoré de pouvoir m'entretenir avec vous de deux grands sujets qui touchent la génétique humaine.

J'aimerais d'abord que nous parlions de votre parcours universitaire qui, bien sûr, a grandement contribué à l'avancement de la médecine génétique au Canada et ailleurs dans le monde. Ensuite – et surtout, pour les besoins de notre étude – je m'intéresse à votre participation au groupe sur la médecine génétique des IRSC[1], anciennement le CRM[2], dont vous avez fait partie de 1975 à 2009, ce qui fait de vous le membre qui a les plus longs états de service.

Avant de parler du groupe comme tel – je pose des questions ouvertes et vous prenez tout le temps que vous voulez pour y répondre – j'aimerais que nous parlions un peu de vous : l'endroit où vous êtes né et avez grandi, vos premières années de vie et d'école, ce genre de choses.

Dr David Rosenblatt : Je suis né le 14 juillet 1946 à Montréal, et mes parents sont également nés tous les deux à Montréal, un en 1909 et l'autre en 1911. Leurs parents étaient d'origine juive ashkénaze; la famille de ma mère venait de Lituanie, et mon père venait d'Afrique du Sud. D'après une rumeur qui courait dans la famille, il était venu au Canada après avoir été plaqué par une femme en Afrique du Sud. La famille de mon père venait de Galice. Ma mère a grandi sur la rue Notre-Dame, tout près du Marché Atwater, et mon père, sur la rue Rachel, dans ce qu'on appelle aujourd'hui le Plateau. Autour de 1921 ou 1922, la famille de ma mère a déménagé dans le quartier qu'on appelle aujourd'hui NDG[3]. Mes parents se sont mariés au début des années 1930, et je suis le benjamin d'une famille de trois : ma sœur avait 12 ans et mon frère, six ans et demi de plus que moi. Ils sont décédés aujourd'hui, tous les deux autour de l'âge de 58 ans. Nous sommes une famille de la guerre et de la dépression; ma sœur est née en 1934, je crois, mon frère, en 1939, et moi, en 1946; comme vous le voyez, on couvre pas mal la période de la guerre. Ma mère avait trois sœurs, et chacune des quatre filles a donné naissance à un fils en 1946, deux à Montréal et deux à New York; nous sommes dans la démographie du baby-boom, je pense. J'ai grandi dans NDG; le père de ma mère est mort en 1948, et mes parents se sont installés dans la maison de mes grands-parents avec ma grand-mère jusqu'en 1963. Mes racines sont donc montréalaises. J'ai fait mon primaire dans une des premières écoles confessionnelles juives, la Shaare Zion Academy. J'ignore si vous voulez tout savoir; vous avez beaucoup de place sur votre enregistreur, alors je l'occupe.

Christopher Canning : Je vous en prie, parlez aussi longtemps que vous le souhaitez.

Dr David Rosenblatt : D'accord. Je ne sais pas si vous êtes au courant de ça, mais la communauté juive de Montréal est intéressante, parce que pendant de nombreuses années,

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada
[3] Notre-Dame-de-Grâce

les écoles étaient confessionnelles. Il y avait deux systèmes scolaires, le catholique et le protestant. Les Juifs étaient des immigrants qui ne parlaient ni anglais ni français, mais ils n'étaient pas admis dans les écoles catholiques, si bien que par défaut, ils sont allés dans les écoles protestantes. C'est pour cette raison que la plupart des Juifs sont anglophones. J'ai donc fréquenté une école confessionnelle. J'ignore pourquoi il n'y avait pas d'écoles juives lors de la mise sur pied du système scolaire confessionnel. C'était à l'époque de la montée du fascisme, alors le contexte politique ne s'y prêtait pas. Puis, dans les années 1950, l'État s'est ouvert aux écoles ethniques, des établissements quasi privés où l'enseignement laïque était aux frais de l'État et l'enseignement religieux relevait du privé. Pour cette même raison, il y a des écoles grecques et arméniennes à Montréal. J'ai donc fait mon primaire dans une école juive confessionnelle comme élève externe, et mon secondaire au public, à l'école secondaire Westmount High. Au début, il y avait la Junior High et la Senior High : la Junior High était dans une école qui donne sur le parc Westmount, dans le « Lower Westmount », et la Senior High était dans l'immeuble qui abrite aujourd'hui l'école Selwyn House, et ils…

Christopher Canning : C'est toujours à NDG, n'est-ce pas?

Dr David Rosenblatt : Non, c'est à Westmount.

Christopher Canning : Westmount.

Dr David Rosenblatt : J'habitais aux confins de Westmount; mon frère et ma sœur avaient tous les deux fréquenté Westmount High, mais je faisais partie de la première cohorte qui a emménagé dans l'école fusionnée de la rue Sainte-Catherine. C'était, oh seigneur, je ne sais pas, en 1959 ou 1960, vous pourrez vérifier en quelle année la Westmount High a ouvert, mais donc c'était la première année dans cette école, où j'ai obtenu mon diplôme d'études secondaires. C'était avant – je ne sais pas si vous savez ce que sont les cégeps à Montréal, mais c'était avant l'arrivée des cégeps. McGill offrait ce qu'on appelait le « programme de médecine de sept ans ». Le programme actuel, qui suit les deux années de cégep, représente à peu près la moitié de ce programme. Aujourd'hui à McGill, ces étudiants suivent… je pense que c'est un programme de six ans qui comprend deux années de base et quatre années d'école de médecine. Vous pourrez vérifier, mais au terme de leurs études, ils n'obtiennent qu'un doctorat en médecine, pas de baccalauréat. Dans mon temps, nous avions le programme de sept ans : pendant les deux premières années, nous faisions le programme de premier cycle en sciences plus un cours supplémentaire; la troisième année, nous avions quatre cours, le cours d'anatomie de la première année de médecine avec la cohorte de médecine, puis nous rejoignions cette cohorte la deuxième année et après sept ans, nous avions un baccalauréat en sciences et un doctorat en médecine.

Christopher Canning : C'est bon, je comprends.

Dr David Rosenblatt : J'ai donc fait ça de 1963 à 1970. Je suis de la promotion de 1970. J'ai fait mes études avec [Abraham] Fuks, ex-doyen [de la Faculté de médecine], qui a lui aussi fait le programme de sept ans.

Christopher Canning : D'accord.

Dr David Rosenblatt : Nous étions 25 dans la promotion de 1970.

Christopher Canning : Je vois ici que vous faisiez partie de la Faculté des arts et des sciences.

Dr David Rosenblatt : Oui, parce que nous avions un baccalauréat en sciences en plus du doctorat en médecine; c'est l'équivalent du programme collégial aujourd'hui, puisqu'il n'y avait pas de cégep à l'époque. La différence aujourd'hui, c'est qu'ils n'ont plus de baccalauréat en sciences, mais seulement un doctorat en médecine, alors ils demeurent au premier cycle jusqu'à ce qu'ils obtiennent ce doctorat.

Christopher Canning : Ah, d'accord, je comprends.

Dr David Rosenblatt : Et il n'y a pas de baccalauréat en sciences aujourd'hui, alors pour l'étudiant qui veut faire des études supérieures, ça complique les choses, si vous voyez ce que je veux dire.

Christopher Canning : Oui.

Dr David Rosenblatt : La sœur de ma mère a épousé un pédiatre de Montréal, William Gavsie, et – courte parenthèse – lui et son frère étaient originaires des Maritimes. Drôle de hasard, ma femme venait elle aussi des Maritimes, de Glace Bay, et le frère de ce pédiatre, Charles Gavsie, a déjà dirigé la… euh, j'oublie le nom, pas la monnaie, mais le gars qui signe les billets de banque [rires].

Christopher Canning : Jetez un coup d'œil à vos billets.

Dr David Rosenblatt : La Banque de Canada. C'est ça. Oui, il a été gouverneur de la Banque du Canada. Toujours est-il que je suivais ce programme, et mon oncle m'a dit : « Tu devrais vraiment travailler avec ce Dr Scriver, c'est un as, ce gars; il revient tout juste d'Angleterre, je vais essayer de t'obtenir un stage d'été avec lui ». Et c'est ainsi que pendant l'été 1967, j'ai travaillé dans le laboratoire du Dr Scriver. J'ai consacré une partie de l'été à compiler des statistiques pour Richard Goldbloom, qui allait devenir chancelier et directeur de la pédiatrie à l'Université Dalhousie. Enfin, je pense qu'il a été chancelier… mais en tout cas il a dirigé la pédiatrie. Je faisais ça à la main, sur de vieilles machines à additionner; c'était pour un projet sur la fibrose kystique. J'ai travaillé avec le Dr Scriver à une étude sur la phénylcétonurie; au moyen d'un analyseur d'acides aminés, on mesurait le ratio phénylalanine/tyrosine pour voir s'il était possible d'établir divers groupes de sujets à partir de ce paramètre. J'ai participé à la collecte de données sur l'éventuelle existence d'autres types d'hyperphénylalaninémie. C'était pour un article; donc, mon premier article, publié dans *Nature*, est le fruit de ce travail avec le Dr Scriver.

Christopher Canning : J'allais dire que vous aviez 22 ans, alors…

Dr David Rosenblatt : C'était grâce à mon travail d'été avec le Dr Scriver.

Christopher Canning : Ah, d'accord. Nous sommes donc à la fin des années 1960, alors.

Dr David Rosenblatt : 1967.

Christopher Canning : L'article est daté de 1968.

Dr David Rosenblatt : Oui, mais je pense que le travail a été réalisé pendant l'été 1967.

Christopher Canning : D'accord.

Dr David Rosenblatt : Je peux vérifier. Je pense avoir travaillé avec lui pendant l'été 1967.

Christopher Canning : D'accord.

Dr David Rosenblatt : J'ai donc fait sa connaissance, et à l'époque…

Christopher Canning : J'imagine que ce fut un grand honneur, non seulement de faire de la recherche avec Charles Scriver, mais aussi de publier un premier article avec ce scientifique très respecté?

Dr David Rosenblatt : Je ne mesurais probablement pas pleinement la portée de cette publication.

Christopher Canning : Oui, j'imagine que vous ne pouviez pas savoir.

Dr David Rosenblatt : Je pensais davantage aux interactions et au plaisir que j'avais à travailler dans le labo, aux gens qui étaient là. Je suis retourné à l'école de médecine et je suis revenu au labo l'été suivant, je crois, pour travailler à un projet sur l'histidinémie qui, lui aussi, a fait l'objet d'un article.

Christopher Canning : D'accord.

Dr David Rosenblatt : À cette époque, le Dr Scriver m'a dit : « Tu sais, la technologie de l'avenir pour l'étude des maladies métaboliques, c'est la culture de fibroblastes humains. As-tu déjà vu ça? Il faudrait qu'on descende voir de quoi ça a l'air au microscope. Mais la technique est somme toute très simple. Il suffit de prendre un instrument – as-tu déjà vu une biopsie cutanée? – qui ressemble à ça [il montre le bout d'un stylo], sauf que les bords sont coupants. Tu n'as qu'à faire comme ça, tu prélèves un bout de peau, tu le mets dans une boîte de Petri et les cellules se développent. C'est une technique mise au point autour des années 1950 et du début des années 1960 par Eagle, non pas l'oiseau, mais bien un certain Harry Eagle. »

Christopher Canning : Est-ce le seul tissu avec lequel vous travailliez à l'époque?

Dr David Rosenblatt : La culture de fibroblastes, mais ce n'était pas monnaie courante à l'époque, et le Dr Scriver m'a dit qu'il aimerait que j'aille à Boston travailler avec John Littlefield.

Christopher Canning : Vous me devancez; j'allais vous demander pourquoi vous étiez allé à Boston.

Dr David Rosenblatt : Eh bien, je me suis retrouvé au Massachusetts General Hospital avec John Littlefield, l'un des pionniers dans l'utilisation de fibroblastes cutanés cultivés; le Dr Scriver s'était dit que je pourrais aller passer quelques années là-bas pour apprendre la technique et la rapporter à McGill. Finalement, j'y suis resté quatre ans; nous pourrons y revenir tout à l'heure.

Ça ne faisait pas trop l'affaire du Dr Scriver. Le Dr Hy Goldman, un gars fort intéressant qui ne faisait pas partie du groupe mais pratique encore à l'Hôpital pour enfants, a mis en place les installations de culture tissulaire à l'Hôpital avec Inez Wong. Aujourd'hui, toutes les lignées cellulaires de l'Hôpital pour enfants portent les initiales « WG » pour « Wong Goldman », la technicienne et le médecin qui les ont créées. J'ai commencé à travailler avec John Littlefield à Boston, et il m'a choisi comme premier boursier d'un jeune membre du corps professoral qui s'appelait Richard Erbe – E-R-B-E – et avait été formé aux NIH[4]. C'est donc ainsi que j'ai participé aux premières études sur le métabolisme du folate dans les cultures cellulaires. J'ai passé deux ans au Massachusetts General Hospital. Le Dr Scriver, qui aimait bien sortir des sentis battus, m'a dit : « Tu n'as pas vraiment besoin de faire une spécialisation en pédiatrie ou de passer un examen ni quoi que ce soit de ce genre ».

Christopher Canning : N'y avait-il pas des règles à suivre?

Dr David Rosenblatt : Non, c'est-à-dire que, comme vous le constaterez, il embauchait souvent des gens qui n'avaient pas de formation en tant que telle. Les aptitudes de la personne importaient davantage à ses yeux.

Christopher Canning : Oui, c'était d'ailleurs le cas de Carol Clow.

Dr David Rosenblatt : Effectivement. Et vous remarquerez que bon nombre des personnes qu'il a embauchées avaient un parcours particulier. Angie, une technicienne qui a travaillé pour moi pendant des années au labo, était une infirmière en dialyse. C'était son style; il était un brin anticonformiste. Après deux ans, il voulait que je revienne à Montréal, mais Linda – ma femme – m'a dit : « Non, David, il faut que tu finisses ta pédiatrie et que tu obtiennes ton diplôme », alors finalement…

Christopher Canning : Était-ce à Harvard ou au MIT[5]?

Dr David Rosenblatt : D'abord, je me disais qu'une autre expérience de labo ne me ferait pas de tort. Je voulais aller dans un autre labo du MIT, celui de David Baltimore, mais Dick Erbe m'a fait entrer dans le labo de Malcolm Gefter, un immunologue qui travaillait aussi sur la synthèse d'ADN au moyen d'ARN. Au labo du MIT, je faisais des trucs très fondamentaux. C'était un milieu très étrange, où les parties de bridge commençaient à minuit, et seul le directeur du labo pouvait avoir son jeu sur la table [rires]. Je suis resté là-bas une année, puis j'ai passé ma dernière année au Boston Children's Hospital pour aller chercher la formation qui me permettrait d'obtenir mon certificat de compétence en pédiatrie. Ma formation en pédiatrie est reconnue aux États-Unis et au Québec. Par contre, je n'ai jamais réussi à passer l'examen de pédiatrie du Collège royal, parce que la formation clinique de la plupart des candidats canadiens était plus poussée que la mienne. Les examens sont toujours plus difficiles au Canada qu'aux États-Unis. Je suis associé du Collège royal, mais à titre de scientifique, pas de pédiatre. J'ai fini par revenir, en 1975, et…

Christopher Canning : Désolé de vous interrompre, mais j'aurais une autre question sur ce que vous avez dit tout à l'heure. Avant d'aller au Massachusetts, saviez-vous que alliez

[4] National Institutes of Health
[5] Massachusetts Institute of Technology

faire de la recherche sur le métabolisme du folate, ou…?

Dr David Rosenblatt : Non. Le hasard y est en partie pour quelque chose. Je vous ai parlé de John Littlefield. Il était célèbre et devait sa notoriété à l'adaptation du milieu de culture HAT – H-A-T – aux cellules de mammifères. Au départ, ce milieu de culture était conçu pour les bactéries et, en gros – que ça vous plaise ou non, je vais vous donner une petite leçon de biochimie…

Christopher Canning : Je vous en prie. Si vous utilisez des termes techniques, je vous demanderais de les expliquer à l'intention du transcripteur.

Dr David Rosenblatt : D'accord. Avez-vous des connaissances en biochimie?

Christopher Canning : Très peu, et je suis un autodidacte. J'ai parcouru vos travaux, mais je n'ai aucune formation scientifique digne de ce nom.

Dr David Rosenblatt : Pas de formation scientifique, donc. Ce sera du charabia… mais bon, en gros, il y a deux façons de fabriquer de l'ADN : on peut recycler des nucléotides, une partie de la structure de l'ADN, les molécules déjà dégradées et utilisées, ou on peut fabriquer les nucléotides *de novo* en construisant carrément leur anneau. Ces deux voies existent dans la cellule humaine. Le « A » de « HAT » signifie « aminoptérine », une substance semblable au méthotrexate, qui bloque le métabolisme du folate. Or, si le métabolisme du folate est bloqué, la synthèse endogène des nucléotides n'aura pas lieu. On peut secourir les cellules avec le « H » – de l'hypoxanthine », un précurseur de la purine – et le « T » – de la thymidine, un précurseur de la pyrimidine. John Littlefield a adapté ce milieu aux cellules de mammifères. Lors de mon arrivée à Boston, il se trouve qu'un patient hospitalisé au Massachusetts General Hospital avait un taux élevé d'homocystéine, et Harvey Mudd, des NIH, se penchait sur son cas. Comme il soupçonnait un blocage du métabolisme du folate, il a proposé d'étudier le métabolisme de cet acide dans des cultures de fibroblastes; voilà comment le métabolisme du folate est entré dans ma vie.

Christopher Canning : Et vous faisiez le travail de laboratoire en étudiant…

Dr David Rosenblatt : C'est-à-dire que tout ce que j'avais comme expérience de laboratoire, c'était les deux étés passés avec le Dr Scriver. J'avais appris à mettre des tissus en culture, à faire pousser des cellules… vous voyez ce que je veux dire. J'ai appris à analyser les enzymes du folate. J'avais produit deux articles avec le Dr Erbe et j'avais également fait de la génétique clinique, suffisamment pour que cette formation clinique soit reconnue en pédiatrie. À l'époque, la génétique était une division de la Pédiatrie au Massachusetts General Hospital.

Christopher Canning : C'est bon, je comprends.

Dr David Rosenblatt : C'est donc comme ça que j'ai commencé à faire de la recherche sur les maladies métaboliques dans des cultures tissulaires. Lorsque je suis revenu en 1975, je savais que le Dr Scriver m'avait inclus dans la demande de 1972.

Christopher Canning : Super. Pouvez-vous me donner des précisions sur votre arrivée dans le groupe?

Dr David Rosenblatt : Lors de mon départ, je savais qu'il travaillait à la demande; je suis parti en 1971 et il a fait sa demande en 1972. Il m'a dit : « À ton retour, tu feras partie du groupe », et il m'a demandé de préparer une demande en prévision de ça. Mais si je me souviens bien, je suis revenu deux années plus tard que ce qu'il aurait souhaité.

Christopher Canning : Et comment était votre relation avec lui?

Dr David Rosenblatt : Elle était bien. Je ne pense pas qu'il était trop content que je prolonge mon séjour, parce qu'il ne voyait pas la nécessité de me soumettre à tout ça, d'obtenir une reconnaissance en bonne et due forme.

Christopher Canning : Je vois.

Dr David Rosenblatt : Ma femme, une pragmatique, me disait que ce serait avantageux pour moi à long terme, et avec le recul, je pense qu'elle avait raison. J'ai passé une année intéressante au MIT.

Christopher Canning : Que voulez-vous dire par là?

Dr David Rosenblatt : Le simple fait de travailler dans un laboratoire où on faisait des trucs très fondamentaux en biochimie a été formateur; cette année-là, je n'ai rien publié.

Christopher Canning : Vous avez reçu une formation en biochimie pendant que vous étiez là-bas?

Dr David Rosenblatt : J'ai fait un peu de biochimie pendant mes deux années au Massachusetts General Hospital et ce que je faisais au MIT, c'était aussi de la biochimie : de la synthèse d'ADN à partir d'ARN, au moyen de ce qu'on appelle aujourd'hui des fragments d'Okazaki. Malcolm Getter avait fait de la synthèse d'ADN avant son arrivée au MIT, mais il se consacrait de plus en plus à l'immunologie. Donc, comme superviseur, il s'éloignait de mon projet, mais ça m'était égal. Ce qui m'intéressait, c'était de voir comment se déroulait la recherche dans divers laboratoires pour enrichir mon expérience postdoctorale. Dick Erbe et moi étions tous les deux d'avis que pour qui aspire à une carrière de chercheur, un séjour dans un seul laboratoire après l'école de médecine ne suffit pas. Après mon année au MIT, j'ai passé une dernière année au Boston Children's Hospital pour obtenir ma reconnaissance clinique. Je me suis fait de bonnes relations; j'ai fait ma résidence avec Paul Goodyer, qui plus tard est devenu chef de la néphrologie pédiatrique ici, à l'Hôpital de Montréal pour enfants.

Christopher Canning : Avez-vous toujours su qu'un jour ou l'autre, vous reviendriez au Canada?

Dr David Rosenblatt : Il y a deux éléments à considérer ici. J'avais un visa J-1 à l'époque, alors l'un des…

Christopher Canning : Qu'est-ce qu'un visa J-1?

Dr David Rosenblatt : C'était un visa d'étudiant. C'était avant le libre-échange et les échanges professionnels, et à l'expiration du visa, le détenteur devait retourner dans son pays. Je pense que si j'avais vraiment voulu rester, j'aurais pu. Les gens se faisaient offrir des emplois et pouvaient rester aux États-Unis, mais j'ai toujours eu l'intention de revenir. Seulement, je suis revenu un peu plus tard que prévu.

Christopher Canning : Je vois qu'une de vos filles est née pendant votre séjour là-bas.

Dr David Rosenblatt : C'est exact. Jacalyn est née à Boston en 1972, alors elle a la citoyenneté américaine. Elle travaille au Beth Israel Deaconess Hospital, à Boston, où elle fait de l'hématologie, des greffes de moelle osseuse. Elle a fait sa médecine et a commencé sa spécialisation à McGill, puis elle a terminé sa spécialisation en hématologie à Boston.

Christopher Canning : Et aujourd'hui elle vit à Boston?

Dr David Rosenblatt : Et aujourd'hui elle vit à Boston, et son mari a obtenu la citoyenneté américaine. Ma deuxième fille, Dana, est née en 1976, donc après notre retour à Montréal. Nous sommes revenus en 1975.

Christopher Canning : Super. Peut-être est-ce clair dans votre esprit, mais ce ne l'est pas tant que ça dans le mien… à quel moment votre intérêt pour la génétique médicale s'est-il manifesté et comment est-ce arrivé? Dans quels domaines de la biologie la rencontre s'est-elle produite, et comment la médecine s'est-elle unie à la génétique à vos débuts?

Dr David Rosenblatt : Non, ce n'est pas tout à fait clair, et je pense sincèrement que c'est en partie en raison de la façon dont les choses se sont faites. Je suis arrivé dans le domaine non pas par intérêt pour la médecine ou la génétique, mais essentiellement grâce à un mentor avec lequel j'ai discuté d'un parcours de carrière qui, en soi, semblait très intéressant. Ce qu'il y a de bien en médecine, c'est qu'il y a un vaste choix de domaines. Lorsque je conseille des étudiants, des personnes fermement résolues à faire ceci ou cela, je leur dis : « Écoute, il y a beaucoup, beaucoup de choses que tu peux faire, et elles peuvent toutes être intéressantes : tu n'as qu'à choisir ». Donc, tout simplement, j'ai vu l'enthousiasme du Dr Scriver pour son travail. C'était l'époque où on découvrait tous les troubles du métabolisme des acides aminés, où on mettait les cellules en culture pour pouvoir élucider les mécanismes morbides dans les cellules elles-mêmes, sans que la présence du patient soit requise. Le domaine était en pleine effervescence. Ce n'était donc pas écrit dans le ciel que j'allais faire de la génétique. C'est plutôt que j'ai été mis en présence d'un passionné qui faisait de la génétique de haut vol et qui m'a pris sous son aile.

Christopher Canning : Avez-vous hésité à embrasser ce domaine qui, en quelque sorte, essayait encore de se faire une place en médecine?

Dr David Rosenblatt : Pas du tout, parce que quand je repense à la raison pour laquelle je suis allé en médecine… je vous rappelle que je suis entré en médecine tout de suite après le secondaire, ce qui à l'époque correspondait à la 11e année.

Christopher Canning : Wow, d'accord.

Dr David Rosenblatt : Je n'ai pas choisi le programme de sept ans nécessairement pour la médecine, mais bien parce que c'était un programme exigeant, dans lequel il était difficile d'être admis et qui m'ouvrait de multiples perspectives. Le bon petit gars juif qui va en médecine pour faire plaisir à sa maman, c'est moi.

Christopher Canning : En fait, c'est une question que je voulais vous poser en début d'entrevue : qu'est-ce que vos parents attendaient de vous lorsque vous étiez enfant, puis lorsque vous avez entrepris votre formation après le secondaire?

Dr David Rosenblatt : Je n'en sais rien. Ma sœur et mon frère n'étaient pas des élèves très motivés. Ma sœur ne l'était pas du tout et mon frère, pas beaucoup plus. Mon frère s'est joint à l'entreprise familiale. J'ai toujours été plus traditionnel, le nez dans les livres, plutôt conformiste, et je pense que mes parents étaient contents que je fasse ma médecine. Un de mes oncles était médecin, mais d'après mes souvenirs, mes parents voulaient simplement que je réussisse bien dans mes études, sans plus. Les études et le milieu universitaire me plaisaient, et j'y voyais sans doute une façon d'entrer dans ce monde-là. Mais je n'avais pas d'objectif clair, je pense. Au Parlement écolier, j'étais chef du Nouveau Parti démocratique. J'ai déjà entendu dire que si tu n'étais pas socialiste à 20 ans, tu n'avais pas de cœur, et que si tu n'étais pas conservateur à 40 ans, tu n'avais pas de tête. C'est bien ça?

Christopher Canning : C'est ce qu'on dit, oui.

Dr David Rosenblatt : Voilà. Mais j'ignore si c'est totalement vrai. Ce qui m'a frappé, je pense, c'est qu'il faut gagner sa vie, bien sûr, mais que la nature du travail a de l'importance en soi. C'est cela qui me motivait : faire avancer le savoir, les connaissances; et l'aspect pratique de la chose me plaisait bien. Au fond, je n'avais probablement pas tant que ça l'étoffe d'un philosophe.

Christopher Canning : Et manifestement, le Dr Scriver n'est pas étranger à cette évolution.

Dr David Rosenblatt : Aucun doute là-dessus : il a été un modèle et m'a fait prendre conscience des possibilités de carrière dans le domaine. Et, toujours, le succès était pour lui une affaire d'équipe. Quand on est jeune, on peut se donner corps et âme à un projet, parce qu'on veut bien faire; et si on est bon dans ce qu'on fait, on continue sans se poser de questions. J'ai adoré Boston, tant pour mon travail que pour la vie là-bas. J'avais de bons rapports avec Richard Erbe et les autres personnes de l'équipe; c'était une super équipe. L'année au MIT a été un peu particulière; c'était du 24 heures sur 24, la plupart des gens étaient célibataires et savaient plus ou moins ce qu'ils voulaient dans la vie.

Christopher Canning : Quels étaient vos rapports avec le Dr Fraser à l'époque? Le Dr Scriver a-t-il été davantage un mentor pour vous?

Dr David Rosenblatt : Quand je suis arrivé, c'était le Dr Scriver qui était en selle. Lui et le Dr Fraser ont des styles complètement différents, mais physiquement, leurs unités étaient très proches. Il se peut que j'aie été exposé au Dr Fraser comme formateur au baccalauréat, mais pas pour des cours complets; j'ai suivi un cours de Boothroyd et un autre de Don Southern, qui étaient tous les deux rattachés au Département de biologie. Je ne saurais dire si j'ai suivi des cours de Clarke comme tels, mais il était toujours là. Lorsque je suis revenu comme jeune membre du personnel, il était toujours là pour les tournées; Clarke, je l'adorais. À bien des égards, il était beaucoup plus accessible que Charles. Les deux ont une très haute opinion d'eux-mêmes, mais je pense que c'était moins évident chez Clarke que chez Charles. Tout ne tournait pas toujours autour de lui, et Clarke avait une façon très intéressante de voir les choses. Jamais il n'aurait

dit un truc du genre « C'est une idée qui ne tient pas debout ». Non, il se demandait plutôt d'où était venue l'idée et si elle ne comportait pas certains éléments de vérité. « Je me demande si les anomalies du tube neural ne seraient pas causées par le mildiou de la pomme de terre en Irlande? » C'est Clarke qui m'a appris à sortir des sentiers battus et à m'ouvrir aux nouvelles idées.

Christopher Canning : Et ces différences entre les Drs Fraser et Scriver quant au style de leadership, les avez-vous remarquées dès votre retour?

Dr David Rosenblatt : Je crois bien, oui, mais c'est sûr que j'étais beaucoup sous… le groupe, à l'époque, c'était Charles, Clarke, Peter Hechtman et moi. Nous travaillions dans des cagibis grands comme ma main au Children's…

Christopher Canning : Et pouvez-vous me dire un mot sur le Dr Gold?

Dr David Rosenblatt : Il y a eu une période de chevauchement avec Rennie Gold. D'ailleurs, vous devriez vous entretenir avec lui… à moins que ce ne soit déjà fait?

Christopher Canning : Il est à l'extérieur en ce moment, mais nous allons nous rencontrer dès son retour.

Dr David Rosenblatt : Lui, c'est un tout autre genre.

Christopher Canning : C'est l'impression que j'ai eue, effectivement.

Dr David Rosenblatt : Il était omnipraticien au Royaume-Uni; un gars très, très brillant, un pianiste classique. Il est arrivé en Saskatchewan lors de la grève des médecins, en 1962.

Christopher Canning : Oui, j'ai entendu parler de ça. En fait, nous en avons parlé il y a quelques semaines, lors du souper.

Dr David Rosenblatt : Comme je le disais, c'est un gars très intéressant et très brillant. Il y avait un autre gars dans l'unité quand je suis revenu, et c'était Francis Glorieux. C'était un spécialiste des maladies osseuses chez l'enfant. Il y a eu un peu de bisbille entre lui et Charles lorsque Francis a quitté l'équipe pour aller diriger un service à l'Hôpital Shriners. Charles ne voit pas d'un très bon œil que les gens partent de leur côté pour poursuivre leur petit bonhomme de chemin.

Christopher Canning : Intéressant. Pouvez-vous m'en dire plus à ce sujet?

Dr David Rosenblatt : Il aime que son monde reste dans son empire. Il a tiré pas mal de ficelles pour que Francis dirige l'unité de recherche qu'ils mettaient en place au Shriners, puis Francis a commencé à voler de ses propres ailes, créé son propre programme de recherche et gagné beaucoup en visibilité. Ça n'a jamais vraiment fait l'affaire de Charles. Francis est quelqu'un de bien, vraiment : c'est un médecin d'origine belge qui a fait son doctorat avec Charles, alors je pense qu'il se sent redevable envers lui, mais c'est quand même un peu tendu entre ces deux-là. Francis est encore dans les parages. En ce moment, il est quelque part pour la réception d'un doctorat honorifique.

Christopher Canning : Pourriez-vous me répéter son nom pour que je le note?

Dr David Rosenblatt : Francis Glorieux.

Christopher Canning : D'accord, je vais y regarder de plus près, c'est certain.

Dr David Rosenblatt : Pendant les dix années qui ont suivi mon retour ici, je travaillais dans un cocon. Le Dr Scriver me gardait à l'abri des responsabilités cliniques.

Christopher Canning : Vous passiez donc le plus clair de votre temps au labo?

Dr David Rosenblatt : Oui, ça a été le cas pendant 10 ans.

Christopher Canning : Wow. Ça a sûrement fait grimper en flèche le nombre de publications à votre actif.

Dr David Rosenblatt : Peut-être, mais ça, c'est secondaire. Ce qui importe, c'est que ça m'a permis d'approfondir mes connaissances dans un domaine.

Christopher Canning : Je comprends. Que faisiez-vous au milieu des années 1970?

Dr David Rosenblatt : De la recherche, essentiellement. Deux choses, plus précisément : la première, c'était de la biochimie. Si je pouvais jeter un coup d'œil au C. V., ça m'aiderait à remettre les choses en contexte; j'ai du mal à déterminer à quel moment exactement le travail a été exécuté à partir uniquement des dates des articles. Donc, l'article de 1977 porte sur le stage de perfectionnement que j'ai fait à Boston avant 1975; là-bas, il n'y avait que Dick Erbe pour la recherche en psychiatrie. Ces articles ont été publiés avant les articles 6 et 7[6].

Christopher Canning : Je vois. D'accord.

Dr David Rosenblatt : Et l'article 3[7] aussi, bien sûr, mais après, il y a du chevauchement et autour de 1978, il y a quelque chose de fort intéressant à McGill qui a retenu mon attention. C'est extraordinaire, parce qu'à mon retour, j'ai eu droit à un autre type de mentorat, mais pas au sein du groupe. Il se trouve que deux vitamines, le folate et la vitamine B_{12}, se croisent à certains carrefours métaboliques, et leur interaction entraîne une manifestation propre à la carence tant en folate qu'en vitamine B^{12}, à savoir une hausse de l'homocystéine et divers effets sur les globules sanguins, dont l'anémie. À l'époque, le Service d'hématologie de l'Hôpital Royal Victoria était dirigé par Bernie Cooper, formé à Boston auprès de chercheurs qui avaient élucidé les mécanismes non pas génétiques, mais plutôt physiologiques, de l'absorption de la vitamine B_{12}. Au cours du dernier siècle, on a attribué deux prix Nobel liés à la vitamine B_{12} : un pour la découverte de son rôle dans l'anémie pernicieuse et l'autre pour la caractérisation de sa structure chimique. Bernie travaillait en étroite collaboration avec les grosses pointures de la vitamine B_{12}. Il était à l'Hôpital

[6] **Article 6** : Rosenblatt DS et Erbe RW (1977). Methylenetetrahydrofolate reductase in cultured human cells. I. Growth and metabolic studies. *Pediatr Res* (11), 1137-1141.
Article 7 : Rosenblatt DS et Erbe RW (1977). Methylenetetrahydrofolate reductase in cultured human cells. II. Genetic and biochemical studies of methylenetetrahydrofolate reductase deficiency. *Pediatr Res* (11), 1141- 1143.

[7] **Article 3** : Rosenblatt DS et Erbe RW (1973). Reciprocal changes in the levels of functionally related folate enzymes during the culture cycle in human fibroblasts. *Biochem Biophys Res Commun* (54), 1627-1633.

Royal Victoria, et Robert MacKenzie – qui ne faisait pas encore partie du groupe – enseignait au Département de biochimie à McGill. Bernie avait alors un stagiaire du nom de Michael Whitehead, qui a ensuite été hématologue à l'Hôpital général de Montréal, puis chef du Service d'hématologie à l'Hôpital de Montréal pour enfants. Lui aussi s'intéressait au folate et aux antagonistes du folate. Les antifoliques ont été les premiers agents chimiothérapeutiques utilisés dans le cancer. Le méthotrexate et l'améthoptérine, les premiers antileucémiques, sont des antagonistes du folate. C'est en partie pour ça que les deux hématologues s'intéressaient au folate et à la vitamine B_{12}. Nous avons créé un « club du folate » qui tenait des rencontres mensuelles; il comprenait deux hématologues, un généticien et un professeur de biochimie.

Christopher Canning : Le biochimiste, c'était Robert MacKenzie?

Dr David Rosenblatt : Robert MacKenzie était le professeur de biochimie, j'étais le généticien, et les hématologues étaient Bernie Cooper et Michael Whitehead. Nous nous rencontrions une fois par mois pour discuter du métabolisme du folate et de la vitamine B_{12} autour d'une bière, d'une baguette et de fromage. Robert était physicochimiste. Bernie faisait de ces envolées… je comprenais à peu près 2 % de la conversation au début, mais après trois ou quatre ans, j'avais quand même saisi certaines notions. Bernie était et est toujours un gars brillant; il a pris sa retraite et vit aujourd'hui à Palo Alto. Je pense qu'il a une affectation clinique à Stanford, mais pour l'essentiel, il est retraité. On lançait un tas d'idées, et je disais à Bernie : « On fait ça! ». J'étais du genre pratico-pratique, celui qui balisait le projet. J'étais celui qui se demandait où ça commence et où ça finit. J'ai également commencé à collaborer étroitement avec Michael Whitehead. Des observations préliminaires semblaient indiquer qu'il était possible de métaboliser le méthotrexate par l'ajout de glutamates. Nous avons convenu d'étudier ce phénomène dans des cellules humaines. Michael et moi avions à notre actif quelques articles qui, en fait, portaient sur l'aspect non pas génétique, mais bien cellulaire du cancer et de la chimiothérapie, sur le métabolisme du méthotrexate, un antifolique, dans les cellules humaines. Puis Michael est revenu sur le sujet plus tard en publiant un article sur les folates, plus précisément les polyglutamates, dans la moelle osseuse des patients atteints de leucémie.

Christopher Canning : Et c'est la publication numéro…?

Dr David Rosenblatt : Numéro 12[8]. À cette époque, le club du folate était prolifique. Plus tard, au début des années 1980, Rima Rozen est entrée en scène. Elle a fait son doctorat avec Charles (Scriver) sur l'acidurie méthylmalonique, elle est allée travailler avec Leon Rosenberg à Yale puis à son retour, elle a commencé à s'intéresser au folate.

Christopher Canning : Avant de passer aux années 1980, j'aimerais revenir sur une chose que vous avez dite. Vous avez mentionné que Charles Scriver ne voyait pas nécessairement d'un bon œil que les gens volent de leurs propres ailes. Que vouliez-vous dire exactement?

[8] **Article 12** : Witte A, Whitehead VM, Rosenblatt DS et Vuchich MJ (1980). Synthesis of methotrexate polyglutamates by bone marrow cells from patients with leukemia and lymphoma. *Dev Pharmacol Ther* (1), 40-46.

Dr David Rosenblatt : Non, non, il n'aimait pas que les gens se détachent du groupe. Le travail scientifique ne posait aucun problème. Tant que vous restiez au sein du groupe qu'il dirigeait… ça ne posait jamais de problème. Si tu voulais devenir chercheur indépendant et que tu faisais bien ton travail, il te laissait tranquille et te protégeait quand le chef de la Pédiatrie voulait t'attribuer d'autres tâches. Ah, d'ailleurs, je me rappelle une anecdote qui illustre bien mon propos : à mon retour à Montréal, une partie de mon salaire provenait d'un fonds de recherche provisionné à même le travail des cliniciens. Mais à cause d'un détail technique, je ne pouvais pas travailler à l'Hôpital de Montréal pour enfants et contribuer à ce fonds. Pour arrondir mes fins de mois et ne pas perdre la main en pédiatrie, j'ai commencé à travailler dans une clinique de l'Hôpital général juif qui assurait la permanence pour 17 pédiatres. C'était en 1975 et je suis encore de permanence tous les samedis, avec Linda. Le chef de la Pédiatrie de l'époque n'était pas d'accord. Mais comme je ne pouvais pas travailler et facturer mes services au sein du Children's, le Dr Scriver m'a appuyé. Sur le plan professionnel, j'ai toujours pu compter sur lui. Comme vous allez le voir, nous avons eu maille à partir une seule fois, et c'est lorsque je suis monté un peu plus haut sur la montagne pour établir ma propre unité dans l'hôpital pour adultes, en 1986. Mais revenons à la recherche. Fin 1970, début 1980, il s'est fait beaucoup de choses intéressantes sur le méthotrexate et les polyglutamates, et j'ai fait beaucoup de recherche fondamentale sur le folate au sein de la cellule. Une théorie intéressante avait cours à l'époque; allez à la publication 21[9], sur le folate et le syndrome de fragilité du chromosome X. Ce syndrome est une cause très fréquente de retard mental chez les hommes, mais au début des années 1980, on en ignorait le mécanisme. Ce que les chercheurs savaient, par contre, c'est que lorsqu'on mettait en culture des fibroblastes de patients atteints du syndrome dans un milieu faible en folate, les zones de fragilité apparaissaient plus clairement. Donc, certains se sont dit qu'il serait peut-être possible de guérir ces patients au moyen de folate. Nous avons mené un tout petit essai clinique, parce que nous avions des jumeaux atteints du syndrome de fragilité du chromosome X, des jumeaux un peu plus vieux; nous avons fait faire un placebo qui ressemblait à un comprimé d'acide folique et nous avons mené un essai clinique. Nous avons fait des évaluations comportementales. Ça s'inscrivait dans un projet de Brad Popovich.

Christopher Canning : Est-ce qu'ils avaient le syndrome tous les deux?

Dr David Rosenblatt : Oui. C'était des jumeaux. Nous avons administré le placebo à l'un d'eux et l'acide folique à l'autre, nous avons fait une permutation au bout de deux semaines, puis nous avons fait les évaluations psychologiques. Il n'y avait aucune différence…

Christopher Canning : Il n'y avait aucun changement?

Dr David Rosenblatt : Aucun. Et à vrai dire, nous ne nous attendions pas vraiment à ce qu'il y en ait un. Aujourd'hui, nous en savons davantage sur la maladie, et le mécanisme est complètement différent. Ce qui nous amène à l'article 23[10]. Je précise que

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9 **Article 21** : Popovich BW, Rosenblatt DS, Cooper BA et Vekemans M (1983). Intracellular folate distribution in cultured fibroblasts from patients with the Fragile *X* syndrome. *Am J Hum Gen* (35), 869-878.

10 **Article 23** : Schuh S, Rosenblatt DS, Cooper BA, Schroeder ML, Bishop AJ, Seargeant LE et Haworth JC (1984). Homocystinuria and megaloblastic anemia responsive to vitamin B_{12} therapy: an inborn error of metabolism due to a defect in cobalamin metabolism. *N Engl J Med* (310), 686-690.

pendant tout ce temps, je continue à recevoir, des quatre coins du monde, des lignées cellulaires qui proviennent de personnes chez lesquelles on soupçonne un trouble inné du métabolisme du folate.

Christopher Canning : Le folate, c'est la vitamine B_9, n'est-ce pas?

Dr David Rosenblatt : Oui, mais je parle plutôt de folate. « Vitamine B_9 » est effectivement son autre nom, mais à peu près personne ne l'utilise. Nous reviendrons là-dessus plus tard aussi. L'article 23 a une importance capitale dans mon parcours. Je n'en suis pas l'auteur principal, mais tout le travail de laboratoire s'est fait à Montréal. La clinicienne à Winnipeg était Susan Chiu, une résidente, et c'est l'équipe de Winnipeg qui a communiqué avec nous. Ils redoutaient un trouble inné du métabolisme du folate chez leur patient et nous ont proposé d'étudier son cas. Et c'est ainsi que nous avons mis au jour un tout nouveau trouble du métabolisme de la vitamine B_{12} et publié le fruit de notre travail dans le *New England Journal of Medicine*.

Christopher Canning : Ici, on passe du folate à la vitamine B_{12}.

Dr David Rosenblatt : Ça, c'est en raison de l'interface entre le folate et la vitamine B_{12}. Nous avons conçu des tests hautement spécialisés qui nous permettaient d'explorer les méandres d'une voie métabolique, puis nous avons tissé un réseau de collaborateurs. Lorsque les gens t'envoient des échantillons cliniques atypiques, il y a des anomalies qui finissent par ressortir avec le temps. Dans l'ancien système des subventions de groupe, ça fonctionnait très bien. Nous avons acquis une expertise qui a été reconnue dans le monde entier. Si j'écris, dans une demande de subvention : « Je vais prendre le temps qu'il faut, approfondir tel domaine, attendre que des cas anormaux pertinents se présentent, trouver de nouvelles voies… », je ne recevrai pas un sou. Mais la structure de groupe m'a donné le temps d'accumuler les cas qui ont mené à la découverte. Ce « cocon de recherche », comme je l'appelle, ce groupe interdépendant qui croyait à la science de première qualité, ça a été une véritable bénédiction pour moi, vous savez; c'était précieux à mes yeux. Par contre, je ne pense pas que la structure de groupe soit nécessairement la seule façon de faire. En France, ils ont des unités de l'INSERM; la hiérarchie a ses bons côtés, je crois. Les gens aiment bien le comité de lecture, parce que chaque projet est décortiqué et évalué au mérite. Ce qui comptait auparavant, c'était davantage la formation de la personne, son sérieux et ensuite seulement les résultats de ses travaux. Et pour ma part, c'est encore comme ça que je vois les choses. Ce n'est pas le projet du chercheur comme tel qui m'intéresse. Donnez-lui un peu de latitude et un peu de temps, et vous jugerez ensuite à la lumière des résultats obtenus.

Christopher Canning : Comme vous le dites, ce n'est pas nécessairement comme ça que fonctionnent les organismes de financement.

Dr David Rosenblatt : Pas du tout, en fait. De plus en plus, il faut presque que le travail pour lequel on demande du financement ait déjà été fait.

Christopher Canning : C'est exact.

Dr David Rosenblatt : Parce qu'ils veulent avoir en main toutes les données préliminaires, ils veulent

s'assurer que le chercheur a tout ce qu'il faut sur toutes les familles.

Christopher Canning : Est-ce que ça a toujours été le cas?

Dr David Rosenblatt : Non. Vous en parlerez au Dr Fraser; sa première demande de subvention tenait probablement sur une page.

Christopher Canning : Oui, il m'a même dit à la blague que de nos jours, il n'aurait pas un sou.

Dr David Rosenblatt : J'aimerais tellement voir sa première demande de subvention, la reconstituer du début à la fin. Elle ne dépassait probablement pas une page. J'estime qu'on devrait juger les gens sur les résultats obtenus, sans la moindre complaisance. Parce qu'une personne peut bien vous promettre mer et monde, la seule chose qui compte en définitive, c'est ce qu'elle fait concrètement. Nous, nous avons commencé avec un patient qui présentait une anomalie jusqu'alors inconnue. Puis peu à peu sont arrivés d'autres patients qui avaient tous leurs particularités, parfois des étapes jamais vues chez des mammifères. Nous avons donc, d'abord et avant tout, procédé à une caractérisation biochimique et eu recours à une technique de base, l'hybridation cellulaire somatique. En gros, on a une batterie de lignées cellulaires différentes les unes des autres. (J'ai appris cette technique de Littlefield, qui l'a mise au point.) En fusionnant deux lignées cellulaires différentes, on peut corriger les anomalies biochimiques présentes dans l'une comme dans l'autre.

Christopher Canning : Un ADN différent?

Dr David Rosenblatt : Non, non, non, non… des anomalies différentes.

Christopher Canning : Intéressant.

Dr David Rosenblatt : D'accord? Donc, d'un côté, on a une lignée cellulaire qui vient d'un patient porteur d'une anomalie inconnue et une batterie de lignées cellulaires qui présentent des anomalies connues. Et de l'autre, on a une épreuve fonctionnelle. On fusionne deux lignées à la fois, une « inconnue » et une « connue ». Si elles se corrigent mutuellement, on conclut qu'elles ont des anomalies différentes. Si on les fusionne et qu'elles ne se corrigent pas mutuellement, on conclut qu'elles ont la même anomalie.

Christopher Canning : D'accord.

Dr David Rosenblatt : Cette cellule-ci a une anomalie et cette autre cellule a une anomalie; elles ne proviennent pas du même patient. Si on les fusionne pour obtenir une seule grande cellule et qu'elles se corrigent mutuellement, on conclut qu'elles avaient des anomalies distinctes, puisque l'anomalie de l'une a pu corriger l'anomalie de l'autre. Si on les fusionne et que les anomalies ne se corrigent pas, on se dit qu'elles devaient présenter la même anomalie, puisqu'elles sont incapables de se corriger mutuellement.

Christopher Canning : Et qu'est-ce qui corrige les anomalies au juste?

Dr David Rosenblatt : Le produit génique. Souvent, nous ignorions tout du produit génique sous-jacent. Pendant la première partie de ma carrière, nous ne faisions que

classifier les patients en différents groupes. Puis pendant l'essentiel de la seconde partie de ma carrière, j'ai collaboré avec Rima Rozen et Roy Gravel pour trouver les gènes à la base des divers groupes d'hybridation. Il a fallu attendre la fin des années 1980 pour qu'arrive la technologie de l'ADN.

Christopher Canning : Mais vous connaissiez déjà…

Dr David Rosenblatt : Mais nous connaissions les fondements génétiques, nous savions que nous avions une seule anomalie ou deux anomalies distinctes.

Christopher Canning : Simplement en fusionnant les cellules.

Dr David Rosenblatt : En fusionnant les cellules, mais il nous fallait aussi une épreuve fonctionnelle. Nous devions montrer que le métabolisme du folate ou de la vitamine B_{12} était perturbé et nous devions trouver une mesure quelconque pour montrer que c'était…

Christopher Canning : Vous rappelez-vous des cellules en question, ou est-ce que la vitamine B_{12} est présente dans toutes les cellules de l'organisme?

Dr David Rosenblatt : Effectivement, ça compte en ce qui concerne la nature du trouble. Il se trouve que dans les troubles et les voies qui nous intéressaient, les cellules d'intérêt étaient les fibroblastes. Nous étudions le métabolisme de la vitamine dans la cellule. Dans d'autres types de problèmes, lorsque la vitamine B_{12} ne peut pas être absorbée dans les voies digestives, les manipulations biochimiques dans les fibroblastes ne fonctionnent pas. Dans certains troubles, seules les cellules cérébrales présentent une anomalie; les patients ne font pas d'anémie. Par ailleurs, nous ne travaillions pas en vase clos. Leon Rosenberg ne chômait pas à Yale : il a mis au jour certaines des étapes antérieures dans la voie métabolique. Il a découvert les groupes cblA, CblB, CblC et CblD – « cbl » pour « cobalamine » – ainsi que le groupe mut, puis nous avons découvert les groupes CblE, cblF et cblG.

Christopher Canning : Et c'est avec lui que Rima Rozen travaillait. Alors évidemment, lorsqu'elle est revenue…

Dr David Rosenblatt : Elle ne faisait pas la même chose à son retour. Nous travaillions chacun de notre côté, mais elle avait mis au point des techniques moléculaires, alors lorsque la révolution biologique moléculaire s'est pointé le bout du nez…

Christopher Canning : C'est la fusion de la biochimie et de la biologie moléculaire?

Dr David Rosenblatt : Exactement. J'avais constitué des groupes de patients bien définis, et nous nous sommes mis en frais de trouver les gènes. Dans certains cas, nous ignorions les fonctions en cause, alors nous n'avions pas d'épreuve fonctionnelle proprement dite. La découverte de mutations dans des gènes de patients atteints de troubles bien définis a démontré que nous avions ciblé les bons gènes. Nous pouvions aller et venir entre le patient et les cellules. À l'époque, j'ai collaboré très étroitement avec Roy Gravel et Rima Rozen. Ils étaient les biologistes moléculaires, tandis que j'étais davantage un biologiste cellulaire et un médecin qui travaillait à l'échelle tant clinique que cellulaire. Nous avons publié de nombreux excellents articles. Nous tirions tous parti de

cette collaboration. Je crois que mon intérêt pour les erreurs innées du métabolisme du folate a piqué la curiosité de Rima à l'égard du gène *MTHFR*, après quoi elle a pris son envol et atteint les plus hauts sommets. Elle s'est intéressée principalement au lien entre les polymorphismes des gènes des folates et des problèmes relativement fréquents plutôt que les erreurs innées, plutôt rares.

Christopher Canning : Comme le cancer?

Dr David Rosenblatt : Le cancer et les malformations congénitales.

Christopher Canning : Je vois.

Dr David Rosenblatt : Et j'ai consacré l'essentiel de mon temps aux maladies rares, où les réponses sont plus claires.

Christopher Canning : Sur quels gènes vous êtes-vous concentré, plus précisément?

Dr David Rosenblatt : Nous avons trouvé ensemble, dans notre groupe, le gène *MTHFR*. Et aussi les gènes *MTR* et *MTRR*. Ensuite, avec des chercheurs extérieurs à notre groupe, nous avons trouvé les gènes *MMADHC* et *MMACHC*. Nous avons aussi trouvé et décrit le gène de la forme cblF, l'une de mes découvertes scientifiques les plus importantes.

Christopher Canning : Pouvez-vous m'indiquer cela sur votre C. V.?

Dr David Rosenblatt : Bien sûr, ça devrait être autour de 1985, donc l'article 27[11].

Christopher Canning : D'accord, merci.

Dr David Rosenblatt : On parle donc d'une anomalie du transport de la vitamine B_{12} à travers la membrane du lysosome. Nous avons découvert la maladie et publié la nouvelle dans la revue *Science* en 1985, mais nous n'avons trouvé le gène qu'en 2009.

Christopher Canning : C'est tout récent, alors.

Dr David Rosenblatt : Oui, et la découverte a été publiée dans *Nature Genetics* en 2009.

Christopher Canning : C'est noté.

Dr David Rosenblatt : C'est l'article 157[12].

Christopher Canning : Wow. C'est l'aboutissement de nombreuses années d'efforts?

Dr David Rosenblatt : Je ne m'éparpille pas et je suis persévérant.

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[11] **Article 27 :** Rosenblatt DS, Hosack A, Matiaszuk NV, Cooper BA et Laframboise R (1985). Defect in vitamin B_{12} release from lysosomes: newly described inborn error of vitamin B_{12} metabolism. *Science* (228), 1319-1321.

[12] **Article 157 :** Rutsch F, Gailus S, Miousse IR, Suormala T, Sagné C, Toliat MR, Nurnberg G, Wittkampf T, Buers I, Shariffi A, Stucki M, Becker C, Baumgartner M, Robenek H, Marquardt T, Hahne W, Gasnier B, Rosenblatt DS, Fowler B, Nurnberg P (2009). Identification of a putative lysosomal cabalamin exporter mutated in the cblF inborn error of vitamin B_{12} metabolism. *Nat Genet* (41), 234-239.

Christopher Canning : Je vois ça.

Dr David Rosenblatt : Mes travaux ont débouché sur une épreuve diagnostique et ça, ça m'apporte une énorme satisfaction. Il y a deux laboratoires dans le monde qui font des diagnostics, le nôtre et le labo de Brian Fowler, en Suisse. J'ai aussi l'habitude de collaborer avec des concurrents. Nous travaillons et publions parfois ensemble, parfois séparément.

Christopher Canning : Au Canada ou ailleurs dans le monde?

Dr David Rosenblatt : Il y a des gens en Suisse et d'autres en Allemagne; alors, oui, ailleurs dans le monde.

Christopher Canning : Y a-t-il beaucoup de chercheurs qui s'intéressent à la vitamine B_{12}?

Dr David Rosenblatt : C'est un groupe relativement restreint qui a autrefois été qualifié de « fraternité ». Un grand prestige l'entoure. Je peux vous montrer certains des ouvrages issus de cette communauté scientifique. Je ne pense pas seulement à celui de Charles Scriver (MMBID, soit *The Metabolic and Molecular Bases of Inherited Metabolic Disease*), mais aussi à des ouvrages qui portent uniquement sur la vitamine B_{12}. Ruma Banerjee, avec laquelle Rima et moi avons collaboré, était en stage auprès de Rowena Matthews à l'Université du Michigan. Ruma est ensuite allée au Nebraska et est aujourd'hui de nouveau en poste à l'Université du Michigan. Ruma Banerjee a révisé un ouvrage sur la vitamine B_{12}; sur la couverture, on peut voir la chercheuse nobélisée Dorothy Hodgkins.

Dorothy Hodgkins a déterminé la structure de la vitamine B_{12} à partir de clichés cristallographiques, ce qui lui a valu un prix Nobel. Cette femme est un modèle de réussite en sciences au plus haut niveau; d'ailleurs, la poste britannique lui a rendu hommage en émettant un timbre à son effigie. Il faudrait que je vous montre le livre; Rima l'a sûrement, elle aussi. Parce que pour bien des raisons, ça met les choses en perspective. Nous assistons à des conférences – c'est ce qu'il y a de bien tant pour le folate que pour la vitamine B_{12} – à des conférences Gordon ou de la FASEB, par exemple… Savez-vous ce qu'est une conférence Gordon? C'est une conférence qui s'adresse à un petit groupe. Même chose pour les conférences de la FASEB. Il y avait 200 personnes à peu près, au tout début peut-être autour de 150; aujourd'hui, ça peut aller chercher dans les 300 personnes. Il est question du folate, du métabolisme monocarboné ou de la vitamine B_{12}; il y a des chimistes purs et durs, dont certains créent des antifoliques pour la chimiothérapie anticancéreuse. Il y a des spécialistes des microorganismes, des cliniciens – ceux qui se servent de la chimiothérapie – ou des spécialistes des anomalies congénitales. J'adorais ça, parce que j'avais un pied dans chaque camp, celui des fondamentalistes et celui des cliniciens. Charles Scriver manœuvre comme un pro là-dedans. Il a toujours parlé de recherche fondamentale aux cliniciens et de médecine clinique aux fondamentalistes. Nous faisons en quelque sorte de la science translationnelle.

Christopher Canning : C'est génial, parce que je voulais vous demander comment ces deux sphères, la médecine clinique et la recherche, s'articulaient au sein du groupe.

Dr David Rosenblatt : J'étais beaucoup dans la mouvance du Dr Scriver et je comprenais ce qu'il

faisait avec le RMGA, le Réseau de médecine génétique appliquée du Québec, avec son programme de dépistage néonatal. Si un médecin fait à l'hôpital le même genre de recherche qu'il ferait en laboratoire sur le campus, pourquoi est-il allé chercher un diplôme en médecine? Comme médecin, c'est ce que je me suis toujours dit.

Christopher Canning : Je vois.

Dr David Rosenblatt : Mon travail, ce n'est pas de faire concurrence aux fondamentalistes; je peux trouver des collaborateurs, apporter mon point de vue, décrire une voie métabolique, je peux discuter avec les cliniciens du bien-fondé de la consultation d'un spécialiste, faire du dépistage… C'est ça, mon travail : bâtir une expertise très ciblée.

Christopher Canning : Et c'est exactement ce que vous faites actuellement.

Dr David Rosenblatt : C'est ma perspective à moi, mais il est évident que n'eût été cet été passé avec le Dr Scriver, ce n'est pas ce que je ferais. Dieu sait que je pourrais fort bien être historien de la médecine ou quoi que ce soit d'autre, et ça m'intéresserait tout autant. Jamais je n'ai affirmé que ce que je faisais était plus important que ce que les autres faisaient; ce que j'affirme, par contre, c'est que je fais quelque chose d'important et qu'il est de mon devoir de protéger cette pensée, ce territoire scientifique. Mais jamais je ne dirai que mon domaine est plus important qu'un autre. Je dirai plutôt que je m'emploie à donner le meilleur de moi-même et qu'au bout du compte, toutes ces petites pierres vont former un tout qui fera avancer les choses.

Christopher Canning : D'accord. Je constate avec intérêt que vous avez vu passer chaque membre du groupe, de 1975 à 2009.

Dr David Rosenblatt : Oui, effectivement.

Christopher Canning : Les membres ont-ils toujours discuté entre eux de la nécessité de maintenir un sain équilibre entre le volet clinique et la recherche fondamentale?

Dr David Rosenblatt : Jamais. Je pense que les gens prêchaient par l'exemple, tout simplement. En fait, c'est intéressant de voir l'évolution du groupe. Nous voyons (Charles) Scriver et (Clarke) Fraser comme des gens qui ont fait de la clinique en plus d'être chercheurs, mais la prestation de soins n'a jamais été leur priorité. Non, ce qu'ils voulaient, c'était de découvrir des choses tout en offrant de bons soins à leurs patients. Mais ils n'ambitionnaient pas d'offrir des soins et des services génétiques au plus grand nombre de patients possible. Peut-être qu'en dépistage néonatal… mais leur but n'était pas de recevoir plus de patients que Sainte-Justine ni d'avoir la plus grosse clinique. Ils voulaient œuvrer dans un centre universitaire pour offrir des services de génétique ciblés. Nous nous sommes retrouvés dans de beaux draps, parce que Québec pensait que nous pouvions assurer la prestation de tous les services et faire de la recherche en génétique avec un budget fixe. Les membres du RMGA ont demandé un budget global à la province, avec lequel ils estimaient pouvoir soigner les patients, et faire de la recherche et de l'épidémiologie. Or, la demande de soins s'est accrue, mais le budget n'a pas suivi, d'où un profond mécontentement. Je ne parle pas du groupe, mais du RMGA, le Réseau de

médecine génétique et appliquée, un tout autre dossier. Un de ces jours, il faudra raconter cette histoire-là aussi.

Christopher Canning : Je n'ai jamais entendu parler de ça avant aujourd'hui.

Dr David Rosenblatt : Les directeurs étaient Charles Scriver et Claude Laberge.

Christopher Canning : Ah, d'accord.

Dr David Rosenblatt : Ça se passait à la même époque.

Christopher Canning : Je vois.

Dr David Rosenblatt : (Charles) Scriver était bon pour établir des structures, ce qui est la marque d'un leader. Dans ces cadres, il pouvait accomplir diverses tâches. Ainsi, il était conscient que pour que les choses marchent rondement au sein du RMGA, il devait s'allier à un francophone brillant, alors il est allé chercher Claude Laberge. Ils ont demandé à Québec – et obtenu – un budget qui leur permettrait d'offrir une gamme complète de services génétiques, et ça a très bien fonctionné à petite échelle. Mais les choses se sont mises à débouler, le diagnostic prénatal est arrivé dans le portrait et est devenu monnaie courante, si bien qu'on les pressait constamment d'accepter de nouveaux patients, d'étendre les services cliniques. Sauf qu'à leurs yeux, là n'était pas leur principale mission, du moins je pense. D'ailleurs, encore aujourd'hui, ce sont des questions d'actualité : que devrait-on faire, quels choix devrait-on faire?

Christopher Canning : De la clinique ou…?

Dr David Rosenblatt : Non, je parle des soins et de la recherche en médecine génétique au Québec. C'est un combat sans fin que je dois livrer dans mes fonctions en milieu universitaire. Nous avons encore beaucoup de choses à apprendre et, dans un centre tertiaire, nous sommes censés faire progresser la science, mais nous devons aussi soigner les patients et enseigner. À mon avis, il est raisonnable de croire que nous pourrons prodiguer des soins spécialisés dans certains domaines seulement. Nous n'arriverons pas à exceller dans toutes les sphères de la génétique; nous devrons nous consacrer pleinement à certains champs d'intervention et laisser à d'autres les autres domaines. Donc il y a toujours des tensions de ce côté-là, mais je ne pense pas que nous nous soyons demandé combien de temps devait être consacré respectivement à la recherche, à l'enseignement et à la prise en charge de patients. La question était plutôt : combien avons-nous de médecins? Au début du groupe, il y avait moi, Charles et Clarke. Après, il y a eu (Leonard) Pinsky, et bien sûr les Ph. D. En général, ceux-là ne se consacraient qu'à la recherche et à l'enseignement, bien que certains, comme (Rima) Rozen, aient aussi eu des responsabilités qui relevaient du laboratoire clinique.

Christopher Canning : Avez-vous l'heure?

Dr David Rosenblatt : Non, je n'ai pas regardé l'horloge.

Christopher Canning : Est-il 14 h?

Dr David Rosenblatt : Il est 14 h 10.

Christopher Canning : D'accord, allons-y pour 15 à 20 minutes encore.

Dr David Rosenblatt : Avec plaisir.

Christopher Canning : Lors de mes échanges avec Charles Scriver et Clarke Fraser, et maintenant avec vous, il a été question de l'importance du lieu de travail du groupe. Où travaillait le groupe à ses débuts? Y avait-il cette nécessité de réunir tout le monde sous un même toit? Dans la demande présentée au milieu des années 1980 – sur laquelle j'aimerais d'ailleurs qu'on revienne – j'ai remarqué que le Dr Scriver en particulier affirmait que le groupe ne devait pas, ou ne devrait pas, s'éparpiller, que tout le monde devait travailler dans un même lieu physique. Alors, j'aimerais connaître votre point de vue là-dessus. Où travailliez-vous au début et comment a évolué l'espace de travail du groupe?

Dr David Rosenblatt : Bon, il y a deux aspects à prendre en considération. Je pense qu'au début, lorsqu'on a défini la notion de « groupe », le partage d'un même lieu de travail était un incontournable. Vous pouvez consulter les règlements du CRM, mais je suis pas mal sûr qu'au début, les gens devaient travailler dans le même lieu physique, au sein d'un seul et même établissement.

Christopher Canning : Selon toute vraisemblance, c'était effectivement le cas.

Dr David Rosenblatt : Les règlements ont changé par la suite. En arrivant, j'ignorais pour ainsi dire tout de ces critères. On m'a donné un bureau qui devait faire, je ne sais trop, 60 ou 50 pieds carrés, et ça me suffisait. Lorsque je suis arrivé à l'Hôpital pour enfants comme étudiant en médecine, le bureau de Charles Scriver était au-dessus de la chaufferie. C'était très serré, mais ça fonctionnait. La constitution du groupe a permis au Dr Scriver de négocier l'obtention d'un nouvel étage, si bien qu'à mon retour de Boston, mon espace de travail était vraiment très bien. Ce n'était pas un grand étage, mais tous ceux qui y travaillaient étaient des collaborateurs de Charles. L'unité de Clarke était à l'étage du dessous, mais comme il faisait surtout de la recherche *in silico*, les laboratoires expérimentaux n'occupaient pas beaucoup d'espace. Il faisait de la recherche clinique à l'Hôpital pour enfants, mais avait aussi un laboratoire à McGill, où il se rendait pour ses travaux sur les souris. Je n'ai jamais fait partie des autorités administratives du groupe. Pendant les dix premières années, je faisais mes choses dans mon coin. Je m'entendais bien avec mes collègues. J'étais vraiment bien, parce que je me sentais à l'abri. En fait, si j'ai voulu voler de mes propres ailes en 1987, c'est probablement en partie pour sortir de ma zone de confort. Je savais qu'on s'attendait à ce que les gens prennent du galon et je ne voulais pas quitter McGill, alors je devais trouver quoi faire dans ce cadre pour que mon apport soit jugé utile en sachant tirer parti des possibilités offertes.

Christopher Canning : Souhaitez-vous que nous nous attardions un peu sur cette année 1987?

Dr David Rosenblatt : Au fil des ans, j'avais reçu quelques offres d'emploi d'autres établissements. On m'avait proposé d'établir une division de médecine génétique au Département de médecine de l'Hôpital général de Toronto. J'ai aussi reçu des offres de Dallas et de Calgary. J'avais toujours promis à Linda, ma femme (qui

vient des provinces de l'Atlantique), que je ne passerais pas beaucoup plus de cinq ans à Montréal. Elle n'a jamais été à l'aise au Québec à cause du climat politique. Mais bon, ça fera bientôt 36 ans, et je suis encore à McGill. Toujours est-il qu'au milieu des années 1980, j'étais à l'affût de postes ailleurs qu'à Montréal. À la même époque, Leonard Pinsky travaillait fort en coulisses depuis un bon moment pour que la génétique sorte de la pédiatrie et trouve sa place dans d'autres domaines. En collaboration avec Phil Gold, de l'Hôpital général de Montréal, et Peter Macklem, de l'Hôpital Royal Victoria, il avait trouvé de l'argent pour créer cette division de génétique en médecine.

Christopher Canning : Oui, en 1979 je crois, au moment où ça aurait dû…

Dr David Rosenblatt : Euh, non, en 1979, c'était le Centre de génétique. C'est complètement différent. On se demandait plutôt s'il devait y avoir une division de médecine génétique au Département de médecine, puisqu'elle avait toujours été limitée à la Pédiatrie. On avait le sentiment que les nouvelles technologies allaient essaimer en médecine générale et que McGill devait être à l'avant-garde de ce mouvement. En fait, j'ai décidé de rester à McGill au moment du renouvellement d'une subvention de groupe qui comprenait des fonds destinés à l'établissement de mon unité à l'Hôpital Royal Victoria. Richard Cruess, alors doyen, a accepté d'avancer les fonds en collaboration avec les hôpitaux. Et je pense qu'il n'a jamais remboursé les hôpitaux qui avaient financé le projet, mais ça, c'est une autre histoire. Vous devriez en parler à Richard Cruess, quoique je ne pense pas qu'il se souvienne des détails de l'affaire. Mais vous devriez le rencontrer quand même; c'est un gars haut en couleur.

Christopher Canning : J'en prends bonne note.

Dr David Rosenblatt : Des histoires formidables à vous raconter, j'en aurais beaucoup, et la plupart finissent bien; en tout cas, nous avons eu bien du plaisir. On se demandait donc quoi faire pour me garder à McGill et faire évoluer ce nouveau domaine, la génétique chez l'adulte. Charles était vraiment très contrarié que quelqu'un quitte le noyau de l'Hôpital pour enfants.

Christopher Canning : Oui, c'est ce que j'ai cru comprendre. J'ai ici une des lettres que le Dr Scriver a adressée au groupe; le changement de structure du groupe et le fait qu'il soit dispersé l'inquiétaient. Il craignait que ça nuise aux futures demandes de subvention et au rendement à venir du groupe.

Dr David Rosenblatt : C'est bien ça. Finalement, ça n'a posé aucun problème, mais il y avait de l'incertitude à l'époque. Le financement était, je pense, le principal motif de préoccupation. Je ne sais pas si le transfert aux facultés se faisait facilement. Charles redoutait aussi que le mandat du groupe ne soit pas reconduit. Il craignait que la demande ne soit pas assez novatrice, que les membres du groupe n'utilisent pas les techniques les plus récentes, parce que nous n'étions pas forts en analyse de l'ADN à l'époque.

Christopher Canning : Il voulait recruter un biologiste moléculaire?

Dr David Rosenblatt : Nous souhaitions tous une transition, mais aucun d'entre nous n'était formé comme il se doit à ce moment-là.

Christopher Canning : Je vois.

Dr David Rosenblatt : Et autour de cette époque, Lou Siminovitch avait fait un virage à 180 degrés à Toronto, il avait demandé à tout le monde de laisser tomber ses projets, tout ce qu'il faisait. Ce n'est pas ce que Charles envisageait, je pense, mais il craignait que nous ne soyons pas concurrentiels. L'ADN le sortait de sa zone de confort et ne faisait pas partie de ses champs d'intérêt à l'époque.

Christopher Canning : Alors en tant que groupe, vous aviez l'impression que le vent tournait?

Dr David Rosenblatt : La technologie évoluait en génétique et nous voulions rester dans le coup, et le fait est que nous avons évolué. Les règles qui régissaient les groupes changeaient aussi. Je ne sais pas exactement pour quelle demande, mais les gens pouvaient travailler à des endroits différents.

Christopher Canning : C'était dans les années 1980, si je ne m'abuse?

Dr David Rosenblatt : J'essaie juste de trouver la dernière publication qui pourrait être qualifiée… alors je pense que nous sommes autour…

Christopher Canning : De la fin des années 1980, je crois.

Dr David Rosenblatt : Oui, mais l'article du JCI[13] était certainement…

Christopher Canning : Connaissez-vous le numéro?

Dr David Rosenblatt : Oui, je cherche le numéro de la publication. Je ne me souviens pas si les travaux qui ont mené à l'article 32[14] ont été réalisés à l'Hôpital pour enfants, mais je pense que oui. Vers 1988-1989, les travaux se faisaient au Royal Victoria, mais la nature de mon travail demeurait inchangée. J'avais simplement pris du galon et j'assumais des responsabilités administratives en raison de la mise en place d'une clinique de génétique destinée aux adultes.

Christopher Canning : C'est donc à ce moment que vous êtes passé de la pédiatrie à un spectre plus large de la médecine?

Dr David Rosenblatt : Oui, puis j'ai été nommé directeur de la médecine génétique chez l'adulte. Nous avons établi un laboratoire diagnostique pour la maladie de Huntington et la polykystose rénale. Nous avons commencé à recevoir des patientes atteintes d'un cancer du sein; j'ai recruté un oncogénéticien, Steven Narod. Cette unité était la première division de médecine génétique rattachée à un département de médecine au Canada.

Christopher Canning : Vous étiez donc rendu là dans votre carrière…

Dr David Rosenblatt : Eh bien, il faut dire que tout ça s'inscrit dans le parcours normal d'un universitaire. Une fois parvenu à un certain niveau, on veut continuer à progresser. De plus, j'avais le sentiment que peu importe les travaux que je

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13 *The Journal of Clinical Investigation*

14 **Article 32 :** Watkins D et Rosenblatt DS (1986). Failure of lysosomal release of vitamin 812: A new complementation group causing methylmalonic aciduria (cbl F). *Am J Hum Gen* (39), 404-408.

faisais à l'Hôpital pour enfants, on aurait toujours l'impression que je marchais simplement dans les traces de Charles Scriver.

Christopher Canning : Je vois. Alors dans un sens, c'est vous…

Dr David Rosenblatt : Mais tout cela se déroulait au sein du groupe.

Christopher Canning : D'accord, parce que d'après ce que je peux voir, ça n'a pas nui au financement.

Dr David Rosenblatt : Non, pas le moins du monde.

Christopher Canning : Non.

Dr David Rosenblatt : Pas le moins du monde, et…

Christopher Canning : Sauf peut-être une légère animosité pendant une année ou deux.

Dr David Rosenblatt : Oui, il y avait une certaine tension, mais nous continuions à publier ensemble, comme en fait foi l'article 46[15]. Je pense que le Dr Scriver se considère comme le grand manitou; c'est SON équipe et c'est lui qui mène.

Christopher Canning : J'ai parlé avec lui de ces années et, étonnamment, il n'a aucun souvenir de ce qu'on pourrait appeler ce conflit, ou de ces changements dans la structure du groupe.

Dr David Rosenblatt : La bonne entente règne de nouveau depuis peu, et à titre de directeur, je l'ai toujours soutenu pour de nombreuses raisons. Il a fait de grandes choses, mais mon inquiétude vient d'une des faiblesses du Dr Scriver; à cause de sa façon de faire les choses, la transition s'est très mal déroulée après son départ. Les gens brillants sont souvent comme ça : quand on estime être la seule personne à pouvoir bien faire les choses, on se ménage une passation de pouvoirs plutôt difficile. Et le fait que ça s'effondre après ton départ montre à quel point tout reposait sur toi.

Christopher Canning : Je vois. Intéressant...

Dr David Rosenblatt : Quand les choses continuent d'aller pour le mieux et que de nombreux coéquipiers continuent de se distinguer après ton départ, tu peux te dire que tu as fait quelque chose de bien. Combien de fois a-t-on vu ça, à McGill : des programmes mis en place par des gens supérieurement intelligents, qui s'effondrent après le départ de ces personnes-là?

Christopher Canning : C'est intéressant; il a effleuré le sujet. Il a dit bon, ce qui est fait est fait.

Dr David Rosenblatt : Je préconisais fortement l'établissement du Département à l'Université, parce je crois en l'importance d'une structure viable à long terme.

Christopher Canning : Le Département où vous êtes en poste actuellement?

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15 **Article 46 :** McGill JJ, Mettler G, Rosenblatt DS et Scriver CR (1990). Detection of heterozygotes for recessive alleles. Homocyst(e)inemia: paradigm of pitfalls in phenotypes. *Amer J Med Genet* (36), 45-52.

Dr David Rosenblatt : Oui, le Département de génétique humaine. C'est moi qui le dirige actuellement, mais on s'est longtemps demandé pourquoi on avait besoin d'un département, qu'est-ce que ça nous apporterait de plus. À cela, je réponds que ça permet de créer la structure qui fera en sorte que l'entité sera stable et ne reposera pas sur les épaules d'une seule personne.

Christopher Canning : Et qu'elle survivra au départ de son fondateur.

Dr David Rosenblatt : Au moins, la passation des pouvoirs peut se faire dans l'ordre et l'harmonie, mais comme je vous le dis depuis le début, j'ai mon propre cadre de travail.

Christopher Canning : Vous faites vos affaires.

Dr David Rosenblatt : Personnellement, je préfère travailler au sein d'une structure. Leonard (Pinsky) était beaucoup comme ça lui aussi, je crois.

Christopher Canning : Je vois.

Dr David Rosenblatt : C'est bien d'avoir un mélange des genres au sein d'une structure.

Christopher Canning : Absolument. Je vais faire un saut vers le milieu des années 1990. Nous avons déjà parlé de ça et c'était fort intéressant. À cette époque, certaines personnes ont reçu du financement, mais pas dans le cadre du groupe, et d'autres n'ont rien reçu du tout. Prenons Emil Skamene : il a reçu une subvention en 1995, mais il n'était plus membre du groupe.

Dr David Rosenblatt : Il y a deux choses à prendre en considération ici. À ses débuts, le groupe était considéré comme une entité à part entière, même si les examinateurs étudiaient les activités de chaque membre individuellement. À titre d'exemple, vous pouvez jeter un coup d'œil aux premières évaluations de Peter Hechtman. On évaluait chaque personne individuellement et si c'était concluant, elle était autorisée à se joindre au groupe.

Christopher Canning : Intéressant.

Dr David Rosenblatt : Alors, il a été jugé et n'a pas été réadmis dans le groupe, évalué alors comme une seule et unique entité; c'est donc lui qui est parti le premier.

Christopher Canning : C'était en 1988?

Dr David Rosenblatt : D'accord, en gros, selon certaines évaluations, il ne contribuait pas au groupe autant qu'il aurait dû. C'était avant l'époque où chaque chercheur du groupe devait présenter sa propre demande de subvention étudiée par des pairs; le groupe était alors jugé dans son ensemble. Après, je pense que le CRM a pris un virage : il évaluait chaque membre du groupe individuellement et déterminait ensuite s'il avait sa place dans le groupe. Donc, ces gens-là pouvaient se dire : « Écoute, ce gars est très bien, mais nous ne voyons pas comment son travail pourrait cadrer dans la thématique du groupe; on va lui donner du financement, mais pas comme membre du groupe ».

Christopher Canning : Je comprends.

Dr David Rosenblatt : C'est donc une décision d'une autre nature. Ils jugent le travail scientifique méritoire en soi, mais ne le trouvent pas en adéquation avec celui du groupe.

Christopher Canning : D'accord. Parce que dans une demande, Eric Shoubridge n'a pas été accepté du tout.

Dr David Rosenblatt : Oui, et ça n'avait aucun sens.

Christopher Canning : Puis on a donné une subvention à Emil Skamene, mais pas au sein du groupe.

Dr David Rosenblatt : Oui, et j'ignore pourquoi Eric Shoubridge n'a pas été accepté du tout. D'après moi, ils ont mal lu sa demande.

Christopher Canning : Peut-être que ses études sur les mitochondries n'avaient pas vraiment la cote?

Dr David Rosenblatt : Eric est un gars génial, aux multiples talents. À ses débuts, il s'intéressait à l'imagerie. Puis peu à peu, il a dévié vers la biologie moléculaire, à laquelle il s'est formé en autodidacte, et il est l'un des meilleurs du monde dans son domaine; son exclusion à l'époque est complètement insensée.

Christopher Canning : Ses articles sont vraiment fascinants.

Dr David Rosenblatt : À vrai dire, c'est le gars lui-même qui est fascinant. Il faut croire que ses travaux n'ont pas séduit les examinateurs, mais c'était une erreur de jugement de leur part.

Christopher Canning : Je vois. Il semble qu'il se soit plutôt bien tiré d'affaire par la suite.

Dr David Rosenblatt : C'est exact, et nous avons pu le ramener dans nos rangs lorsque nous nous débattions – disons-le bien franchement – pour trouver des gens qui avaient l'étoffe nécessaire pour garder le groupe en vie.

Christopher Canning : Puis-je vous demander pourquoi vous n'avez jamais dirigé le groupe?

Dr David Rosenblatt : Euh, probablement parce que ça n'aurait pas fait l'affaire de certaines personnes.

Christopher Canning : D'accord. Mais encore?

Dr David Rosenblatt : Je pense qu'ils tenaient mordicus à ce que le groupe soit dirigé par quelqu'un **xxx**.

Christopher Canning : Oui, j'ai ça ici.

Dr David Rosenblatt : Ce qui est intéressant, c'est que pendant cette période, je n'avais pas accès aux fonds principaux.

Christopher Canning : D'accord.

Dr David Rosenblatt : Pendant ce cycle du groupe, mais ce n'était pas grave, parce que les fonds dont je me servais étaient subventionnés de toute façon. J'utilisais les installations principales surtout pour la banque de cellules; j'allais chercher des

lignées cellulaires d'un peu partout, et elles étaient conservées à l'Hôpital pour enfants. Jamais on ne m'a empêché d'utiliser la banque de cellules, mais s'il restait des fonds dans le budget principal à la fin de l'année, je ne faisais pas partie de ceux qui en recevaient.

Christopher Canning : Lors du symposium, Charles Scriver a mentionné – il ne me reste que quelques questions. Nous pouvons toujours revenir…

Dr David Rosenblatt : C'est comme vous voulez.

Christopher Canning : Charles Scriver a mentionné, pendant le symposium, que le groupe avait toujours fonctionné suivant une approche collaborative, et je trouve ça très intéressant sur le plan sociologique. Puis-je vous demander ce qu'il voulait dire par là, selon vous? Ce que ça voulait dire dans ce groupe, qui a eu le vent dans les voiles pendant tellement d'années? L'approche collaborative, ça veut dire quoi au juste?

Dr David Rosenblatt : Je pense que le Dr Scriver n'est jamais intervenu directement dans la pensée scientifique des fondamentalistes ni dans leur programme de recherche. Les chercheurs s'alliaient à des membres du groupe, mais aussi à des personnes extérieures au groupe qui pouvaient contribuer à leurs travaux. Nous formions des alliances naturelles qui finissaient par se dissoudre, puis nous en formions de nouvelles ou collaborions avec des gens qui possédaient une expertise particulière. Ce n'est pas comme si quelqu'un était arrivé en déclarant : « OK, les gars, la fibrose kystique, c'est aujourd'hui que ça se règle; voici ce que vous allez faire ». Chacun faisait son travail en échangeant avec les collègues dans le cadre défini. Puis il y avait des démarcheurs, des diplomates et des politiciens qui ficelaient tout ça. Et ça a fonctionné. Ça a même très bien fonctionné, et avec divers patrons. Ce groupe est à l'origine du Centre de génétique humaine et du Département de génétique humaine à McGill. C'est grâce à lui que ces entités ont vu le jour.

Christopher Canning : C'est formidable. Mais dites-moi, sur quoi portent vos recherches actuellement?

Dr David Rosenblatt : J'ai 63 ans, j'ai fait ma demande de subvention l'an dernier, et le comité de génétique des Instituts de recherche en santé du Canada l'a placée à la tête du classement. Ils m'ont demandé s'ils pouvaient s'en servir comme modèle pour d'autres chercheurs. J'étais drôlement fier. Je me consacre actuellement à deux champs de recherche. Après avoir découvert des gènes, on doit se demander d'abord quelle est l'importance de ces gènes et s'il est possible qu'ils soient liés à des problèmes fréquents, par exemple des anomalies congénitales. Et ensuite, on doit étudier l'interaction entre ces produits géniques dans la cellule. Dans un cas comme dans l'autre, on est dans le long terme. Dans ma demande de subvention la plus récente, j'ai ajouté une recrue comme cocandidate. Loydie Majewska est une biologiste du développement qui travaille à l'Hôpital pour enfants. C'est une généticienne de la souris, alors d'ici à peu près cinq ans, j'ai l'intention de lui confier les rênes de ce projet qui, selon moi, devrait s'étendre sur une bonne dizaine d'années. Si tout se passe comme prévu, ce sera elle qui présentera la prochaine demande de subvention à titre de chercheuse principale. Je collabore également avec quelqu'un du Département de microbiologie, James Coulton, qui fait de la purification

d'enzymes et de la biologie structurale. Pour ce volet du projet, j'ai un boursier postdoctoral en poste dans son laboratoire, et c'est à lui que je compte passer le relais.

Christopher Canning : Est-ce qu'on parle ici de génomique fonctionnelle? Est-ce quelque chose qui vous intéresse encore?

Dr David Rosenblatt : Oui, mais il s'agit davantage de mécanismes d'action, de produits géniques et de relations entre les gènes. Aujourd'hui, on a besoin de décrire précisément ce qu'on fait en donnant des termes à tout, mais oui, c'est de la génomique fonctionnelle. On veut voir ce que ces gènes font, comment ils interagissent les uns avec les autres. Dans le cas des souris, lorsqu'on introduit les mutations, les petits ne se rendent pas à terme et ils ont parfois des anomalies congénitales. Nous essayons de faire ce que Rima Rozen a fait avec la souris *MTHFR*, mais avec les nouveaux gènes que nous avons découverts.

Christopher Canning : Je vois. Vous avez publié tout récemment un article sur la modification épigénétique du gène responsable de la vitamine B_{12}.

Dr David Rosenblatt : Il vient de mon labo.

Christopher Canning : Oui, de votre labo. Je vous pose la question par pur égoïsme, parce que l'épigénétique m'intéresse. Sentez-vous que l'épigénétique se taille une place de plus en plus grande dans votre travail?

Dr David Rosenblatt : Oui, et il y a plusieurs raisons qui expliquent ça. J'ai un exemple intéressant à vous donner. Il y a de cela quelques années, un chercheur de l'Université d'Ottawa du nom de Robert Liteplo a communiqué avec moi pour m'informer qu'il avait une lignée de cellules de mélanomes qui, en culture, ressemblaient aux lignées cellulaires d'une de nos anomalies liées à la vitamine B_{12}. En collaboration avec David Watkins, il a constaté qu'en milieu de culture, ces cellules ne corrigeaient pas les cellules d'une de nos erreurs innées. Nous pensions que dans ces cellules, le gène responsable de cette maladie serait défectueux. Lorsque nous avons cloné le gène (article 141[16]), nous avons isolé la lignée cellulaire pour voir s'il y avait des mutations dans le gène. Il n'y en avait pas, mais ensuite, nous avons vérifié si le gène était exprimé… et il ne l'était pas. Nous avons donc formulé comme hypothèse que le problème, c'était la méthylation du promoteur du gène, et ça s'est révélé juste. Le lien avec l'épigénétique, il est donc là.

Christopher Canning : Ça fait un bon moment que vous vous intéressez à la méthylation.

Dr David Rosenblatt : C'est parce que nos gènes interviennent dans la transméthylation, c'est-à-dire la conversion de l'homocystéine en méthionine, puis en SAM[17]. Voilà pourquoi je m'intéresse à l'épigénétique.

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16 **Article 141 :** Lerner-Ellis JP, Tirone JC, Pawelek PD, Dore C,Atkinson JL, Watkins D, Morel CF, Fujiwara TM, Moras E, Hossack AR, Dunbar GV, Antonicka H, Forgetta V, Fobson CM, Leclerc D, Gravel RA, Shoubridge EA, Coulton JW, Lepage P, Rommens JM, Morgan K, Rosenblatt DS (2006). Identification of the gene responsible for methylmalonic aciduria and homocystinuria, *cb/C* type. *Nat Genet*, 38(1), 93-100. Erratum. *Nat Genet*

17 S-adénosylméthionine

Christopher Canning : Et surtout maintenant qu'on explore l'épigénétique dans une optique héréditaire.

Dr David Rosenblatt : Absolument. Avez-vous déjà entendu parler des travaux sur les souris Agouti?

Christopher Canning : Oui, tout à fait.

Dr David Rosenblatt : Disons-le d'emblée, c'est intéressant en soi. Et c'est aussi une excellente façon d'expliquer la pertinence de nos travaux sur ces maladies obscures, de mettre en lumière les mécanismes qui conduisent au recyclage de l'atome de carbone lié à la méthylation. Dans nos demandes de subvention, nous écrivons systématiquement que nos travaux sont pertinents dans le cancer et les maladies cardiaques, et c'est le cas : nous faisons ces recherches pour faire progresser le savoir dans un domaine effectivement pertinent en médecine.

Christopher Canning : Pendant combien de temps encore allez-vous demeurer à la tête du Département de génétique humaine?

Dr David Rosenblatt : Mon mandat se termine officiellement au printemps 2010. Je m'attends à ce qu'il soit prolongé d'un an pour diverses raisons; il y a eu un battement d'un an lors de ma nomination, si bien que mon premier mandat n'a été que de quatre ans et en 2011, j'aurai 65 ans, alors je pense qu'on va prolonger ça d'une année. Je n'ai pas l'intention de rester passé août 2011.

Christopher Canning : Et vous avez parlé tantôt d'une demande de subvention sur un projet de dix ans ou quelque chose du genre. Comptez-vous prendre votre retraite à ce moment-là?

Dr David Rosenblatt : Je ne sais trop. Je ne prendrai probablement jamais une vraie retraite, pas tant que je serai en santé et que j'aurai encore des idées. Il y a d'autres choses à faire. Le diagnostic précoce des maladies mendéliennes rares n'a pas évolué autant que je l'aurais souhaité, et ça me déçoit. J'aimerais faire davantage de recherche appliquée pour essayer de mobiliser les unités partout sur le campus. Au lieu d'avoir une multitude de petites unités qui se font concurrence, j'aimerais voir une unité diagnostique qui n'a rien à envier aux meilleures équipes du genre dans le monde et n'a rien à son épreuve.

Christopher Canning : Qui se spécialiserait dans les maladies mendéliennes?

Dr David Rosenblatt : Exactement. Mais je crains que les laboratoires de diagnostic moléculaire soient pris d'assaut par des gens qui diagnostiquent le H1N1 et les changements somatiques dans le cancer du sein. Le problème avec la plupart des maladies mendéliennes, c'est que ce sont habituellement des troubles rares, mais il y en a des milliers, et il faut pouvoir offrir des services diagnostiques aux patients. Ça va jouer des coudes, parce qu'on se disputera âprement les ressources. Notre système de soins de santé est de compétence provinciale, et ça, c'est un problème. Je sais qu'il y a un laboratoire national pour les maladies infectieuses à Winnipeg, mais je pense qu'il est à peu près impossible de mettre en place un laboratoire national au Canada. Par contre, peut-être qu'au Québec, on pourrait arriver à centraliser une partie de ces services. J'aimerais voir un consortium universitaire, qui réunirait tous les acteurs de McGill, offrir ces services diagnostiques. Il y a des endroits où on a

réussi à faire ça, entre autres aux universités Baylor et Emory. C'est pour ça que je suis disposé à investir de l'énergie dans ce type de projet.

Christopher Canning : C'est formidable. Je me tiens à votre disposition. Je vous remercie sincèrement pour le temps que vous m'avez consacré.

FIN DE L'ENTRETIEN

Rima Rozen, le 16 février 2010

Andrew Hoffman : Ici Andrew Hoffman en compagnie de Rima Rozen, au Département de génétique humaine. Il s'agit bien d'un département, n'est-ce pas?

Rima Rozen : C'est exact. Je suis professeure au Département de génétique humaine et de pédiatrie.

Andrew Hoffman : J'oubliais la pédiatrie. Nous sommes le 16 février 2010. C'est un véritable honneur et privilège pour moi de pouvoir m'entretenir avec vous de deux grands sujets qui touchent la génétique humaine. J'aimerais que nous abordions d'abord votre parcours universitaire, qui vous a permis de contribuer grandement à l'avancement de la génétique médicale au Canada et ailleurs dans le monde.

Ensuite, et c'est le principal thème de notre étude, j'aimerais parler de votre participation au sein du groupe, et non du département, sur la génétique médicale des IRSC[1] – anciennement le CRM[2] – de McGill, dont vous avez été un membre important. Si je ne me trompe pas, ce groupe a existé jusqu'en septembre dernier sous la direction, entre autres, des D^rs^ Clarke Fraser et Charles Scriver.

Rima Rozen : Disons plutôt que plusieurs personnes se sont succédé à la tête du groupe.

Andrew Hoffman : Pour commencer, et j'espère que vous n'aurez pas à trop vous répéter, pourriez-vous nous parler de votre lieu de naissance, de votre enfance, de vos premières années d'école, etc.?

Je vois dans votre CV que vous êtes née en Union soviétique, et que vous avez étudié à l'Université McGill. Il sera intéressant de savoir d'où vous venez et quelle incidence votre histoire personnelle a eue sur votre travail comme scientifique.

Commençons donc par le tout début.

Rima Rozen : Je ne dirais pas que mon histoire personnelle a eu une influence sur mon domaine de recherche. Mais les études étaient importantes pour les familles immigrantes du Canada et des États-Unis. Je tenais donc à faire de grandes études et à obtenir un diplôme pour quelque chose d'important. Mais au-delà de ça, on ne m'a jamais vraiment poussée vers la biologie, la génétique ou autre chose. Mes parents, qui avaient survécu à l'Holocauste, n'ont pas poursuivi leurs études après l'école secondaire. Ils ne connaissaient pas les sujets comme la génétique, la biochimie ou le métabolisme. Mon éducation familiale n'a donc pas joué un grand rôle pour la suite.

Andrew Hoffman : Mais ils vous ont soutenue…

Rima Rozen : Dans mes études? Absolument. Et ça leur importait peu que je choisisse la

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

médecine, le droit, la recherche ou la physique. Mon père aurait bien aimé que je choisisse la physique, mais il avait un point de vue soviétique. Je crois qu'à cette époque, son goût pour les mathématiques et la physique, combiné à la Guerre froide et au programme spatial, a influencé sa façon de penser. Mais mes parents ne nous ont jamais poussées vers des domaines en particulier, ma sœur et moi. Ils voulaient juste que nous fassions des études.

Andrew Hoffman : Vous aviez donc peut-être un léger penchant pour les sciences?

Rima Rozen : Oui.

Andrew Hoffman : Et est-ce que votre sœur est aussi…

Rima Rozen : Ma sœur a un doctorat en biochimie et travaille dans le secteur privé. Elle est analyste scientifique pour le financement des sciences par le secteur privé. Nous sommes toutes les deux en sciences : moi du côté universitaire et elle du côté de l'investissement. Il y a donc des différences entre nous, mais c'est peut-être une simple question d'époque.

Andrew Hoffman : D'époque?

Rima Rozen : Ma sœur a huit ans de moins que moi. Et je crois que pendant ma formation, la carrière universitaire était à peu près la seule option pour les détenteurs d'un doctorat. Quand elle a terminé ses études, il y avait plus d'options.

Andrew Hoffman : À votre avis, avez-vous eu une influence sur sa carrière?

Rima Rozen : Pas vraiment. Elle a commencé une carrière universitaire, mais des occasions l'ont menée vers le privé.

Andrew Hoffman : Donc, votre famille a émigré de l'URSS vers…

Rima Rozen : Vers la Pologne, puis vers le Canada.

Andrew Hoffman : Et c'était en quelle année?

Rima Rozen : Nous sommes arrivés en 1960. J'ai fait toute ma scolarité à Montréal. Je n'ai pas commencé l'école ailleurs.

Andrew Hoffman : Vous aviez environ huit ans lorsque vous…

Rima Rozen : J'avais six ans. C'est pour ça que je parle anglais sans accent. Sauf peut-être un accent canadien. Comme j'ai appris l'anglais ici, à l'école, je n'ai aucun accent, mais l'anglais était ma quatrième langue. J'aime les langues, les différentes cultures, les immigrants, les différentes communautés. Peut-être que ça m'a poussée vers la génétique, mais je n'ai jamais réfléchi à la question sous cet angle.

Andrew Hoffman : Est-ce que vous vous intéressiez déjà aux sciences à l'école primaire ou secondaire?

Rima Rozen : Oui, oui. J'aimais les mathématiques, la biologie.

Andrew Hoffman : Vous avez donc décidé de faire un baccalauréat en sciences spécialisé en biologie?

Rima Rozen : Exactement. Un baccalauréat en biologie, qui est ensuite devenu un genre de programme de génétique. La génétique n'est pas un domaine indépendant au premier cycle. La seule façon d'étudier en génétique à McGill était d'entrer au Département de biologie. Le programme d'études supérieures en génétique a été créé plus tard, mais nous n'avons toujours pas de programme de premier cycle en génétique.

Andrew Hoffman : Donc, pendant votre baccalauréat en sciences, est-ce que la génétique était…

Rima Rozen : La génétique était enseignée, oui. C'était une concentration ou une majeure, je ne me souviens pas du nom qu'on donnait au programme à l'époque, mais il y avait d'excellents cours et une véritable orientation en génétique humaine à McGill. En fait, Charles Scriver et Clarke Fraser, et d'autres comme Peter Hechtman, ont été mes professeurs. C'est eux qui rendaient la génétique si attrayante, et c'est essentiellement pour ça que j'ai choisi ce domaine.

Andrew Hoffman : Diriez-vous que pendant votre baccalauréat la génétique était un domaine qui changeait ou qui prenait de plus en plus de place dans le programme d'études?

Rima Rozen : Oui, bien sûr. Il était clair que le domaine de la génétique se transformait. Au début, en génétique, on se contentait d'observer les patients. On s'est ensuite intéressé à l'aspect chimique, puis à l'aspect moléculaire. On voyait bien que la discipline évoluait et qu'elle allait devenir fascinante.

Andrew Hoffman : Vous vous rappelez avoir pensé ça à l'époque?

Rima Rozen : Est-ce que je pensais ça à l'époque? Probablement pas. Mais si vous me le demandez rétrospectivement, je pourrais avoir l'air très intelligente et vous dire que oui, je savais…

Andrew Hoffman : Vous saviez que cela allait arriver.

Rima Rozen : Pendant mon baccalauréat, je pouvais voir clairement que la génétique avait de l'avenir.

Andrew Hoffman : Nous parlerons des détails un peu plus tard. Vous avez dit avoir travaillé… ou avoir eu les D^{rs} Fraser et Scriver comme professeurs et…

Rima Rozen : Je me souviens que Peter Hechtman était également un excellent professeur. Ces personnes étaient les maîtres à penser, les gourous.

Andrew Hoffman : Quelle influence ont-ils eue sur votre choix de carrière après votre baccalauréat en biologie?

Rima Rozen : Je suis devenue doctorante et j'ai travaillé avec Charles, mais j'ai aussi fait un projet de recherche spécialisé. Nous devions réaliser un projet de recherche au baccalauréat, et j'ai choisi la génétique, mais pour une raison qui m'échappe, j'ai été jumelée à Reynold Gold, qui était membre du groupe. Je ne

me rappelle pas pourquoi je l'ai choisi, plutôt que Charles; peut-être que Charles était absent ou qu'il n'était pas joignable. C'est difficile à dire.

Toujours est-il que j'ai travaillé dans les locaux du groupe de génétique, au 7e étage de l'aile A. J'ai rencontré tout le monde et je me suis intéressée à bien d'autres sujets, en plus des recherches de Reynold Gold. D'ailleurs, je trouvais ses recherches un peu arides.

Andrew Hoffman : Le 7e étage de l'aile A de…

Rima Rozen : De l'hôpital. Le groupe a toujours été là. Il a aussi été créé là. Mais pas au 7e étage; je ne me rappelle plus très bien où le groupe a commencé.

Andrew Hoffman : Je crois que c'était au 6e étage.

Rima Rozen : C'est possible. Mais quand je suis arrivée, il était au 7e étage, et je crois que Charles était le directeur. J'ai commencé à travailler avec le groupe grâce à Reynold Gold, mais ce sont les recherches de Charles qui m'intéressaient. Je l'ai donc approché pour mes études supérieures.

Andrew Hoffman : Donc, vous avez suivi un cours qui portait précisément sur la génétique humaine?

Rima Rozen : Plusieurs cours en fait, mais je ne me rappelle plus les détails.

Andrew Hoffman : Au cours des autres entretiens, j'ai appris que les cours étaient donnés par les Drs Scriver et Fraser, ainsi que par Peter Hechtman et Reynold Gold. Je voulais donc vous demander quels cours vous aviez suivis et comment…

Rima Rozen : Je les ai probablement tous suivis, ou peut-être seulement quelques-uns. Peu importe. Mais oui, ce sont eux qui donnaient les cours de premier cycle, et ils étaient d'excellents professeurs.

Andrew Hoffman : Vous avez suivi les cours un à la fois? Plusieurs à la fois? Vous rappelez-vous?

Rima Rozen : Je ne me rappelle pas.

Andrew Hoffman : Vous avez dit avoir fait un projet de recherche spécialisé en génétique au premier cycle.

Rima Rozen : C'est exact. Un projet de recherche spécialisé pendant ma dernière année au premier cycle.

Andrew Hoffman : Et vous souvenez-vous de ce que vous avez fait pendant ce projet?

Rima Rozen : Oui, je m'en souviens. J'examinais des cheveux et je mesurais les composés soufrés ou les protéines soufrées liés à une anomalie génétique qu'on étudiait à l'époque. Je ne me souviens pas du nom de cette anomalie. C'est ça que je faisais. Je mettais au point une technique qui ne fonctionnait pas bien, ce qui était frustrant, mais je pense que j'ai fini par recueillir des données. On peut dire que c'était un sujet un peu aride.

Andrew Hoffman : Je vois. Est-ce que c'est à ce moment que vous avez décidé…

Rima Rozen : Que je voulais faire de la recherche, mais que je ne souhaitais pas continuer à travailler à ce projet ou dans ce domaine, donc…

Andrew Hoffman : Mais la génétique vous intéressait?

Rima Rozen : Oui.

Andrew Hoffman : Vous avez donc entrepris de faire votre doctorat à McGill, avec le Dr Scriver. C'est bien ça?

Rima Rozen : Oui, c'est ça.

Andrew Hoffman : Il était votre superviseur principal?

Rima Rozen : Oui.

Andrew Hoffman : Et quel a été votre premier projet?

Rima Rozen : C'est une histoire intéressante. Comme je m'intéressais aux maladies métaboliques et aux erreurs innées du métabolisme, il m'a donné un projet qui consistait à détecter une anomalie particulière dans une erreur innée du métabolisme. Il pensait qu'il pouvait s'agir d'une nouvelle anomalie de la voie métabolique. Nous avions un patient qui semblait touché par cette anomalie. Nous avions donc accès aux cellules du patient.

J'ai travaillé sur ce projet pendant deux ans. C'était palpitant parce que j'ai eu l'occasion d'aller à Toronto pour y apprendre de nouvelles techniques, que j'ai rapportées à McGill.

En fait, c'est intéressant parce que j'ai appris ces techniques auprès de Roy Gravel, à Toronto. Je suis revenue pour travailler sur ce projet, et au bout de deux ans, j'ai démontré qu'il ne s'agissait pas d'une nouvelle anomalie comme le Dr Scriver l'espérait. C'est moi qui le dis, mais mes résultats étaient très clairs et ne comportaient aucune irrégularité. Ce n'était pas une nouvelle anomalie. J'ai réussi à prouver qu'il s'agissait plutôt d'une anomalie qui avait déjà été décrite. Elle ne convenait donc pas à une thèse de doctorat.

Andrew Hoffman : C'était une variante d'une anomalie ou simplement…

Rima Rozen : Pas vraiment. Il s'agissait essentiellement d'un problème qui avait déjà été décrit dans la littérature scientifique. Donc, après deux ans de travail, je devais entreprendre un nouveau projet, complètement différent.

Andrew Hoffman : Vraiment?

Rima Rozen : Je n'en veux pas à Charles. Je lui ai pardonné.

Andrew Hoffman : J'ai l'impression que cette situation se produit très souvent. Ça ne m'est pas arrivé, mais…

Rima Rozen : J'avais commencé à travailler dans un domaine très différent.

Andrew Hoffman : Pourriez-vous me parler de l'anomalie ou…

Rima Rozen : Je ne pense pas que ce soit pertinent dans l'histoire du groupe.

Andrew Hoffman : Vous avez dit être allée à Toronto et avoir rapporté des techniques qui n'avaient jamais été utilisées à McGill.

Rima Rozen : C'était une technique que Roy Gravel maniait de main de maître.

Andrew Hoffman : De quoi s'agissait-il?

Rima Rozen : De sa technique de complémentation. À mon retour, j'ai utilisé la technique avec mon patient pour voir s'il s'agissait bien d'une nouvelle anomalie et j'ai découvert que ce n'était pas le cas.

Andrew Hoffman : Pourriez-vous décrire le processus de complémentation…

Rima Rozen : Vous prenez de l'assurance, on dirait. Je ne pense pas que vous ayez besoin de connaître des détails à ce sujet.

Andrew Hoffman : Seulement quelques renseignements de base au sujet de ce que vous avez rapporté et…

Rima Rozen : Disons que ce n'était pertinent que pour ce patient en particulier, que pour ce projet, que j'ai décidé de ne pas continuer. Ce n'est donc pas quelque chose que j'ai apporté à McGill. Et David Rosenblatt fait beaucoup de travail en complémentation. Je ne pourrais donc jamais être reconnue comme experte en complémentation. J'ai appris cette technique et je l'ai utilisée pour mon patient, mais je n'y ai plus retouché.

Andrew Hoffman : Mais vous avez travaillé sur ce projet à McGill avant le D^{r} Rosenblatt, n'est-ce pas?

Rima Rozen : Je ne pourrais pas dire.

Andrew Hoffman : En résumé, vous avez rapporté la technique avec vous, vous l'avez utilisée pour les besoins de votre projet et vous vous êtes rendu compte que le sujet de vos recherches n'était pas nouveau.

Quelle a été l'étape suivante?

Rima Rozen : À ce moment-là, je devais travailler sur un projet déjà en cours ou quelque chose qui allait me permettre d'obtenir un doctorat. Je ne voulais pas faire des recherches qui allaient me demander encore six ans. J'ai donc travaillé sur le transport des acides aminés chez les souris, plus précisément sur le transport de la taurine. Apparemment, le taux de taurine dans l'urine n'était pas le même chez toutes les souris à cause de différences dans le transport des acides aminés. J'ai donc dû apprendre de nouvelles techniques dans le domaine du transport qui étaient très différentes de celles que j'avais utilisées auparavant. Et il s'agissait de souris, non de personnes. Et il était question de transport, non

de métabolisme.

J'ai fait le travail, j'ai rédigé ma thèse et j'ai publié de bons articles, mais je savais que je ne voulais pas continuer à travailler dans ce domaine.

Et je dois mentionner que pour la majeure partie de ce projet, c'est Susie Tenenhouse qui était l'experte. Je ne me rappelle plus si elle faisait partie du groupe à ce moment-là ou si elle était adjointe à la recherche. Elle a été adjointe à la recherche avec Charles avant de devenir professeure et membre du groupe. C'est elle qui m'a supervisée de façon régulière, et elle était l'experte à consulter lorsque Charles partait donner des conférences, ce qu'il faisait souvent.

On peut donc dire que c'est avec Susie Tenenhouse que j'ai appris la démarche scientifique.

Andrew Hoffman : C'est Charles qui vous a attribué votre projet, c'est bien ça?

Rima Rozen : Oui, et nous nous rencontrions pour en discuter, mais c'est Susie qui m'a appris à faire les expériences et qui m'a guidée de façon régulière.

Andrew Hoffman : Vous deviez donc travailler avec deux personnes. Comment décririez-vous votre relation avec le Dr Scriver?

Rima Rozen : Oh! C'était fantastique de parler avec lui. Il avait toujours de nouvelles idées, et il s'exprimait très bien. Ce qui était particulier, c'est qu'il pouvait écrire aussi bien qu'il faisait son travail en sciences. Mieux que la plupart des scientifiques, en fait.

Lorsque vous remettiez un brouillon de manuscrit à Charles, votre document vous revenait rempli de marques rouges. Son mentorat était différent de celui de Susie, mais les deux ont été très importants.

Andrew Hoffman : Susie a-t-elle fini par superviser le projet de façon officielle?

Rima Rozen : Je ne crois pas. Je pense qu'elle était toujours adjointe à la recherche. Elle ne pouvait donc pas avoir une tâche de supervision. Il faut être professeur pour superviser de façon officielle. Elle était donc ma superviseure au quotidien. C'était généralement la façon de faire à l'époque. Il y avait beaucoup plus d'argent pour la recherche. Les gens créaient de petits empires, en quelque sorte. Les directeurs de projet pouvaient créer de gros groupes avec beaucoup de moyens et avoir un bon nombre d'adjoints à la recherche, etc. Il était assez fréquent que les chercheurs importants aient des adjoints à la recherche chargés de former un étudiant.

Andrew Hoffman : Vous remarquez donc des différences entre les pratiques de financement de l'époque et celles d'aujourd'hui. Nous en reparlerons plus tard, mais croyez-vous que c'est cette structure qui vous a vraiment permis de réussir dans vos recherches? Ce que je veux dire, c'est que techniquement, votre projet était dirigé par une personne, alors que dans votre travail de tous les jours, vous étiez supervisée par une autre personne.

Rima Rozen : Ce n'était pas un problème. Ça fonctionnait même très bien. Je vois cette situation très souvent dans mon propre laboratoire aujourd'hui. Je ne suis pas ici aussi souvent que je le devrais, et les adjoints à la recherche ou les postdoctorants participent à la formation des étudiants. Ça semble être une méthode fréquente pour la formation des étudiants dans les gros groupes.

Andrew Hoffman : Est-ce que Susie Tenenhouse vous a aidée à bien définir votre projet?

Rima Rozen : Oui, pour les détails peut-être. Mais c'est Charles qui a donné l'orientation générale. « Voici le projet sur lequel tu dois travailler. » Évidemment, nous nous rencontrions pour en discuter. Ils m'ont tous deux aidée à préciser mon travail, mais c'est bien Charles qui a établi le sujet de recherche.

Andrew Hoffman : Aviez-vous votre mot à dire dans l'orientation du projet?

Rima Rozen : J'avais certainement le potentiel de le faire. Je ne me rappelle pas si j'avais besoin qu'on me supervise de près ou non. Ça fait trop longtemps. Ils devaient penser que j'étais capable de faire le travail, sinon, ils ne m'auraient pas laissée continuer.

Andrew Hoffman : Vous disiez donc que le projet fonctionnait… C'était le projet avec les souris sur le transport des acides aminés, donc la physiologie des acides aminés et le transport. Est-ce qu'il portait aussi sur le métabolisme de l'homocystéine et du folate?

Rima Rozen : Non. Ça, ce sont les recherches sur lesquelles je travaille actuellement. À l'époque, il s'agissait d'un acide aminé appelé « taurine ».

Andrew Hoffman : Mais c'est à peu près à ce moment-là que votre intérêt pour les acides aminés…

Rima Rozen : Il s'agissait en fait du premier projet. J'ai beaucoup aimé travailler sur le cas d'un patient, sur les erreurs innées du métabolisme. Deux conversions. C'est le premier projet qui m'a le plus intéressée, et le travail que je fais maintenant est beaucoup plus lié à mon premier projet qu'au transport des acides aminés chez les souris.

Andrew Hoffman : J'imagine que c'est pour ça que vous avez dit que ce projet vous a permis de publier de bons articles, mais…

Rima Rozen : Mais qu'il ne m'intéressait pas assez pour que je désire approfondir le sujet.

Andrew Hoffman : Je vois. D'après vos souvenirs, comment s'est déroulée la transition entre votre travail avec des personnes et votre travail avec des souris?

Rima Rozen : Je ne travaillais pas directement avec des personnes, je travaillais plutôt avec des cellules.

Andrew Hoffman : Des cellules humaines.

Rima Rozen : Exact. J'ai travaillé avec des cellules humaines, puis avec des cellules de souris. Ce ne sont pas tant les techniques utilisées ou la nature du matériel de

recherche qui comptent, mais plutôt la nature de la science. Dans ce cas, il s'agissait du transport. Selon moi, on ne peut pas vraiment étudier un sujet dans son ensemble du point de vue du transport, du moins pas de la façon dont on étudie le transport. Le transport est un aspect très isolé. Il faut isoler des fragments de rein, des membranes du rein, et tout se fait *in vitro*.

Ce que je veux dire, c'est qu'il faut aussi tenir compte de l'ensemble du sujet étudié, mais pas dans la même mesure que lorsqu'on étudie un patient porteur d'une maladie. À ce moment-là, on ne s'intéresse pas à un seul tissu, à une seule membrane. On essaie plutôt de comprendre ce qui se passe dans le corps.

Je me suis déjà demandé si je devais faire ma médecine ou faire de la recherche. J'ai envisagé les deux options pendant mon baccalauréat. Pourquoi j'ai choisi la recherche? Je pense qu'il n'y avait pas suffisamment de mentors à cette époque. J'ai toujours eu peur de ne pas avoir le temps de faire ce que les autres femmes font ou aiment faire.

Autrement dit, je voulais le beurre et l'argent du beurre. Je voulais avoir une carrière, mais je voulais aussi fonder une famille et avoir des enfants, etc. Et je n'étais pas certaine de pouvoir faire tout ça sans sacrifier sérieusement soit l'un, soit l'autre. J'ai pensé que la recherche pourrait être la meilleure option. Est-ce que c'était un bon choix? J'ai une famille et des enfants, alors j'imagine que oui.

Est-ce que j'aurais pu faire la même chose tout en pratiquant la médecine? Je n'en suis pas convaincue. Je ne sais pas. Mais j'ai beaucoup de collègues médecins, et je constate qu'ils ont peu de temps à consacrer à la recherche. J'ai reçu une meilleure formation que la plupart des médecins. Je ne dis pas que les titulaires de doctorat sont plus brillants que les médecins, mais notre formation est plus complète. Nous sommes donc souvent plus efficaces dans notre façon de réfléchir.

Nous sommes peut-être plus rigoureux.

J'ai probablement pris la bonne décision parce que je peux faire de la recherche comme ça me plaît tout en ayant une vie de famille. Et peut-être que je n'aurais pas pu faire de la recherche au même niveau ou avec la même qualité, ou le même type de recherche, avec un diplôme en médecine.

Bref, ce que je voulais dire, c'est que j'ai toujours été attirée par les projets liés à la médecine.

Andrew Hoffman : Et je crois que ça s'est concrétisé dans votre carrière.

Rima Rozen : Exactement. Quand je travaillais avec un patient atteint d'une maladie métabolique, il y avait un aspect médical que j'aimais beaucoup. Lorsque j'ai commencé à étudier des acides aminés radioactifs et des membranes perméables, je ne trouvais pas ça aussi intéressant. Par la suite, j'ai principalement axé mes recherches sur les maladies métaboliques.

Andrew Hoffman : C'est un peu ce que je voulais dire quand j'ai parlé de personnes. Je ne parlais

pas nécessairement de l'ensemble du corps humain.

Rima Rozen : Je vois. Le corps humain dans son ensemble par rapport à un système organisé.

Andrew Hoffman : C'est ça. Donc, après les recherches qui vous ont demandé …

Rima Rozen : Six.

Andrew Hoffman : Six années de votre vie.

Rima Rozen : Deux ans sur le premier projet, puis quatre ans. C'est bien ça.

Andrew Hoffman : On parle donc…

Rima Rozen : D'un doctorat de six ans.

Andrew Hoffman : C'est beaucoup plus rapide que pour les sociologues, mais pas dans mon cas, j'espère. Vous avez donc terminé votre doctorat à McGill et avez commencé un postdoctorat, toujours à McGill.

Rima Rozen : À McGill et à Yale.

Andrew Hoffman : Commençons par parler de McGill. Vous avez travaillé avec Gordon Shore.

Rima Rozen : Oui.

Andrew Hoffman : Vos recherches portaient sur l'hépatome de Morris, c'est bien ça?

Rima Rozen : En fait, mes recherches portaient sur les enzymes métaboliques, encore une fois. Elles étaient liées aux troubles métaboliques dans le foie, mais du point de vue de la régulation génique.

Je crois que c'était en 1981. La génétique moléculaire commençait à prendre de plus en plus de place, mais toute ma formation avait été basée sur les acides aminés et les protéines, en quelque sorte. Je devais donc acquérir des connaissances en génétique moléculaire pour réussir comme généticienne.

J'ai donc choisi de travailler dans un laboratoire beaucoup plus axé sur la génétique moléculaire, au lieu de compter le nombre de fois où les souris urinaient dans un godet et de mesurer les acides. Quand je suis arrivée dans le laboratoire de Gordon, ils ont tous ri de moi parce que c'était la première fois que je faisais une analyse sur gel. Ils ne pensaient jamais voir quelqu'un qui n'avait jamais fait d'analyse sur gel.

Andrew Hoffman : Et qu'est-ce qu'une analyse sur gel, en termes simples?

Rima Rozen : C'est une technique qui permet de séparer les protéines dans un appareil composé d'une structure qui ressemble à du gel. Les protéines passent dans le gel, et elles sont séparées en fonction de leur poids moléculaire. C'est une technique très courante en chimie, mais pour quelqu'un qui arrivait en génétique moléculaire sans avoir fait de biochimie, c'était nouveau. C'était en

fait de la biochimie des protéines, ce que je n'avais jamais vraiment fait. J'ai ensuite étudié l'ARN dans le laboratoire de Gordon et j'ai commencé à mieux me débrouiller en génétique moléculaire.

Andrew Hoffman : C'était donc un postdoctorat de deux ans?

Rima Rozen : Oui, deux ans. J'étais déjà mariée à l'époque… À McGill, on nous disait, peut-être pas de façon officielle, qu'il était préférable de ne pas faire toute sa formation au même endroit parce qu'on risquait de revoir les mêmes techniques ou d'être toujours soumis aux mêmes influences, ce qui est ridicule. Même si j'avais fait une transition entre deux disciplines qui étaient si différentes que ça ne dérangeait pas du tout que je reste à McGill ou non.

Malgré cela, je me suis dit que ça pourrait être une bonne idée de faire une formation ailleurs, et à cette époque, on parlait beaucoup de génétique moléculaire et de travaux sur les maladies humaines. J'ai cherché un endroit pendant un an. Comme j'avais mon propre salaire, je pouvais aller où je voulais. J'ai donc regardé du côté de quelques laboratoires aux États-Unis qui réalisaient des travaux qui m'intéressaient sur la génétique moléculaire et les maladies humaines.

J'ai passé un an à Yale, mais mon mari est resté à Montréal. C'est pour ça que je n'y suis restée qu'un an et que je n'y suis pas allée directement. Nous avons dû nous préparer; ce n'était pas si simple. J'ai donc passé un an à Yale.

Andrew Hoffman : Et vous avez travaillé avec le Dr Leon Rosenberg?

Rima Rozen : Pas directement avec le Dr Rosenberg. Il occupait un poste similaire à celui de Charles et avait un laboratoire énorme. En fait, il était peut-être doyen de la Faculté de médecine à cette époque. Je ne me rappelle plus. Mais une chose est sûre, il n'était pas au laboratoire très souvent. Il avait des adjoints à la recherche. En fait, ces personnes avaient beaucoup plus d'expérience que des adjoints, même à McGill, parce que c'était difficile d'obtenir des postes à Yale et dans d'autres universités. Des gens passablement expérimentés restaient au niveau d'adjoint à la recherche pendant un bon moment.

Mon travail était donc supervisé par un ou deux adjoints à la recherche dans le laboratoire du Dr Rosenberg, et ce fut une expérience formidable. Ce sont ces recherches qui ont formé la base de mes travaux par la suite.

Je dirais que cette année a défini ma carrière. Et ce fut une belle occasion parce que les travaux du laboratoire de Gordon Shore étaient plus axés sur la chimie que sur la génétique humaine proprement dite. J'ai eu la chance d'apprendre quelques techniques, mais les gens qui travaillaient dans ce laboratoire n'avaient pas une optique de généticiens ou de cliniciens, mais plutôt de biochimistes.

Ici, les diagnostics occupaient une place de plus en plus importante, et c'est ce que j'ai fait à Yale. J'ai travaillé en génétique moléculaire, avec l'ADN et…

Andrew Hoffman : Toujours dans les maladies métaboliques?

Rima Rozen : Oui, mais il était surtout question de diagnostics génétiques à ce moment-là.

Andrew Hoffman : Je vois. J'ai vu qu'il avait écrit ou révisé un manuel sur les maladies métaboliques, et qu'il avait également une formation de biologiste moléculaire.

Rima Rozen : Qui? Leon Rosenberg?

Andrew Hoffman : Oui.

Rima Rozen : Non, pas du tout. Il est plus âgé que Charles [Scriver]; la biologie moléculaire n'existait donc pas pendant sa formation. Ce sont ses étudiants postdoctoraux et ses adjoints à la recherche qui faisaient de la génétique moléculaire. Il était bien au-delà de ça. Il faisait de la médecine génomique alors que les autres faisaient de la génétique moléculaire.

Andrew Hoffman : Peut-être que…

Rima Rozen : Oui, il a écrit tous ces articles grâce à ses adjoints à la recherche, mais il n'a pas eu de formation dans ce domaine. Sa formation portait sur le métabolisme et le transport des acides aminés et était très similaire à celle de Charles. D'ailleurs, ils ont coécrit des articles et des livres et sont de très bons amis. C'est une coïncidence que je sois allée à Yale. Ce n'est pas Charles qui me l'a recommandé; j'étais simplement intéressée par les travaux sur le métabolisme.

Andrew Hoffman : Cela pourrait expliquer en quelque sorte la façon dont les laboratoires fonctionnaient, et fonctionnent peut-être encore souvent aujourd'hui, avec une tête dirigeante.

Rima Rozen : Oui, absolument.

Andrew Hoffman : J'aimerais revenir sur quelque chose que vous avez mentionné. Vous avez dit avoir remarqué une transition au moment où vous avez commencé votre postdoctorat à McGill, par rapport à une approche plus traditionnelle de la génétique humaine, comme la génétique mendélienne, j'imagine?

Rima Rozen : C'est exact. Et aussi la classification des patients et essayer de comprendre…

Andrew Hoffman : La lignée et…

Rima Rozen : Comprendre le fondement de la maladie, sans nécessairement avoir les outils technologiques dont nous disposons aujourd'hui. Nous sommes passés des approches cliniques et descriptives, et aussi biochimiques, à des études axées sur les protéines et les cellules. Il y a ensuite eu les études du génome, de l'ADN. C'est vers la fin des années 1970 et le début des années 1980 que la génétique moléculaire a vraiment débuté.

Andrew Hoffman : Pourriez-vous nous parler de cette transition? Est-ce quelque chose que vous avez perçu lorsque vous étiez…

Rima Rozen : Absolument. Je me souviens d'avoir prélevé du sang au niveau des yeux des souris pour étudier la composition des acides aminés, entre autres, dans le laboratoire de Charles. J'analysais également l'urine des souris. Les fluides

étaient un outil facilement accessible; c'est ce que nous faisions.

Quand je suis arrivée dans le laboratoire de Gordon, j'ai travaillé sur la biochimie des protéines et j'ai commencé à faire des analyses sur gel et à m'intéresser à l'ARN. Quand j'ai déménagé à Yale, l'ADN a pris toute la place. Et c'est toujours le cas.

Andrew Hoffman : McGill était donc peut-être un peu en retard?

Rima Rozen : Oui, tout à fait.

Andrew Hoffman : Je ne veux pas vous faire dire des choses que vous n'avez pas dites.

Rima Rozen : On ne faisait pas encore de recherche en génie moléculaire à McGill, du moins pas à grande échelle. En fait, c'était en quelque sorte mon mandat quand j'ai été embauchée par McGill à mon retour de Yale, en 1984. Je devais apporter la génétique moléculaire.

Andrew Hoffman : Vous êtes donc arrivée en 1984.

Rima Rozen : Oui, à McGill.

Andrew Hoffman : Vous êtes revenue de Yale pour travailler à McGill et vous avez établi votre laboratoire de recherche à l'Hôpital de Montréal pour enfants.

Rima Rozen : En fait, j'ai travaillé dans le Pavillon des sciences biologiques Stewart pendant un an parce que lorsque je suis revenue, personne ici ne faisait de génétique moléculaire. Et je devais me réinstaller chaque fois que je changeais de laboratoire et de projet. Je n'ai rien rapporté de Yale. C'est une longue histoire…

Andrew Hoffman : Comme du matériel?

Rima Rozen : Je n'ai rapporté aucun matériel. Rien du tout. Évidemment, j'ai appris à utiliser la technologie, mais très souvent, un étudiant qui fait une formation de postdoctorat dans un laboratoire peut rapporter le projet sur lequel il a travaillé. Ce projet devient son travail en tant que chercheur indépendant. Cela fait même partie de notre mandat. Un étudiant postdoctoral prêt à travailler par lui-même devrait pouvoir repartir avec un petit projet. Ça ne s'est pas passé comme ça pour moi… Je ne veux pas parler de ça.

Je n'avais pas de projet quand je suis arrivée ici. J'ai dû partir de zéro avec une nouvelle idée et un tout nouveau projet, et faire des demandes de subvention pour des recherches sur lesquelles je n'avais jamais travaillé.

Andrew Hoffman : Ce qui était…

Rima Rozen : Ça n'a pas été facile.

Andrew Hoffman : Quand vous êtes arrivée, qu'avez-vous…

Rima Rozen : J'ai dû trouver ce que j'allais faire. J'ai commencé à travailler sur une enzyme

du métabolisme du folate avec Bob MacKenzie, qui n'est devenu membre du groupe que bien des années plus tard. Comme je m'intéressais aux gènes et aux maladies métaboliques, j'ai approché Bob et je lui ai parlé de ce projet. C'était tout nouveau. C'était un peu frustrant d'avoir à recommencer à zéro.

Je l'ai fait. J'ai eu ma première subvention en 1985. J'avais eu une autre subvention salariale à mon arrivée, mais je crois que c'est en 1985 que j'ai reçu ma première subvention des IRSC.

Andrew Hoffman : Votre subvention de démarrage a donc principalement servi à installer le laboratoire que vous…

Rima Rozen : Mon propre laboratoire, c'est bien ça. J'ai eu une subvention salariale du FRSQ[3]. Cette subvention vient avec 25 000 dollars pour le démarrage d'un laboratoire. Je ne me souviens pas de ce que j'ai fait entre-temps. J'ai ensuite trouvé un projet et fait une autre demande de subvention. J'ai reçu ma première subvention indépendante du CRM en 1985.

Andrew Hoffman : Avec l'argent de votre subvention de démarrage, qu'avez-vous acheté pour votre laboratoire? Vous deviez avoir besoin…

Rima Rozen : Du petit matériel.

Andrew Hoffman : Quel type de matériel? Du matériel traditionnel?

Rima Rozen : Non, c'était plutôt du matériel moléculaire. Mais pas beaucoup de choses. Et au départ, je ne voulais pas travailler ici parce qu'il n'y avait personne qui pouvait me guider dans mes travaux de génétique moléculaire. On a donc décidé que j'allais travailler au Pavillon des sciences biologiques Stewart pendant une année, où il y avait probablement plus de programmes en génétique moléculaire qui m'aideraient à démarrer, et que j'allais revenir ici ensuite.

Andrew Hoffman : Vous êtes donc revenue en 1985?

Rima Rozen : C'est bien ça, mais je suis devenue professeure dans ce département en 1984. Ce sont seulement mes installations qui ont été au Pavillon Stewart pendant un an. J'ai ensuite tout ramené ici en 1985.

Andrew Hoffman : En 1984, vous êtes donc arrivée comme chercheuse indépendante.

Rima Rozen : Sans projet.

Andrew Hoffman : Sans projet.

Rima Rozen : Je me suis dit que je finirais par avoir une idée.

Andrew Hoffman : Vous avez fait deux choses : vous avez créé votre propre laboratoire et vous avez mis sur pied le Service de diagnostic génétique moléculaire.

[3] Fonds de la recherche en santé du Québec, devenu le Fonds de recherche du Québec – Santé (FRQS)

Rima Rozen : Oui, et on y faisait principalement des activités de recherche et développement à l'époque. En fait, c'était essentiellement une activité de recherche; ce n'était pas une activité constante. Les travaux étaient liés à ce que j'avais fait à Yale; j'avais donc la crédibilité nécessaire pour mener à bien ce projet et ça m'intéressait. J'ai donc créé ce service. Nous avons commencé en 1985 et j'y ai travaillé jusqu'en 2003.

Andrew Hoffman : Et vous avez aussi dû faire entrer de nouvelles technologies dans ce service.

Rima Rozen : C'est exact. J'ai dû trouver de l'argent pour faire fonctionner le Service. L'argent était entièrement utilisé pour les activités de recherche et développement. J'ai eu une subvention du FRSQ, puis du financement ici et là. J'ai ensuite eu un peu d'argent de l'hôpital; le Service de diagnostic ne recevait pas de financement sur une base régulière. Malgré tout, nous avions de la crédibilité, nous offrions un service et nous finissions toujours par avoir de l'argent du gouvernement. Je ne me rappelle pas tout, mais notre laboratoire a été l'un des premiers à recevoir du financement pour le Service.

Andrew Hoffman : Du FRSQ?

Rima Rozen : Le FRSQ est un organisme de recherche. Il nous a donc accordé du financement pour la recherche et le développement. Nous avons utilisé ces fonds pour réaliser quelques travaux, et une fois que notre crédibilité a été établie, et qu'il est devenu évident que nous ne faisions plus de la recherche et que nous fournissions plutôt un service…

Andrew Hoffman : Clinique ou…

Rima Rozen : Exactement. Nous sommes passés par l'hôpital et nous nous sommes plutôt adressés à un ministère pour obtenir des fonds pour un service.

Andrew Hoffman : S'agit-il des 8 400 $ que vous avez reçus de la Faculté des études supérieures?

Rima Rozen : Non. Ça, c'était pour du matériel, je crois.

Andrew Hoffman : Je regardais les chiffres et j'ai vu que vous aviez eu 12 500 $ de…

Rima Rozen : En fait, c'était 50 ou 60, je ne m'en souviens plus. C'était suffisant pour qu'un technicien s'en occupe. J'ai pratiquement arrêté de travailler dans le laboratoire; je devais donc avoir de l'argent pour embaucher un technicien qui allait fournir le service. J'ai donc eu un technicien à partir de 1985 ou 1986.

Andrew Hoffman : J'imagine que le financement venait de sources différentes pour ces deux différents…

Rima Rozen : Exactement. Mes propres recherches étaient financées par le CRM, mais le Service de diagnostic recevait des subventions du FRSQ pour la recherche et le développement, ou encore de petites sommes ici et là, ou encore par l'intermédiaire de l'hôpital.

Andrew Hoffman : Et quel était le lien entre les outils que vous aviez à ces différents endroits, dans votre laboratoire et au Service de diagnostic, et le sujet de vos recherches?

Rima Rozen : Les recherches ne se recoupaient pas beaucoup. Tout relevait de la génétique moléculaire, mais ce sujet est vaste. Le Service de diagnostic se base entièrement sur l'ADN. On isole l'ADN d'un échantillon de sang ou de cellules, par exemple, puis on vérifie si un patient est porteur d'une mutation, ou s'il y a délétion ou polymorphisme.

Les recherches, du moins les miennes, ne se sont jamais limitées à l'ADN, particulièrement dans les sciences fondamentales. On étudie l'ARN, les protéines, les molécules. On utilise des souris ou des cultures cellulaires pour étudier des sujets précis. Le travail de diagnostic n'est axé que sur l'ADN parce que c'est la seule chose à laquelle nous avons accès avec un patient. L'ARN est propre à un tissu. Je ne sais pas quelles sont vos connaissances en biologie moléculaire, mais…

Andrew Hoffman : J'ai des connaissances en cytogénétique, mais c'est tout.

Rima Rozen : D'accord. L'ADN est présent dans toutes les cellules et il est identique dans toutes les cellules et tous les tissus. L'ADN sert en quelque sorte de modèle pour la synthèse de l'ARN, mais pour un tissu en particulier. Autrement dit, l'ARN n'est pas identique dans tous les tissus. Par exemple, pour les gènes exprimés dans le foie, vous trouverez l'ARN dans le foie, vous ne le trouverez pas dans le rein. Ou vous avez un ARN cérébral qui n'est pas exprimé, etc.

On utilise l'ADN parce qu'il est facile de prélever du sang et que l'ADN est le même dans tout le corps, alors que si on isole l'ARN du sang, il ne reflétera pas nécessairement la composition de l'ARN présent dans le tissu porteur de la maladie.

Andrew Hoffman : Donc, si vous vous intéressez au cancer du foie…

Rima Rozen : Exactement. Si vous vous intéressez à la fibrose kystique, une maladie pulmonaire sur laquelle nous avons travaillé pendant des années, vous n'arriverez à rien en étudiant l'ARN du sang. Donc, pour les diagnostics génétiques, nous utilisons l'ADN.

Andrew Hoffman : Y avait-il un lien entre vos travaux dans le laboratoire de diagnostic et vos travaux dans…

Rima Rozen : Au début, peut-être…

Andrew Hoffman : Cela vous aidait peut-être à trouver des cas intéressants, par exemple?

Rima Rozen : Nous avons fait des études populationnelles. Mon travail a toujours porté sur la science fondamentale. Mes subventions servaient donc très souvent à repérer des mutations ou à étudier des cellules ou des souris, par exemple.

Mais nous avons aussi souvent reçu du financement supplémentaire pour des recherches sur la génétique des populations, par exemple, parce que lorsque nous avons commencé à faire des diagnostics, nous avons déterminé les types de mutation que nous avions le plus de chance de trouver dans notre population, c'est-à-dire la population du Québec, qui est évidemment unique

du point de vue génétique. Nous avons établi tout le spectre des mutations que nous voulions étudier pour les Canadiens français ou pour une population mixte, par exemple, qui n'était peut-être pas le même spectre de mutations qu'on aurait étudié ailleurs dans le monde.

Nous maîtrisions cet aspect. Nous avons fait beaucoup de recherches sur la fibrose kystique. Nous avons aussi beaucoup étudié la phénylcétonurie. Charles s'intéressait à la phénylcétonurie, mais nous nous occupions de la génétique moléculaire. Autrement dit, nous repérions les mutations présentes dans la population canadienne-française dans le but de trouver le traitement le mieux adapté au génotype.

Andrew Hoffman : Vous avez dit que vous vous occupiez de la génétique moléculaire pour les études sur la phénylcétonurie et que Charles faisait plutôt…

Rima Rozen : C'était toujours des traitements axés sur le patient. Il s'intéressait aussi beaucoup à l'histoire des populations. Nous avons évidemment travaillé avec lui sur ce sujet, parce que pour retracer l'histoire d'une population, il faut étudier les mutations. Mais il n'était pas généticien moléculaire; il ne pouvait pas superviser les travaux en génétique moléculaire. Nous avions donc un étudiant qui travaillait dans mon laboratoire et qui repérait les mutations, puis qui discutait de l'histoire des populations ou de démographie avec Charles.

Andrew Hoffman : Récapitulons un peu. En 1984, vous avez reçu une subvention de recherche pour travailler sur un projet d'analyse génétique des protéines multifonctionnelles et du métabolisme du folate.

Rima Rozen : C'est comme ça que j'ai commencé, effectivement.

Andrew Hoffman : Et ce thème vous a suivi pendant plusieurs années par la suite.

Rima Rozen : Pendant un certain temps. Je suis ensuite passée à la génétique populationnelle de la phénylcétonurie et de la fibrose kystique, et à partir de…

Andrew Hoffman : Ce sont des applications plus concrètes, ne trouvez-vous pas?

Rima Rozen : Absolument. Les études sur la fibrose kystique et la phénylcétonurie ont des applications plus concrètes. Puis, vers 1990, en raison du travail que nous avions fait sur un gène et sur le métabolisme du folate, nous avons entrepris de cloner ce gène, et nous travaillons sur ce sujet depuis. Depuis le début des années 1990, nous nous limitons à ce gène très intéressant parce qu'il est en cause dans tellement de troubles. Nous examinons aussi les interactions entre les aliments et les gènes, et d'autres mutations dans la voie, ainsi que des troubles courants. Les sujets sont nombreux.

Andrew Hoffman : Je me trompe peut-être, mais il semble y avoir une certaine dichotomie dans votre travail. Certains de vos travaux sont propres au laboratoire, alors que d'autres ont une application clinique évidente.

Rima Rozen : En effet.

Andrew Hoffman : Nous en avons déjà parlé, mais j'essaie de…

Rima Rozen : C'est vrai que j'ai toujours aimé ces deux aspects. Malheureusement, à cause de mes responsabilités administratives et d'autres tâches, je ne pouvais plus tout faire. C'est ainsi que j'ai renoncé au Service de diagnostic en 2003. Est-ce que je regrette d'avoir eu à faire ça? Bien entendu.

Andrew Hoffman : Mais le Service existe toujours. Il est simplement dirigé par quelqu'un d'autre…

Rima Rozen : C'est vrai, mais je n'ai plus rien à voir dans son fonctionnement. Je suis contente d'avoir mis ce service sur pied. Ça me manque parfois. Mais il était temps de le confier à une personne qui pouvait y accorder plus de temps. Le Service avait considérablement grossi et je ne pouvais plus m'en occuper dans mes temps libres, si je puis dire. McGill ne paie pas les titulaires de doctorat pour qu'ils dirigent des services. Personne ne paie les titulaires de doctorat pour faire ça. On les paie pour qu'ils enseignent et qu'ils fassent des recherches qui attireront les subventions. Le Service de diagnostic n'allait pas nous permettre d'obtenir des subventions. Je suis devenue directrice de recherche en 1999, mais à un certain moment je ne pouvais plus tout faire et j'ai dû renoncer à quelque chose. Et j'ai renoncé au Service.

Andrew Hoffman : C'est en 1987 que vous êtes devenue chercheuse principale au sein de ce qu'on appelait le « groupe du CRM » à l'époque, c'est bien ça?

Rima Rozen : C'est ça. On l'appelait encore le « groupe du CRM » à l'époque.

Andrew Hoffman : C'était donc le groupe de génétique médicale du Conseil de recherches médicales. Pourriez-vous me dire comment vous avez fini par travailler avec ce groupe qui, de toute évidence, vous intéressait beaucoup?

Par exemple, vous a-t-on approchée ou avez-vous fait des démarches vous-même? Est-ce que le fait que vous aviez votre propre laboratoire à l'Hôpital de Montréal pour enfants y est pour quelque chose?

Rima Rozen : Bien entendu, et c'est en grande partie grâce à Charles que je suis revenue à McGill. Il s'était passé un certain temps après le moment où j'ai quitté son laboratoire avec mon diplôme, mais je crois qu'il a toujours su que je pourrais revenir, et il a tout fait pour ça. C'est l'une des raisons pour lesquelles je suis revenue dans cet hôpital.

Je suis donc revenue, avec le bagage de connaissances que j'avais acquises au sein du groupe pendant mon baccalauréat, et j'ai eu mon propre domaine de recherche, sans oublier le travail de diagnostic. Je pense que personne ne s'en souvient, mais on m'a recrutée pour travailler en génétique moléculaire parce que personne ne le faisait. Je développais donc de nouvelles compétences que les autres membres du groupe ne possédaient pas, il me semble. Je ne me rappelle plus très bien. Au moins, j'apportais une expertise nouvelle qui allait devenir importante et que le groupe devait posséder afin d'avoir de la crédibilité en tant que groupe de recherche moderne et pertinent.

Ça m'intéressait, évidemment. Ces personnes étaient mes mentors. C'était très stimulant pour moi de les avoir comme collègues. Charles devenait ainsi mon collaborateur, au lieu d'être mon mentor, tout comme Peter Hechtman, qui avait

été mon professeur.

Tout ça était très stimulant de mon point de vue, et j'avais probablement un rôle à jouer dans ce nouveau domaine de génétique moléculaire.

Andrew Hoffman : Et peut-être qu'ils se fiaient un peu à vous pour…

Rima Rozen : Probablement en ce qui concerne les travaux de génétique moléculaire que je faisais avec Charles. C'était quelque chose qu'il devait faire pour poursuivre ses recherches sur la phénylcétonurie et l'histoire des populations.

Andrew Hoffman : Est-ce que d'autres personnes ont rapidement suivi vos traces en génétique moléculaire?

Rima Rozen : Ici? Oui. Je ne peux pas vous donner de nom, et je ne me rappelle pas quand Roy s'est joint au groupe. Savez-vous en quelle année Roy est devenu directeur de l'Institut? 1994, 1995?

Andrew Hoffman : Je crois bien que c'est en 1995.

Rima Rozen : C'était son domaine d'expertise. Quand il est arrivé, il a vraiment fait progresser l'Institut grâce aux ressources qu'il avait et au matériel qu'il pourrait acheter, etc. Nos travaux ont beaucoup avancé à ce moment-là.

Andrew Hoffman : S'il est arrivé en 1995, il y a tout de même sept années pendant lesquelles vous…

Rima Rozen : C'est vrai. Qu'est-ce que j'ai fait? Nous avions un service de génétique, avec lequel je travaillais. Nous réalisions différents travaux ici et là.

Est-ce que je me souviens de qui nous avons recruté en génétique moléculaire à cette époque? Non, je ne m'en souviens pas. Mais comme je venais d'arriver, je ne m'occupais pas des embauches. C'est le directeur de l'Institut qui avait cette responsabilité.

Andrew Hoffman : Est-ce qu'une foule de gens ont été embauchés?

Rima Rozen : Non, les nouveaux employés ne sont pas arrivés en masse. Les Ph. D. sont toujours une denrée rare dans un service de pédiatrie. En fait, quand je suis revenue grâce aux efforts de Charles, le directeur du Service de pédiatrie n'était pas trop chaud à l'idée d'avoir un Ph. D. dans son équipe. Traditionnellement, la pédiatrie est de toute évidence un service médical, et à l'époque, les Ph. D. n'étaient pas aussi bien accueillis que les médecins l'étaient. Et le recrutement était restreint, évidemment.

Je ne suis pas certaine que le directeur du Service de pédiatrie aurait ouvert toutes grandes les portes à 20 biologistes moléculaires. Je ne me rappelle pas quand le directeur de l'époque est parti, mais je sais que lorsque Dick Hamilton a pris les rênes du Service de pédiatrie, le Service a pris une tournure plus progressiste. Comme il n'y avait pas de département de génétique humaine, seulement un centre de génétique humaine, nous ne pouvions pas recruter. Le recrutement officiel se faisait donc en pédiatrie.

Andrew Hoffman : Ça devait jouer un peu des coudes pour…

Rima Rozen : Oui, les gens jouaient un peu des coudes pour avoir un Ph. D. en pédiatrie, entre autres. Heureusement, j'ai réussi à obtenir ma propre bourse salariale, alors il n'avait pas à... Cela faisait probablement partie de l'entente, mais je n'ai pas de souvenir à ce sujet. Quelque chose du genre : « Si elle obtient sa propre bourse salariale, la prendrez-vous dans votre service? ». Et comme j'ai eu ma bourse, la question s'est trouvée réglée.

Mais est-ce qu'ils auraient offert de me payer? Peut-être. Tout dépendant du pouvoir de persuasion de Charles. Chose certaine, le directeur de l'époque n'était pas très ouvert à l'idée de faire une place à des Ph. D. et à des généticiens moléculaires.

Andrew Hoffman : Lorsque vous êtes arrivée, vous êtes-vous sentie la bienvenue? De toute évidence…

Rima Rozen : Non. Je dois admettre qu'en pédiatrie, à l'époque et surtout ici, les Ph. D. étaient un peu à l'écart. Nous n'avions pas beaucoup de contacts avec le personnel clinique. Je voyais d'autres personnes grâce à mon service, ce qui était pratique, mais comme nous nous intéressions à certaines maladies seulement, je ne connaissais que les médecins qui s'occupaient de ces maladies-là. En fait, étant donné nos travaux sur la fibrose kystique, j'ai appris à bien connaître les médecins qui traitaient cette maladie dans la province. Nous offrions nos services à tout le monde. C'est un peu comme ça que la génétique fonctionne, et lorsque nous avons commencé à nous intéresser à la fibrose kystique, nous offrions nos services à toute la province.

Andrew Hoffman : Vous agissiez en quelque sorte comme un laboratoire central.

Rima Rozen : Absolument! Nous étions un laboratoire central pour les maladies sur lesquelles nous faisions des essais.

Andrew Hoffman : La fibrose kystique?

Rima Rozen : Oui. Nous avons commencé avec les thalassémies, puis la maladie de Tay-Sachs et un peu de phénylcétonurie, puis est venue la MTHFR, que nous étudions actuellement dans le laboratoire de recherche; c'est devenu un test, mais juste un test. Mais nous avons principalement travaillé sur la fibrose kystique pendant une bonne période. Cette maladie frappe beaucoup de personnes, 1 000 et 2 000…

Andrew Hoffman : Et cette maladie a de nombreuses variantes, n'est-ce pas?

Rima Rozen : Oui, beaucoup de variantes. Et la prévalence est particulièrement élevée au Saguenay : environ 1 personne sur 900. Nous recevions donc beaucoup d'échantillons et notre service a continué à grossir. Au moins, j'aimais travailler avec des cliniciens.

Andrew Hoffman : Pendant combien de temps le laboratoire de diagnostic a-t-il agi comme laboratoire central pour la province?

Rima Rozen : C'est toujours le cas pour certaines maladies. Il est toujours le laboratoire de diagnostic central pour la fibrose kystique, pour la maladie de Tay-Sachs et pour la phénylcétonurie. Aujourd'hui, il y a des gens qui fournissent quelques services, parfois un médecin veut explorer un sujet. Mais pour ce qui est d'un service centralisé, toute la province faisait appel à nous, et elle le fait encore.

Andrew Hoffman : Je ne savais pas ça, mais je ne suis pas un expert sur l'histoire du laboratoire.

Rima Rozen : Pour le diagnostic génétique, c'est logique d'avoir un laboratoire centralisé. Ça ne sert à rien d'avoir trois laboratoires qui travaillent sur la fibrose kystique en utilisant des techniques et des contrôles de qualité différents.

Andrew Hoffman : Avez-vous établi vos propres normes dans le laboratoire pour…

Rima Rozen : Oui, absolument. Nous sommes partis de zéro. À nos débuts, le gène n'avait pas encore été cloné et nous faisions les diagnostics par analyse de liaison. Je ne vais pas aborder ce sujet aujourd'hui, mais il faut juste savoir que le gène n'avait pas encore été cloné et que nous établissions des marqueurs, en quelque sorte.

Quand le gène a été cloné vers 1989, nous pouvions rechercher des mutations directement. Nous avons donc modifié nos méthodes et avons commencé à faire des épreuves directes, puis nous avons mis l'accent sur les transporteurs et le diagnostic prénatal. Nous dirigions un service régulier, même si je n'avais pas reçu de formation en gestion de laboratoire. Connaissez-vous le Collège canadien de généticiens médicaux?

Andrew Hoffman : En êtes-vous membre?

Rima Rozen : Oui.

Andrew Hoffman : De quoi s'agit-il exactement?

Rima Rozen : Cette organisation a pour mission d'offrir des formations et de faire progresser le volet médical de la génétique. Il a fallu du temps pour que ça devienne une spécialité officielle. Les universités ne proposaient pas cette spécialité. Des personnes, dont Clarke Fraser, ont donc fondé un collège canadien. Je sais que Clarke Fraser a joué un rôle important, mais je ne sais pas si c'est aussi le cas de Charles.

Les fondateurs ont créé ce collège pour que des personnes aux expériences diverses en génétique puissent se rassembler pour mettre au point des méthodes d'utilisation des outils génétique, faire connaître la discipline, etc.

Andrew Hoffman : À quand remonte la fondation de ce collège?

Rima Rozen : Dans les années 1970, je crois. Il faudrait vérifier sur le site Web.

Andrew Hoffman : Le Collège existait donc lorsque vous êtes arrivée dans la profession.

Rima Rozen : Oui, mais il ne s'intéressait pas encore beaucoup à la génétique moléculaire,

qui était une discipline assez nouvelle. Et c'était le seul domaine que je connaissais bien. Il avait tout de même commencé à mettre en place des sous-spécialités, et il y en avait une en génétique moléculaire. Le Collège compte actuellement quatre sous-spécialités – clinique, biochimique, cytogénétique et moléculaire – qui résument en quelque sorte l'histoire de la génétique : il y a d'abord eu la génétique clinique, et la génétique moléculaire a été la dernière sous-spécialité créée.

À l'époque, il y avait déjà des personnes qui suivaient une formation et recevaient une certification en génétique moléculaire. La sous-spécialité existait, et c'est à ce moment-là que j'ai passé l'examen pour recevoir une certification en génétique moléculaire et ajouter de la crédibilité à mon service.

Andrew Hoffman : C'est l'année où vous êtes arrivée ou…

Rima Rozen : Non, c'est plus tard. J'ai passé l'examen en 1990. Avant, je pense que le Collège n'avait pas développé suffisamment sa sous-spécialité de génétique moléculaire. Aujourd'hui, il existe une formation officielle. Il faut passer un an et demi ou deux ans dans un laboratoire certifié pour acquérir les connaissances techniques, mais à l'époque, comme le programme en était à ses débuts et que j'avais acquis une bonne expérience à Yale, puis avec le Service ici, on m'a…

Andrew Hoffman : Vous avez été admise automatiquement…

Rima Rozen : Non. J'ai dû passer l'examen. Charles a été admis automatiquement. Il n'a pas eu à passer l'examen parce que le Collège venait d'être créé. Mais je n'ai pas eu à suivre la formation parce qu'on a considéré que mon expérience de travail et mes compétences de directrice étaient suffisantes, mais j'ai dû passer l'examen comme tout le monde. J'ai donc obtenu ma certification en 1990.

J'ai été la première directrice accréditée en génétique moléculaire au Québec. J'étais donc la seule à pouvoir offrir le service.

Andrew Hoffman : Donc, vous avez non seulement rapporté la génétique moléculaire à McGill et…

Rima Rozen : Je ne dirais pas à McGill; je dirais plutôt à l'hôpital. Beaucoup de gens faisaient de la génétique moléculaire ou de la biochimie, mais pas à l'hôpital. Et certainement pas à l'Hôpital de Montréal pour enfants.

Andrew Hoffman : D'accord. Vous avez introduit la génétique moléculaire à l'Hôpital de Montréal pour enfants, mais vous l'avez aussi en quelque sorte introduite au Collège puisque vous avez été la première…

Rima Rozen : Oui, la sous-spécialité. Et j'ai été la seule généticienne moléculaire accréditée au Québec pendant de nombreuses années. Je pense que vers la fin des années 1990 ou le début des années 2000, une ou deux autres personnes ont reçu leur certification dans cette discipline.

Andrew Hoffman : Est-ce que le fait que vous étiez membre du Collège était avantageux pour le Service de diagnostic?

Rima Rozen : Oui, absolument, parce que cela apportait de la crédibilité à notre Service.

Beaucoup de gens offraient des services de recherche. Je ne veux pas insinuer qu'ils n'étaient pas compétents, beaucoup d'entre eux l'étaient, et je ne dis pas que nous étions meilleurs, mais nous avions passé l'examen qui établissait la norme nationale.

Andrew Hoffman : Et estimez-vous que le travail que vous avez fait a aidé à faire progresser la génétique moléculaire dans la province et à créer d'autres types de pratiques?

Rima Rozen : Absolument. L'utilisation de ces services est devenue courante. Personne ne pensait aux tests de génétique moléculaire pour leur maladie de prédilection. Notre laboratoire a été le premier à offrir ces tests en tant que service accrédité, mais il était probablement connu uniquement de ceux qui s'intéressaient à la fibrose kystique, à la thalassémie ou à la maladie de Tay-Sachs. N'empêche que nous étions reconnus en tant que laboratoire provincial, ce qui a permis à l'hôpital d'obtenir du financement pour faire de la génétique moléculaire. Nous avons été parmi les premiers, peut-être même les premiers, à obtenir un budget dans un cadre hospitalier parce que nous offrions le service depuis longtemps.

Andrew Hoffman : Et c'était dans la sphère clinique.

Rima Rozen : En effet.

Andrew Hoffman : Il ne me reste que quelques questions.

Rima Rozen : Vous vous intéressez vraiment beaucoup à l'histoire. Nous n'avons pas parlé du tout de ce qui s'est fait au cours des 20 dernières années.

Andrew Hoffman : Je sais. Nous voulons raconter l'histoire du groupe et nous assurer que…

Rima Rozen : D'accord, je comprends. Vous mettez mon cerveau à rude épreuve, mais ça va.

Andrew Hoffman : Nous savons déjà ce que vous avez fait au cours des dernières années. Vous avez donné une entrevue à la revue britannique *Pharmacogenomics* en 2008, je crois.

Rima Rozen : D'accord. Mais faites-vous référence à la génétique moléculaire ou à mes recherches ou…

Andrew Hoffman : En fait, la prochaine question porte sur votre arrivée dans le groupe. D'après ce que je peux constater, à part Susie Tenenhouse, vous êtes la seule femme à avoir fait partie du groupe.

Rima Rozen : C'est exact. Susie et moi étions les seules femmes membres du groupe.

Andrew Hoffman : Êtes-vous devenue membre du groupe avant elle, techniquement parlant?

Rima Rozen : Bonne question. J'avais tout ça…

Andrew Hoffman : J'ai probablement les dates et…

Rima Rozen : Moi aussi j'ai écrit les dates quelque part, j'en suis sûre. Mais je ne m'en

souviens pas.

Andrew Hoffman : Je pourrais simplement vous demander…

Rima Rozen : En fait, elle s'est sûrement jointe au groupe avant moi. Ah oui, elle est devenue membre du groupe avant moi. Je me rappelle les photos maintenant. Oui, c'est bien ça.

Andrew Hoffman : Le fait que vous faisiez partie d'une minorité au sein du groupe, et probablement de l'hôpital, a-t-il déjà posé problème pour vous?

Rima Rozen : Je dois avouer que je n'ai jamais vraiment remarqué de préjugés évidents. Mais je ne sais pas si on parlait derrière mon dos.

Andrew Hoffman : De toute évidence, cela ne semble pas vous avoir empêchée de…

Rima Rozen : Cela ne m'a jamais influencée de quelque façon que ce soit. Et je dois dire que je n'y pense pas. Je n'ai jamais pensé que je devais être traitée différemment. J'ai fait mon travail sans me préoccuper de ce genre de choses.

Andrew Hoffman : J'imagine que vous avez simplement dû prendre des décisions et, comme vous l'avez dit, peut-être renoncer à certaines choses pour avoir une famille, entre autres.

Rima Rozen : Je ne peux pas dire que je n'ai pas eu à renoncer à certaines choses…

Andrew Hoffman : Ou à prendre certaines décisions.

Rima Rozen : C'est exact.

Andrew Hoffman : Désolé.

Rima Rozen : J'ai dû faire des compromis. Il y a évidemment des différences entre les hommes et les femmes en recherche et en médecine. Je me suis souvent dit : « J'aimerais tellement avoir une épouse à la maison qui me préparerait mon souper et qui s'occuperait des enfants et du reste ». Mais je n'ai pas ce luxe. J'ai donc dû jouer les rôles de femme à la maison et de chercheuse en même temps.

Les femmes ont évidemment du potentiel intellectuellement, mais elles n'ont pas toutes le même potentiel. Beaucoup d'entre nous ont une vie de famille remplie et une carrière professionnelle fructueuse. Pour moi, il ne fait aucun doute que les femmes doivent travailler plus fort.

Les femmes qui réussissent tout ça sont faites d'une autre étoffe. La situation est très différente aujourd'hui, mais à cette époque, c'était particulièrement vrai. Les femmes doivent posséder certaines compétences que les hommes n'ont pas nécessairement besoin d'avoir.

Andrew Hoffman : Avez-vous des exemples?

Rima Rozen : La gestion du temps, la capacité à faire des compromis, la volonté de s'adapter.

Je trouve que la gestion du temps est le nerf de la guerre.

Andrew Hoffman : Je reviens un peu en arrière, mais comme nous parlons du groupe… Historiquement, mais aussi plus récemment et de façon générale, on remarque deux approches et différentes personnes, de différents niveaux dans le département. Par exemple, vous avez apporté vos compétences en génétique moléculaire en vous joignant au groupe. Mais il y avait déjà des gens en place, plus expérimentés, avec qui vous avez travaillé au début de votre carrière, comme les D[rs] Fraser et Scriver.

Rima Rozen : En fait, je n'ai jamais vraiment travaillé avec le D[r] Fraser.

Andrew Hoffman : Ah bon?

Rima Rozen : Jamais directement.

Andrew Hoffman : Mais ici, vous avez travaillé avec lui, n'est-ce pas? Peut-être pas pendant vos études, mais au sein du groupe?

Rima Rozen : J'essaie de me rappeler. C'est possible qu'il ait été codirecteur pour l'une des subventions du groupe peu de temps après mon arrivée dans le groupe. Mais je n'ai jamais travaillé avec lui à proprement parler.

Andrew Hoffman : Je vois.

Rima Rozen : Il était là, mais je ne suis pas certaine qu'il était directeur au moment où j'étais dans le groupe.

Andrew Hoffman : Ma prochaine question ne s'applique peut-être pas à lui, mais est-ce que les membres plus anciens qui n'avaient pas nécessairement travaillé en génétique moléculaire avant votre arrivée ont continué à utiliser des méthodes disons « plus traditionnelles », alors que les recrues, comme vous et les personnes qui vous ont suivie, travaillaient selon un nouveau modèle de pensée? Pourriez-vous nous parler des sous-groupes au sein du groupe du CRM?

Rima Rozen : Au fil de sa longue histoire, le groupe a sûrement touché à tous les aspects de la génétique, mais la génétique moléculaire a pris de plus en plus de place. Pendant les dix dernières années, par exemple, tous les chercheurs faisaient de la génétique moléculaire.

En fait, comme Charles n'était plus membre vers la fin, je crois que littéralement tout le monde faisait de la génétique moléculaire. De nos jours, la science couvre tous les aspects, pas seulement le volet moléculaire.

Les personnes qui étaient dans le groupe vers la fin touchaient à tous les aspects. Nous avons travaillé avec les protéines, l'ADN, des souris, des humains. Nous étions censés tout faire. Mais dans les premiers temps, les membres du groupe travaillaient surtout en fonction de leur spécialisation. Par exemple, Charles a toujours travaillé en génétique métabolique et en génétique biochimique. Il n'a jamais fait de cytogénétique. Moi non plus, d'ailleurs.

Mais la discipline a progressé, et il est possible que Charles ait invité des

personnes qui pouvaient faire le travail à se joindre au groupe, puisque lui-même n'était pas un expert en la matière.

Ça fonctionne de la même façon aujourd'hui. Dans mon laboratoire, certaines personnes font des choses que je n'ai jamais faites de ma vie, même en génétique moléculaire. Nous évoluons tous. Nous ne mettons pas nécessairement les techniques en pratique, mais nous étudions la théorie et apprenons de nos étudiants. C'est pour ça que c'est agréable de travailler en groupe et d'avoir des stagiaires. Les autres ne nous enseignent pas nécessairement comment faire le travail, mais ils nous apprennent à comprendre et à interpréter leurs travaux. C'est très utile d'avoir un programme de groupe ou un grand groupe, si on peut se permettre d'accueillir huit ou dix personnes dans un laboratoire. On peut apprendre des plus jeunes.

Je ne suis pas certaine d'avoir répondu à votre question. Disons que je pense que tout le monde évolue à sa façon pour apprendre ce dont il a besoin pour faire son travail.

Andrew Hoffman : Mais compte tenu de la structure de la formation scientifique, surtout au niveau du doctorat, votre réponse semble indiquer que les choses se dérouleront inévitablement de cette façon… comme ça l'est depuis longtemps et comme ça le restera probablement… tant qu'il y aura de nouveaux collègues qui travaillent avec les technologies les plus récentes…

Rima Rozen : Exactement, exactement, exactement. Nous devons évoluer avec eux; ils nous aident à devenir de meilleurs scientifiques.

Andrew Hoffman : Lorsque les membres travaillaient sur différents projets, est-ce que cela avait un effet sur la publication des travaux du groupe? Par exemple, est-ce que certaines recherches étaient publiées principalement dans des revues consacrées à la génétique moléculaire et d'autres dans des revues de recherche fondamentale uniquement, ou de pratique clinique?

Rima Rozen : Je crois effectivement que la nature des revues reflétait l'expertise de la personne qui y publiait ses articles. Toutefois, la structure du groupe était intéressante pour nous parce que nous avions tous nos propres projets, nos propres maladies et notre propre technologie. Nous n'étions pas obligés de collaborer ni de travailler tous sur la même chose. C'est ce qui a fait le succès de notre groupe.

Dans ce cas, pourquoi formions-nous un groupe, me direz-vous? Parce que nous choisissions tous un problème clinique et tentions de le disséquer le mieux possible en utilisant différentes méthodes pour parvenir à un but commun. Nous prenions une maladie et cherchions à la comprendre. Ce qui était bien avec le programme du groupe, du moins à l'époque, c'est que nous n'étions pas obligés de travailler tous sur le même thème, alors qu'aujourd'hui, lorsque nous obtenons des subventions d'équipe, nous optons pour un thème et nous l'exploitons à fond. C'est bien, mais c'est une approche différente.

Par exemple, de nos jours, si vous obtenez une subvention d'équipe pour travailler sur le diabète, dix personnes travailleront sur le diabète et feront des recherches sur différents aspects de la même maladie. Il n'y a rien de mal à

procéder comme ça, mais ce n'était pas la façon de faire du groupe. Nous pouvions travailler sur sept maladies différentes, même si parfois nos recherches se chevauchaient un peu. C'était intéressant d'apprendre les uns des autres au sujet des différentes maladies.

Je n'aurais jamais pu en apprendre autant sur les os autrement. J'ai appris énormément sur les troubles mitochondriaux grâce à Eric Shoubridge. Nous avions des projets complètement différents; nous nous intéressions à des maladies très différentes, mais les approches étaient parfois très similaires et nous apprenions au contact des autres.

Andrew Hoffman : Lorsque vous dites qu'il y avait un problème clinique commun au groupe, c'était…

Rima Rozen : C'est exactement ce que je dis : tout le monde travaillait sur son propre problème clinique, sa propre maladie.

Andrew Hoffman : Je comprends. Il n'y avait donc pas de problème clinique commun à tous…

Rima Rozen : Exactement. Tout à l'heure, je faisais une comparaison avec la façon dont les subventions d'équipe sont structurées de nos jours. Si le gouvernement veut que de l'argent soit injecté dans la recherche sur le diabète, par exemple, tout le monde travaillera sur le diabète. Dans un autre cas, tout le monde pourrait travailler sur le cancer. Nous faisions des recherches sur des maladies différentes, mais nous nous intéressions aux mêmes questions et réponses. Comment cette personne a-t-elle contracté la maladie? Quel gène est en cause? De quel élément nutritif parle-t-on? Quelle voie métabolique est en cause? La maladie est-elle traitable? Que peut-on faire pour qu'elle soit traitable? Que faut-il étudier au niveau de la protéine, de la cellule, du patient lui-même? Peut-on faire des tests sur des souris? Nous avions tous les mêmes questions, mais sur des maladies différentes. C'est ce qui était intéressant.

Andrew Hoffman : Mais vous aviez tous des méthodes différentes, n'est-ce pas?

Rima Rozen : Oui, parfois, mais nous avons tous progressé pour trouver les meilleures méthodes possible. Et si vous étiez un jeune scientifique en formation, vous appreniez à manier les outils de la génétique moléculaire. Ça ne signifiait pas que vous deviez abandonner vos travaux sur les protéines ou sur les patients, mais que vous alliez utiliser des méthodes de pointe, en fonction de la technologie disponible.

Évidemment, tout dépendait du moment où vous arriviez dans le groupe. Les personnes qui étaient là au début, comme Charles, n'allaient pas devenir des experts en génétique moléculaire, mais elles pouvaient apprendre certaines techniques. Elles ont utilisé et conservé leurs compétences en chimie des protéines, par exemple, mais elles ont aussi adopté les nouvelles technologies.

Andrew Hoffman : Vous venez de répondre à ma prochaine question. Si je comprends bien, les scientifiques en recherche fondamentale ne travaillaient pas d'un côté et les scientifiques en recherche clinique de l'autre?

Rima Rozen : C'est ça.

Andrew Hoffman : Croyez-vous que le fonctionnement, contrairement à ce qu'on voit aujourd'hui, reflétait la structure du savoir? Comme vous l'avez dit, depuis 10 ans, tout le monde fait de la biologie moléculaire. Quand vous avez commencé, ce n'était pas le cas. En fait, vous étiez l'une des seules. Vous en savez plus que moi à ce sujet, mais peut-être que les demandes de subvention étaient moins évidentes à faire dans un domaine qui n'était pas encore bien défini, comparativement à aujourd'hui, et que le financement est plus généreux lorsque la palette est plus large. J'imagine que non, mais je vous pose la question.

Rima Rozen : Non. Je crois en fait que les modèles de financement ont changé. Les sommes accordées par personne sont moins élevées qu'auparavant. Il y a évidemment toutes sortes de nouvelles initiatives, mais je crois que nous nous intéressons plus à la mégascience, aux grandes plateformes et aux grandes technologies.

Andrew Hoffman : Qu'entendez-vous par « plateformes »?

Rima Rozen : Je pense aux grosses plateformes technologiques, comme les installations centrales. On met beaucoup plus l'accent sur ça et sur la mégascience, les gros groupes et les grosses équipes qui se concentrent sur un domaine, comme le cancer ou le diabète. Nous étions essentiellement des chercheurs qui faisaient cavalier seul et…

Andrew Hoffman : Par opposition aux plateformes ou…

Rima Rozen : Ou à la science ciblée, ce que l'on fait davantage aujourd'hui. Nous travaillons aussi beaucoup moins sur les questions fondamentales. Notre travail est beaucoup plus ciblé et on se demande constamment – aux IRSC, par exemple – quelle importance il faut accorder à la science fondamentale et aux découvertes fondamentales en comparaison avec les retombées cliniques, les plateformes ou la mégascience; c'est une question de politique publique, aussi. Par opposition à simplement laisser les gens faire leur travail en sachant qu'ils vont présenter quelque chose d'intéressant en fin de compte. De toute évidence, il faut fournir des subventions aux bonnes personnes, et parfois, en finançant les travaux des bonnes personnes, on obtient toutes sortes de surprises, de bonnes surprises.

Andrew Hoffman : Tous les membres du groupe se trouvaient plus ou moins au même endroit, même s'ils travaillaient sur leurs propres trucs. J'imagine que…

Rima Rozen : Au début, oui. Puis nous avons commencé à nous disperser un peu parce qu'à l'Hôpital de Montréal pour enfants, nous ne recrutions pas autant de spécialistes en génétique que nous l'aurions voulu. De plus, la génétique commençait à prendre sa place à différents endroits sur le campus et nous voulions avoir accès aux meilleurs chercheurs pour notre groupe sans nous limiter à ceux de l'Hôpital de Montréal pour enfants.

Andrew Hoffman : Mais vous et le Dr Scriver étiez toujours à l'Hôpital de Montréal pour enfants, n'est-ce pas?

Rima Rozen : Je suis restée à l'Hôpital de Montréal pour enfants, tout comme Charles. Puis

Roy est venu nous y rejoindre. Les membres dirigeants ont toujours été ici, à l'Hôpital de Montréal pour enfants, mais nous avons choisi des chercheurs qui s'intéressaient aux mêmes questions que nous; ils n'avaient pas nécessairement besoin de travailler à l'Hôpital.

Andrew Hoffman : Aviez-vous peur, par exemple, que votre groupe ait du mal à obtenir du financement parce que les membres étaient un peu plus dispersés?

Rima Rozen : Nous avons eu quelques craintes, mais pas nécessairement à cause des lieux de travail. Je crois que nous nous sommes sentis obligés de trouver des chercheurs qui travaillaient sur les mêmes types de troubles que nous pour ainsi définir une sorte d'activité centrale intéressante pour les organismes.

Autrement dit, nous avons essayé de conserver certains centres d'intérêts communs. Par exemple, plusieurs d'entre nous s'intéressaient au folate et à la vitamine B_{12}, aux maladies métaboliques. Disons que nous voulions pouvoir présenter une structure cohérente. Nos choix étaient donc influencés par ça aussi.

Par contre, c'est toujours la science qui a guidé nos choix de chercheurs, et c'est ce qui primait dans les demandes de subvention, et c'est encore le cas. Très souvent, pour un grand nombre de programmes auxquels je participe à titre d'administratrice, entre autres, c'est encore la science qui l'emporte, et je m'en réjouis. L'excellence prime. Ce n'est pas une question de jeux de coulisses ou de favoritisme. L'excellence est toujours un critère important qui est récompensé.

Andrew Hoffman : Ce qui est bien, j'imagine. Voici enfin ma dernière question. En raison de cette transition d'une génétique mendélienne à une génétique plus axée sur la biologie moléculaire, dont nous avons un peu parlé, et des liens qu'entretenait le groupe avec les D^{rs} Fraser et Scriver, par rapport à leur intérêt plus marqué pour l'aspect clinique et le fait qu'ils ont continué à travailler…

Rima Rozen : Sur des problèmes cliniques, comme le reste du groupe. Comme je l'ai déjà dit, ce qui nous unissait, c'est que nous nous intéressions tous à un problème clinique. Disons que nous nous y prenions simplement différemment pour faire nos expériences. Au fur et à mesure que le groupe accueillait de nouveaux membres, souvent plus jeunes, les travaux portaient de plus en plus sur la biologie moléculaire. Mais l'aspect clinique n'a jamais disparu. Les applications médicales ou cliniques, c'est ce qui a fait le succès de notre groupe.

Nous avons gardé le mot « médical » dans notre nom – le groupe de génétique médicale des IRSC – pour indiquer que nous partions tous d'une maladie pour ensuite l'étudier de différentes façons, surtout au fur et à mesure que la technologie s'appuyait sur des stratégies de génétique moléculaire. Nous utilisions tous ces stratégies, mais ça n'avait pas vraiment d'importance parce que l'aspect clinique était toujours présent et que nous l'abordions en fonction du sujet.

Certains sujets se prêtent mieux aux méthodes non moléculaires que d'autres. C'est là que l'excellence entre en ligne de compte. Un scientifique utilisera les bonnes méthodes et en apprendra de nouvelles au besoin afin de vérifier une

hypothèse sur une maladie en particulier.

Andrew Hoffman : À ce moment-là, est-ce que les scientifiques obtenaient les subventions de façon individuelle pour travailler dans le laboratoire?

Rima Rozen : Les choses ont changé au fil du temps. Je pense qu'au début, nous ne faisions que des demandes de groupe. Je ne sais pas quand cette façon de faire a cessé. Probablement au début des années 1990, lorsque j'ai commencé. J'ai commencé en 1997. Mais à un certain moment, pour recevoir une subvention de groupe, nous devions aussi obtenir des subventions individuelles.

Andrew Hoffman : Donc, pour obtenir du financement pour le groupe, vous deviez également faire des demandes et obtenir des subventions chacun de votre côté.

Rima Rozen : Exactement. On éliminait ainsi l'idée que certains obtenaient un traitement de faveur ou que tous n'étaient pas évalués en fonction des mêmes critères. Il fallait passer par les deux systèmes. Nous devions faire évaluer nos demandes par les comités habituels, comme tout le monde, puis passer par un deuxième processus pour une subvention de groupe. D'une certaine façon, nous devions subir deux évaluations.

Je devais présenter ma propre demande de subvention pour mon propre sujet de recherche à un comité en particulier, puis tous les cinq ans, ou lorsque le financement de groupe prenait fin, nous présentions une demande de groupe. Il fallait alors prouver que chaque membre avait sa propre subvention.

Andrew Hoffman : Cependant, vous n'avez jamais fait une véritable distinction entre la science fondamentale et les questions d'ordre médical ou clinique, n'est-ce pas?

Rima Rozen : L'utilisation de la science fondamentale avait toujours des fins médicales. La science fondamentale est un outil. Pour moi, « fondamental », ça veut dire… pour certains, « fondamental » renvoie à la molécule.

Andrew Hoffman : C'est plus un travail de laboratoire, alors que, comme vous le dites, le Dr Scriver était plutôt un clinicien?

Rima Rozen : C'est exact. Mais il avait aussi souvent recours aux travaux en laboratoire pour trouver des réponses à certaines questions. Au Children's, il ne travaillait pas uniquement avec des patients.

Andrew Hoffman : Je vois. Une autre question rapide. En ce qui concerne vos publications, y avait-il des divergences entre vos travaux et ceux du Dr Scriver et des autres? Je pose la question, parce que si on consulte la liste des publications, il semble qu'on pourrait établir une séparation entre les vôtres et celles du Dr Scriver…

Rima Rozen : Parce qu'il s'agissait de sujets complètement différents. Charles n'a jamais travaillé sur le folate, alors que tous nos travaux depuis 1987, que ce soit sur différentes enzymes ou différentes voies… J'ai étudié le folate pendant de nombreuses années, alors que Charles n'a jamais travaillé dans ce domaine.

En plus de mes travaux sur le folate, il m'arrivait de collaborer avec Charles sur d'autres sujets, comme la phénylcétonurie. Mais les travaux sur le folate

n’avaient rien à voir avec Charles. En fait, je dois admettre que lorsque vous faites votre formation avec une personne, vous devriez vraiment travailler dans un autre domaine. Et même si j’ai commencé à travailler sur la phénylcétonurie avec Charles, par exemple, je savais que je devais développer mes propres travaux pour qu’on ne considère pas que je faisais partie de son équipe ou de sa sphère d’influence. J’ai donc commencé à travailler sur le folate, ce qui n’avait rien à voir avec Charles.

Andrew Hoffman : Vous avez donc acquis votre indépendance professionnelle en quelque sorte.

Rima Rozen : Oui. Il faut le faire. C’est quelque chose que tout le monde doit faire. Parfois, c’est plus difficile parce que, comme je l’ai déjà dit, certaines personnes font une formation postdoctorale dans un certain domaine et elles développent une expertise dans le même domaine. Si elles continuent de travailler avec leur ancien superviseur ou de publier avec lui, la question de l’indépendance va forcément se poser.

Heureusement ou malheureusement, il n’avait jamais été question de folate au cours de ma formation. Je faisais donc preuve d’indépendance, mais d’un autre côté, je n’avais aucun outil qui aurait pu m’aider à démarrer rapidement. J’ai dû créer mon propre matériel. Mais tout ça est maintenant à moi. Charles, ni aucun autre de mes superviseurs, n’y a jamais contribué. Ces personnes n’ont jamais rien eu à voir avec le folate, ce qui est une bonne chose pour moi, même si ce fut effectivement difficile au début.

Andrew Hoffman : Bien. Je n’ai plus de questions pour aujourd’hui.

Rima Rozen : Pour aujourd’hui?

Andrew Hoffman : Mais peut-être un suivi pour éclaircir…

Rima Rozen : Très bien. Et vos questions étaient très différentes, même si j’avais déjà abordé certains sujets avec Chris. Donc tout est parfait selon moi.

Andrew Hoffman : D’accord. C’est bien, alors.

FIN DE L’ENTRETIEN

Dr Charles Scriver, le 2 mars 2010

Andrew Hoffman : Nous sommes le 2 mars 2010. Ici Andrew Hoffman en compagnie du Dr Charles Scriver, du Département de génétique humaine. Dr Scriver, je suis honoré de pouvoir m'entretenir avec vous aujourd'hui des grandes lignes ou, devrais-je plutôt dire, d'explorer plus en profondeur la première partie de votre carrière, vos origines familiales et ce genre de choses. Le reste a déjà été exploré et est dûment consigné.

Alors, commençons par le commencement – votre lieu de naissance, l'endroit où vous avez grandi, vos études – pour voir dans quelle mesure votre histoire personnelle a pu influer sur votre travail comme scientifique. Avec un peu de chance, nous ne serons pas interrompus.

Dr Charles Scriver : Je suis né le 7 novembre 1930 dans une famille trigénérationnelle, puisqu'en raison de la situation économique difficile, les parents de mon père habitaient avec nous. Avec le recul, je me rends compte que ma famille n'était pas banale : mes deux parents étaient des professionnels du monde de la médecine et de l'enseignement à l'Université McGill. J'y reviendrai plus tard au besoin.

Je suis allé à l'école à Montréal, d'abord à l'école primaire située sur la rue où j'habitais. Mais ensuite dans une école un peu particulière, à la mission pédagogique ambitieuse : le Lower Canada College. Je dirais que l'instruction que j'y ai reçue ne m'a pas nui; c'était sans conteste un lieu propice à l'excellence.

Après l'obtention de mon diplôme, je suis allé à McGill; je me suis inscrit à la Faculté des arts et des sciences humaines, et j'ai obtenu un diplôme en géographie et en littérature comparée. C'est une expérience que j'ai adorée à l'époque et dont je garde un excellent souvenir. Mon opinion n'a pas changé d'un iota. Lors de l'obtention de mon baccalauréat, je pensais sincèrement devenir géographe; il faut dire que le Département de géographie de McGill était l'un des plus réputés à l'époque.

Mes parents n'ont pas du tout fait pression sur moi. Seulement, en les observant, j'ai constaté à quel point leur travail les rendait heureux. Ils adoraient la médecine et étaient au service du patient, de la famille, de leurs semblables. À leurs yeux, c'était la chose à faire dans le monde dans lequel nous vivions, alors ils étaient de bons modèles. Peut-être pour leur faire honneur, je ne saurais dire quelle était exactement ma motivation, mais toujours est-il que j'ai fait une demande en médecine. À l'époque, on n'envoyait pas notre candidature dans les 16 écoles de médecine. J'ai fait une demande dans une seule école, à McGill, et j'ai attendu. Et on m'a accepté comme étudiant en médecine.

J'ai donc sauté dans le train. C'était une époque formidable. On est alors en 1951. J'étais diplômé en arts, comme je l'ai dit, et le groupe était tellement différent de celui que j'avais connu en sciences humaines et en géographie. J'étudiais avec des Américains qui profitaient de leur dernière année d'admissibilité au *G.I. Bill of Rights*. Ces étudiants en avaient vu d'autres.

Ils avaient vu le meilleur et le pire des comportements humains, les conflits, les combats, et leurs valeurs ont probablement un peu déteint sur moi. Quoi qu'il en soit, j'ai adoré mes études en médecine. J'avais déjà étudié en biologie humaine et j'avais de bons résultats. Ma biologie me donnait une longueur d'avance, mais il y a aussi les circonstances qui m'ont été favorables et m'ont permis de faire ma médecine.

Bon, voilà comment j'ai obtenu mon diplôme en médecine, le fameux « MDCM » comme on l'appelle à l'Université McGill, en 1955. J'avais un diplôme en arts. Et voilà que j'en obtenais un en médecine avec distinction, ce qui témoigne quand même d'une certaine intelligence.

Andrew Hoffman : Je vous interromps un instant si vous le permettez. Vous dites que votre cohorte de médecine était constituée en grande partie d'Américains qui profitaient des dernières années du *G.I. Bill* et que leurs valeurs avaient déteint sur vous. Que voulez-vous dire par là? De quelles valeurs parlez-vous exactement?

Dr Charles Scriver : Eh bien, je pense qu'une des choses – ici encore, rétrospectivement, parce que je ne peux pas dire que j'en étais conscient à l'époque – mais je crois que les valeurs des gens de mon âge dans les années 1950… je pense que certains considéraient qu'aller à l'université était presque un droit et qu'ils pouvaient se permettre de prendre ça plutôt à la légère. Or, ces gars de notre cohorte de médecine avaient combattu en Europe et en Asie. Ils avaient vu de près la mort et la souffrance. Ils avaient fait la guerre et savaient parfaitement pour quelles valeurs ils s'étaient battus. Et les gens comme moi, nous n'avions pas vécu ça, alors notre vision des choses était différente. C'étaient pour la plupart des gars sérieux, et ça nous a influencés, consciemment ou non.

Andrew Hoffman : Nous reviendrons à votre formation en médecine, mais si on remonte encore plus loin, j'ai une note ici qui indique que la musique était importante dans votre famille.

Dr Charles Scriver : J'ignore d'où vient cette note, mais c'était ma mère qui était musicienne. Jeune adulte, je pense qu'elle a eu la possibilité de faire carrière en musique, comme accompagnatrice; elle avait du talent et a joué du piano avec aisance jusqu'à presque cent ans. Mon père, lui, ne jouait d'aucun instrument. Il n'avait pas étudié la musique, mais c'était un mélomane qui collectionnait les vinyles des symphonies de Mahler. Les gens se disaient que ça frisait la folie. Cet amour profond de la musique, je pense qu'il me l'a transmis. À Lower Canada, je formais un trio avec deux amis. Je jouais de la basse – je ne jouais pas bien, mais j'aimais ça – et vers la fin de l'adolescence et le début de l'âge adulte, j'étais un grand admirateur de musiciens comme Duke Ellington. Je collectionnais toutes ses œuvres, et j'ai commencé à m'intéresser à d'autres grands noms du jazz, l'un des trésors que le XXe siècle nous a légués. Après Ellington, vers la fin de la quarantaine, je me suis mis à collectionner tout ce que je pouvais trouver sur Bill Evans, le pianiste; encore aujourd'hui, ce sont deux musiciens que j'écoute avec beaucoup de plaisir.

Andrew Hoffman : La musique a-t-elle fait partie de votre parcours scolaire et de votre enfance?

Dr Charles Scriver : Seulement pendant la dernière année dans ce trio; nous jouions un peu partout en ville.

Andrew Hoffman : Vous avez suivi des cours ou vous êtes autodidacte?

Dr Charles Scriver : Je suis autodidacte. Je ne jouais pas bien, mais j'aimais ça…

Andrew Hoffman : Et aujourd'hui, êtes-vous encore amateur de jazz?

Dr Charles Scriver : Absolument. J'écoute encore le jazz dans une sorte de recueillement. Nous aimons la musique dans la famille. Ma femme s'y connaissait aussi.

Elle lisait la musique et faisait partie de la chorale de McGill. Un de nos enfants est musicien, et son nom figure sur album qui a gagné un Grammy, comme ingénieur du son. Notre fille aînée est diplômée en musique et en mathématiques de l'Université Mount Allison. La deuxième a dansé dans Les Grands Ballets Canadiens de Montréal, mais a réorienté sa carrière après une blessure. Quant à notre fils aîné, il enseigne l'architecture à l'Université d'Adélaïde, en Australie. Tout comme moi, c'est un amoureux de la musique.

Andrew Hoffman : C'est donc un amour qui s'est transmis de génération en génération?

Dr Charles Scriver : Oui, on dirait bien. Il y a de l'inné et de l'acquis, j'imagine.

Andrew Hoffman : Revenons un peu en arrière. Le Lower Canada College n'était pas vraiment un collège, mais plutôt l'équivalent d'une école secondaire?

Dr Charles Scriver : Oui, mais il fallait réussir l'examen d'admission pour y entrer. Je dirais que ce n'était pas une école égalitaire, parce qu'il y avait des droits de scolarité, et ce n'était pas l'école la plus abordable de Montréal.

L'éducation était primordiale pour mes parents, alors ils étaient disposés à payer pour m'envoyer à cette école. Ils avaient le sentiment que c'était une meilleure école que les autres établissements du quartier. Et je ne l'ai jamais regretté.

Je ne pense pas que j'aurais pu recevoir dans d'autres écoles du quartier la formation que j'ai reçue là-bas en littérature, en histoire, en géographie et en sciences.

Andrew Hoffman : Étiez-vous un bon élève?

Dr Charles Scriver : Oui. Et un des grands avantages d'être bon élève dans cette école était qu'il y avait une cérémonie de remise de prix à la fin de chaque année, et ce prix, c'était un livre, que l'élève pouvait choisir à sa guise. J'ai encore plusieurs de ces livres. Pour moi, c'était une grande source de motivation, et l'amour des livres m'a suivi toute ma vie.

Andrew Hoffman : Et c'est peut-être de là que vient votre intérêt pour la géographie?

Dr Charles Scriver : Oh, oui. Le directeur de l'école, Stephen Penton, était un des grands pédagogues du pays. Il enseignait la géographie et le faisait avec brio; son enseignement m'a marqué, c'est incontestable.

Andrew Hoffman : Bon, faisons un saut dans l'avenir. Je suis désolé que…

Dr Charles Scriver : Je vous en prie, ce sont des questions intéressantes.

Andrew Hoffman : Ce que nous voulons faire, Dr Scriver, c'est raconter l'histoire du groupe, mais aussi l'histoire de ses membres. Alors, si on peut faire d'une pierre deux coups… Et qui sait, peut-être que quelqu'un fera un jour une recherche sur les généticiens et se demandera lesquels étaient amateurs de jazz.

Donc, à McGill, vous avez étudié en arts, en géographie; c'était la voie que vous aviez choisie, puis…

Dr Charles Scriver : C'est la littérature qui m'a toujours influencé; j'aimais la littérature russe, pas en russe, mais en version traduite.

Andrew Hoffman : Puis un jour, comme vous l'avez souligné, que ce soit pour rendre hommage à vos parents ou pour une autre raison, vous avez bifurqué vers la médecine, que vous avez étudiée à McGill.

Vous dites que vos deux parents étaient médecins?

Dr Charles Scriver : Oui. Je vous mets en contexte. Ils étaient tous les deux brillants et avaient de la facilité à l'école. Si je ne m'abuse, ma grand-mère maternelle insistait pour que ma mère entre dans le moule en devenant missionnaire ou quelque chose du genre. Ma mère croyait se souvenir que l'enseignement était une autre voie qu'on avait envisagée pour elle. Mais elle, elle ne voulait pas enseigner à la maternelle ni au primaire, et elle s'est rendu compte que le missionnariat n'était pas pour elle non plus.

Son père, qui était à la tête des minoteries montréalaises, lui a dit : « Tu peux faire tout ce que tu veux. Tu n'as qu'à choisir. » Elle lui a répondu qu'elle pourrait suivre les cours d'Ogilvy, obligatoires pour l'admission en médecine. Il lui a donné le feu vert.

Elle s'est donc rendue à Harvard, a suivi les deux cours dont elle avait besoin et s'est retrouvée dans la première cohorte mixte de McGill en médecine. Car, jusqu'à ce moment, seuls les hommes étaient admis. Elle était donc l'une des cinq femmes du groupe, et, devinez quoi, ces femmes se sont toutes classées dans les 10 premières places sur une classe de 100 étudiants. La pression de sélection était considérable.

Diplôme en main, elle s'est dit qu'elle devait être à la hauteur de cette chance d'étudier qui lui avait été donnée. Et elle l'a été. Elle a fait ses études aux cycles supérieurs ici même à Montréal, elle a fait de la recherche fondamentale intéressante sur la drépanocytose. Elle a exploré les facteurs nutritionnels chez le nourrisson et, en 1930, elle avait quelques articles à son actif. Mais les gens lui disaient : « Jesse, ce ne sont pas ce qu'on pourrait appeler des "sujets

chauds” en médecine. Pourquoi ne te consacres-tu pas à des choses utiles? » En gros, c’est ce qu’elle m’a raconté.

C’est ainsi qu’elle a commencé à s’intéresser à la prématurité. Elle a mis sur pied l’une des premières pouponnières pour bébés prématurés au pays. Puis elle est devenue un excellent médecin, qui faisait des visites à domicile à toute heure du jour ou de la nuit. Elle était un véritable modèle pour les femmes qui ont embrassé la médecine après elle. Et elle était également une bonne mère. Ce dont il faut se souvenir ici, c’est qu’elle était consciente de la chance qu’elle avait eue et avait le sentiment qu’elle devait se montrer à la hauteur.

Donc, vous vous demandez comment elle a réussi à être à la fois épouse, mère et médecin? Je vous le donne en mille : elle a reçu en entrevue des femmes pas banales qui avaient quitté la Grande-Bretagne après la Première Guerre mondiale. Leur fiancé avait été tué ou je ne sais trop. Enfin, l’une d’elles s’appelait Effie Salter. Plus tard, ma femme et moi nous sommes demandé laquelle des deux avait interviewé l’autre : est-ce Effie qui avait interviewé ma mère ou l’inverse? Parce qu’elles étaient toutes les deux des professionnelles, chacune à sa façon.

Andrew Hoffman : D’accord, et Effie, que faisait-elle exactement?

Dr Charles Scriver : Je dirais qu’elle était gouvernante. Elle est arrivée chez nous en 1930, ce qui veut dire qu’après avoir accouché de moi, ma mère a pu reprendre sa pratique médicale. J’avais donc une mère qui travaillait, et Effie était une partenaire de la famille. Elle a passé 16 ans chez nous. Elle a pris soin de mes grands-parents, elle les a vus mourir tous les deux dans notre maison, elle s’est occupée de moi avec ma mère et elle est devenue un membre à part entière de notre famille.

Mon père a fait la Grande Guerre, mais il a attrapé la fièvre typhoïde, ce qui lui a épargné une mort dans les tranchées. Il a été démobilisé, et l’armée a perdu ses états de service. Il s’est donc enrôlé une deuxième fois et s’est joint à l’équipage des navires-leurres, qui devaient régler le problème des sous-marins. Il a survécu – je précise que c’était ce qu’il y avait de plus dangereux dans la marine, hormis les combats directs.

Donc il est revenu et a fait deux diplômes de front, un en arts et l’autre en médecine. Il adorait le volet scientifique de la médecine. Je l’entends encore me parler du rein comme organe d’adaptation et d’évolution. Puis il est devenu médecin-chef à l’Hôpital Royal Victoria, une réalisation digne d’admiration. Il était, lui aussi, un excellent médecin. Ma mère et lui savaient tous les deux écouter le patient afin de découvrir la source de ses maux et de lui prodiguer des conseils; l’un comme l’autre, ils sortaient du strict cadre de la médecine pour tenir compte d’une foule d’autres facteurs, comme la situation sociale par exemple.

Bref, nous reviendrons peut-être là-dessus, mais le meilleur conseil que j’ai reçu en carrière vient de mon père. Je vous en reparlerai tout à l’heure.

Andrew Hoffman : D’accord. J’en prends note pour ne pas l’oublier. Alors, vous avez terminé vos études en médecine en quelle année?

Dr Charles Scriver : Nous sommes rendus à ma résidence, oui, en 1955.

Andrew Hoffman : D'accord.

Dr Charles Scriver : J'ai commencé ma résidence; à cette époque à McGill, les rotations se faisaient beaucoup à l'Hôpital Royal Victoria. En 1956, 1957 – cette année-là, il y a eu du nouveau dans le programme de McGill, et j'ai pu étudier la médecine pendant six mois et la pédiatrie pendant six mois. J'ai donc pu approfondir davantage la pédiatrie, et j'ai bien aimé. Même que j'étais plus à l'aise en pédiatrie qu'en médecine interne.

J'ai également fait la connaissance du médecin-chef du Service de pédiatrie, le Dr Alan Ross. « Alan » s'écrit « A-L-A-N. Alan Ross était l'un de ces êtres d'exception toujours prêts à mettre leur ego de côté pour venir en aide aux autres, et il a réuni autour de lui ceux d'entre nous qui souhaitaient se creuser les méninges, qui se demandaient pourquoi telle personne avait tel problème à un moment X de sa vie, qui voulaient trouver l'origine et la cause de la maladie. Il a mis sur pied un service qui était probablement l'un des meilleurs au pays, et il nous a fait profiter de ses judicieux conseils et de son soutien inestimable.

Il n'a jamais fait mine de tout savoir de ce que nous faisions, mais il a su nous prendre sous son aile pour que nous puissions nous ménager la carrière de notre choix.

Andrew Hoffman : Et c'était un service de pédiatrie?

Dr Charles Scriver : À l'Hôpital [de Montréal] pour enfants. Il y avait un service de pédiatrie à l'Hôpital Royal Victoria, qui était aussi le grand hôpital général universitaire. Ma mère était pédiatre-chef dans ce maillon pédiatrique du réseau de McGill.

Andrew Hoffman : Je vois. Les circonstances étaient particulières lors de votre arrivée au Royal Vic; il y a eu, si mes renseignements sont bons, une rencontre avec Ronald Christie?

Dr Charles Scriver : Oui. C'est l'une des grandes rencontres de ma carrière. Comme médecin-chef dans les années 1950, mon père avait eu connaissance de certains problèmes fonctionnels au Service de médecine expérimentale. Son directeur était quelqu'un de réputé, un certain JSL Brown, John Brown. C'était un grand penseur, mais il avait des lacunes comme administrateur; il était là lors de la découverte de la cortisone et des études sur son emploi à des fins médicales.

Mon père a constitué un comité pour la recherche d'un nouveau médecin-chef. Il souhaitait passer le flambeau. Le comité a choisi Ronald Christie, qu'il a fait venir d'Angleterre pour rebâtir ici, à McGill, ce qui allait devenir le Service de médecine universitaire le plus renommé du pays; du moins c'est la réputation qu'il a eue pendant un certain temps.

Ronald Christie avait un collègue, un commandant en second si on peut dire, qui s'appelait John Beck. Ces deux gars étaient des figures de proue de la médecine au Canada et à McGill, et ils étaient toujours à l'affût de gens brillants pour le réseau mcgillois. C'était l'âge d'or du clinicien-chercheur au Canada; à

l'époque, le diplôme en médecine façonnait votre vision des choses et vos façons de faire.

Me voilà donc dans le bureau du médecin-chef. Il était assis dans sa chaise, et John Beck était assis ou debout à côté de la sienne. En gros, ils voulaient savoir : « Alors, Charles, qu'est-ce que tu veux faire quand tu seras grand? » « Je n'en sais trop rien, leur ai-je répondu. Mais je pense que j'aimerais être médecin enseignant, comme mes parents. » Puis ils m'ont demandé ce que je pouvais leur apporter de particulier, parce que, ont-ils précisé, « nous n'avons pas besoin d'un autre généraliste ». Comme je n'avais toujours pas de réponse à leur offrir, ils m'ont conseillé de passer à la bibliothèque pour essayer d'en trouver une.

Je suis donc allé à la bibliothèque de l'Hôpital Royal Victoria. C'était une belle bibliothèque, et ce que je vais vous raconter est authentique. Les revues étaient disposées de manière à ce que la couverture soit bien visible; on voyait donc défiler les couvertures en marchant. Des bandes rouge-blanc-rouge sur une revue ont accroché mon regard.

La bande rouge faisait mention du titre de la revue et de l'année, et la blanche renfermait la table des matières. Comme la couverture avait attiré mon attention, j'ai pris un exemplaire de la revue. C'était un numéro du *British Medical Bulletin* sur la chromatographie; cette méthode physico-chimique suscitait depuis peu énormément d'intérêt et avait même mérité un prix Nobel.

Andrew Hoffman : Un prix Nobel, vous dites?

Dr Charles Scriver : Oui. À la fin, il y avait un article de Charles Dent et Walsh sur le recours à la chromatographie pour l'examen de la composition chimique de personnes atteintes de différentes maladies. Et comme je m'y connaissais en arts et que j'avais grandi dans une famille où on appréciait l'art, j'aimais les couleurs des chromatogrammes. Alors, ce côté esthétique m'attirait, mais le volet intellectuel de la chose m'intimidait. Mais je me suis dit : « Wow, ça, c'est vraiment intéressant! »

Lorsque je suis retourné voir Ronald Christie et John Beck, je leur ai dit que je voulais faire de la chromatographie et que j'avais constaté que cette expertise n'existait pas à McGill.

Andrew Hoffman : Vous rappelez-vous avoir pensé que vous feriez ainsi bonne impression, ou était-ce simplement une idée qui s'était présentée comme ça?

Dr Charles Scriver : C'était simplement une idée. En fait, ils m'avaient dit de trouver ce que je pouvais leur apporter de particulier, et je leur ai dit voici, je pense que c'est ce que j'ai envie de faire. Et comme ils étaient plutôt futés, leur question suivante a été : « Où aimerais-tu aller? Nous avons deux endroits à te proposer. Le premier est l'Institut Rockefeller, à New York, et l'autre est la Faculté de médecine du University College de Londres, où travaille Charles Dent. »

Je leur ai demandé si j'allais pouvoir travailler auprès des patients à l'Institut Rockefeller, parce je voyais l'aspect clinique de la chose. Ils m'ont répondu que non, mais que je pourrais probablement travailler dans le laboratoire de

Stanford Moore et en apprendre beaucoup sur la chromatographie. Je n'y suis pas allé, parce que je tenais à être au chevet des malades, mais j'ai fait la connaissance de Stan Moore plus tard. Il a été bon pour moi, il m'a donné des conseils et en plus, il a gagné le prix Nobel pour la mise au point de la chromatographie quantitative et des instruments qui permettent de la réaliser.

Donc, un séjour dans son laboratoire aurait certainement été intéressant, mais j'ai plutôt opté pour Londres, où j'ai côtoyé Charles Dent. J'y ai passé deux ans. Après les six premiers mois, j'avais le moral à plat, parce que je constatais que mes connaissances n'étaient pas suffisantes et que je n'arrivais à rien. Charles Dent m'a dit qu'après six mois de formation dans ce domaine, c'était tout à fait normal. Il m'a encouragé à persévérer, et je l'ai écouté. J'ai fait quelques découvertes intéressantes qui ont lancé ma carrière. Mais en réalité, c'est le « Qu'est-ce que tu veux faire quand tu seras grand? » de Ronald Christie et de John Beck qui a allumé l'étincelle. Puis la découverte fortuite de la chromatographie et le fait qu'on m'ait suggéré d'aller à Londres. Mais encore fallait-il que je me rende à Londres. Ronald Christie et John Beck ont donc soumis ma candidature pour la bourse de voyage McLaughlin. Je l'ai décrochée; elle m'a ouvert la porte de Londres et a été renouvelée après la première année. J'ai donc passé deux ans à me perfectionner à Londres.

Andrew Hoffman : Si je comprends bien, vous conserviez des liens avec McGill même si vous travailliez à Londres?

Dr Charles Scriver : Oui, j'étais un étudiant de McGill qui faisait ses études postdoctorales dans un laboratoire réputé, celui de Charles Dent, et découvrait le concept des erreurs innées du métabolisme. Et ce n'est nul autre que Harry Harris qui me guidait. Il avait entrepris sa quête dans l'immeuble d'en face, au Galton Laboratory, mais à cette époque il s'était installé au King's College.

Harry a été très bon pour moi. Il savait que je voulais répondre à la question : pourquoi telle personne souffre-t-elle de telle maladie à un moment X de sa vie? Il savait que la chromatographie m'intéressait et que je souhaitais m'en servir. Et à ce stade déterminant de ma carrière, il m'a apporté un énorme soutien sur les plans intellectuel et social.

Andrew Hoffman : Quelle est votre plus grande réalisation de l'époque où vous travailliez sous… travailliez-vous sous sa supervision?

Dr Charles Scriver : Je travaillais… dans le laboratoire de Charles Dent, il fallait être autonome. Si tu savais te tirer d'affaire, tu pouvais compter sur eux pour te prêter main-forte. Sinon, ils tentaient de mettre le doigt sur le problème. Et s'ils sentaient que tu avais peu de chances de bâtir une carrière solide, ils te conseillaient probablement de te réorienter, du moins je pense.

Andrew Hoffman : Il semble donc que ce laboratoire ne fonctionnait pas selon une approche collaborative.

Dr Charles Scriver : L'approche collaborative, je dirais que oui. Il y avait d'autres personnes dans le laboratoire. Prenons Mary Efron, par exemple : elle s'intéressait à la chromatographie, elle est retournée à Harvard et a mis au point le dépistage

néonatal par chromatographie, notamment, dans les années 1960; c'est aujourd'hui un grand nom dans ce domaine.

Et il y avait d'autres personnes… elles m'ont enseigné la biochimie des acides aminés. C'était ça, l'approche collaborative; nous nous transmettions nos connaissances respectives pendant le dîner, quelques fois par semaine. Je dois souligner ici l'apport de Roland Westall. Je dirais que la collaboration venait en grande partie de ces gens. Le principe, c'était « fais ton bout de chemin, et tu pourras compter sur nous ».

Nous n'avons pas parlé de la période entre McGill, les stages, le début de la résidence en médecine et Londres, et c'est l'année que j'ai passée au Children's Medical Center de Boston.

Andrew Hoffman : Donc c'est après votre scolarité de médecine?

Dr Charles Scriver : Exactement. Nous sommes en 1957-1958. Alan Ross aimait bien que ses étudiants aillent élargir leur expérience ailleurs. Le Children's Medical Center de Boston était génial, parce que ses médecins venaient de partout dans le monde. C'était une véritable plaque tournante.

Donc je suis allé là-bas travailler avec le personnel de l'hôpital, des hommes et des femmes remarquables. Ce fut une année extraordinaire pour moi, tout simplement parce que j'ai vu là des affaires qu'on ne voit jamais ailleurs en médecine… et je viens d'utiliser « affaires », un mot plutôt familier. J'ai rencontré là de formidables professeurs qui ont été de grands mentors.

J'ai côtoyé des collègues pour qui l'approche collaborative, l'entraide, était un mode de vie. Cela dit, il y avait de la rigueur et de la discipline dans la formation; si vous surviviez au rythme et à tout le reste, vous sortiez de là transformé après un an. J'étais de garde [au Children's Medical Center] au début de 1958, si ma mémoire est bonne. Un enfant est arrivé en crise d'épilepsie; au moment de la prise des antécédents, la mère m'a regardé et m'a dit : « Je vous en prie, écoutez-moi ».

Cinquante années plus tard, je me dis : « Mais pourquoi est-ce que je ne l'écouterais pas? Je suis ici pour ça. » Seulement, si elle a senti le besoin de le demander, c'est que nous ne le faisons pas toujours. Et en fait, ce qu'elle voulait me dire, c'est qu'un autre de ses enfants avait fait des crises d'épilepsie.

Bon, je n'avais pas assez de connaissances en hérédité ou en génétique. Mais je me suis dit qu'on avait probablement affaire à quelque chose de biologique, d'héréditaire.

Andrew Hoffman : Désolé de vous interrompre, mais cette façon de penser vous a-t-elle été inculquée à l'école de médecine, parce que nous parlons ici de la naissance de votre intérêt pour la génétique.

Dr Charles Scriver : J'ignore d'où ça vient, parce que la génétique est arrivée pas mal tôt en médecine. Alors, peut-être que je suis juste… et peut-être que j'imagine ça, mais avec le recul…

Andrew Hoffman : Je pense que ce serait intéressant de déterminer à quel moment de votre carrière s'est produite cette révélation, cette épiphanie.

Dr Charles Scriver : Ah oui, je peux vous relater quelques moments d'épiphanie. Mais avant, je vais poursuivre mon premier récit. Alors, nous en étions à la prise des antécédents. Cet enfant a de gros problèmes de convulsions. Aucun médicament n'en vient à bout, et la mère a peur, parce que son premier enfant avait les mêmes symptômes et est mort à l'âge de quatre mois.

J'étais fatigué, mais mes mentors, les chefs de service, etc. m'avaient conseillé de lire les revues, de ne jamais cesser de lire. Alors, ce soir-là, c'est ce que j'ai fait; et une fois de plus, le hasard a bien fait les choses. En ouvrant la revue *Pediatrics*, je suis tombé sur un article de Bessey et de ses collaborateurs où il était question de l'efficacité de la vitamine B6 contre les convulsions, dans certaines conditions.

Le matin suivant pendant la tournée, j'ai proposé l'essai de la vitamine B6 chez cet enfant. Ni lui ni aucun autre membre de sa fratrie n'en avaient reçu. Alors, nous avons décidé de lui en donner. En fait, ce n'est pas tout à fait comme ça que ça s'est passé. Nous avons consulté, parce que c'était nouveau comme intervention.

Sydney Gellis est donc venu du Boston City Hospital, et nous avons donné de la vitamine B6 à l'enfant. Je ne me souviens pas si nous avons opté pour l'injection ou la voie orale, mais je pense que nous l'avons injectée. Et au bout de 10 minutes, les convulsions ont cessé. Ça, c'est une sorte d'épiphanie; nous avons décidé de refaire l'expérience pour confirmer l'efficacité du traitement. La fois suivante, nous l'avons fait avec électroencéphalogramme et avons vu la modification du tracé et le changement dans le comportement du nourrisson.

La deuxième expérience a donné le même résultat : la crise a cessé. Nous venions de découvrir une forme d'épilepsie qui répondait à la vitamine B6. Et comme le problème touchait deux membres d'une fratrie, peut-être allions-nous mettre au jour un éventuel problème de métabolisme cérébral.

J'ai rédigé un article sur ce cas. Il a été publié en 1960 dans *Pediatrics*.

Andrew Hoffman : En étiez-vous le seul auteur?

Dr Charles Scriver : Oui. Et c'était une revue avec comité de lecture et tout le tralala. Ce sont là, sans doute, les débuts de ma carrière de chercheur. J'aimerais vous donner le fin mot de cette histoire, parce que nous avions plusieurs hypothèses sur ce qui pouvait se passer dans le cerveau, mais toutes étaient erronées.

Cinquante ans plus tard, Peter Clayton, du Great Ormond Street Institute de Londres, a élucidé le mystère de l'épilepsie pyridoxino-dépendante, ou vitamine B6-dépendante. Il s'agit d'une erreur innée du métabolisme de la lysine à l'étape de l'alpha aminoadipate semialdéhyde. L'enzyme qui intervient dans ce processus, l'antiquitine, a subi une mutation.

Il y a donc blocage de la voie métabolique. Les éléments qui circulent sur cette voie subissent une série de transformations chimiques, et un des produits de

ces transformations se lie à la vitamine B6, à la molécule entière, et la retire de la circulation. C'est donc une déficience provoquée. Et comme la vitamine B6 n'est plus là, d'autres enzymes qui en dépendent sont inhibées, ce qui déclenche les convulsions. Il a fallu 50 ans pour comprendre ce qui…

Andrew Hoffman : C'est donc une découverte toute récente?

Dr Charles Scriver : Elle a été publiée il y a quelques années, et elle a résolu le mystère de l'épilepsie pyridoxino-dépendante. Quoi qu'il en soit, un autre soir au Children's Medical Center de Boston, je suis au service des urgences avec un autre résident, Irwin Schafer. Arrive un petit garçon atteint d'une méningite, que nous prenons en charge. Si je me souviens bien, c'était une méningite virale.

Comme nous nous occupions nous-mêmes de tous les examens et des épreuves de laboratoire, j'examine les urines, nous regardons le sang et les diverses possibilités de traitement, puis je me rends compte qu'il y a beaucoup de globules rouges dans l'urine. Il y a donc hématurie. Alors, la mère nous dit – il est à peu près 1 h 30 du matin – elle nous dit : « Vous avez peut-être remarqué que Francis n'entend pas très bien. La surdité court dans la famille, le problème vient de ma famille et il semble en avoir hérité… Bref, nous avons devant nous un garçon qui souffre d'une méningite virale. Il a une hématurie. Et il est sourd. Et comme on nous encourage à lire et à poser des questions, Irwin et moi concluons que le patient est atteint du syndrome d'Alport.

À cette époque, on en sait fort peu sur le syndrome d'Alport, à part le fait que c'est une maladie héréditaire transmise sur un mode dominant. Pour la deuxième fois en un an, me voici donc devant une maladie héréditaire mendélienne, monogénique. C'est ici que nous laissons Francis pour un moment. Pour ma part, je quitte le service et je vais à Londres. Je me joins à l'équipe du laboratoire de Charles Dent. Je reçois alors une lettre d'Irwin Schafer qui dit : « Je n'ai pas oublié Francis. Puis-je t'envoyer un échantillon d'urine et de sang pour que tu voies si tu ne pourrais pas faire quelque chose avec ta chromatographie? ». On cherche, on gratte, on fouille…

Donc le sang – ou plutôt le plasma – arrive, l'urine arrive, j'examine tout ça avec mes petites techniques et je vois dans le sang une grosse marque de proline. Nous savons que c'est anormal, parce que Charles Dent nous avait dit que dans tout ce qu'il avait examiné, il n'avait jamais vu d'hyperprolinémie. Alors, j'examine l'urine et trois marques s'y détachent : de la proline, de l'hydroxyproline et de la glycine.

Ce garçon a une hyperprolinémie, un trouble, avons-nous découvert, à transmission autosomique récessive. Et dans l'urine, il y a trois taches. Intéressant, non? Nous allons… pour conclure cette histoire, je précise qu'il n'y a aucun lien entre l'hyperprolinémie et le syndrome d'Alport. Nous sommes donc en présence d'un patient qui a deux anomalies génétiques distinctes.

Plusieurs éléments m'incitent à aller dans cette direction, mais la grande question est : pourquoi trois taches dans l'urine et une seule dans le sang? Cette histoire est véridique. Je marche dans le corridor et je passe devant l'armoire vitrée dans laquelle sont rangés les béchers et le reste du matériel. En tournant le coin, ça m'a sauté aux yeux. Mais oui! La proline est sur un

transporteur dans le rein et elle bloque l'entrée des deux autres acides aminés, tout en se répandant. Elle sature un transporteur qui reconnaît la forme de ces trois molécules.

Andrew Hoffman : Alors, elle se déverse dans l'urine, mais pas uniquement après avoir rejoint la circulation sanguine?

Dr Charles Scriver : Exactement. La hausse du taux de proline dans le sang est causée par un trouble du métabolisme, une déficience enzymatique. Il y a donc hyperprolinémie. La proline occupe un transporteur du tubule rénal censé recevoir les trois acides aminés, alors ils se retrouvent tous dans l'urine.

C'est ce qu'on appelle l'observation, l'un des outils de la science. L'outil suivant est l'expérimentation. « Bon, je fais quoi maintenant? » C'est là que m'est venue une super idée : je vais m'injecter de la proline pour provoquer une hyperprolinémie, puis examiner mon urine. À l'époque, ce genre de pratique était acceptable. Je l'ai fait et j'ai triplé mon aminoacidurie. Ça frappait l'imagination, parce c'étaient les balbutiements de la biologie des systèmes de transport. Voici ce qu'il faut comprendre : les membranes lipidiques doivent contenir des transporteurs qui prennent les molécules hydrosolubles et leur font traverser la barrière lipidique; les reins sont très importants dans l'étude du mécanisme de transport.

En nous servant d'animaux et de quelques autres personnes dans le labo, nous avons mis au jour un nouveau type d'aminoacidurie et un transporteur rénal dont nous ignorions l'existence.

Andrew Hoffman : Et ça s'est passé à Londres?

Dr Charles Scriver : Le travail a été fait à Londres, mais une fois encore, John Beck et Ronald Christie m'ont encouragé à consigner tout ça dans un résumé et à le soumettre à l'American Society for Clinical Investigation. Je me suis retrouvé en séance plénière pour parler de cette expérience. J'étais terrorisé. L'objectif était de présenter des données qui montraient l'existence de transporteurs à bord desquels montaient les molécules hydrosolubles pour traverser la barrière lipidique.

C'est donc une des toutes premières pièces de la littérature sur les systèmes de transport, et elle marque l'entrée du chercheur clinique que j'étais dans la sphère scientifique de la découverte. Ici encore, le hasard a joué en ma faveur : on m'a permis de présenter mon travail devant l'American Society for Clinical Investigation, qui était LE grand congrès à l'époque. Et cette présentation à Atlantic City, pendant l'assemblée plénière, m'a valu une invitation d'Alec Beam, un autre pionnier, l'un des premiers à dresser l'état des connaissances en biochimie génétique. Rétrospectivement, je constate que mon article n'était pas très bon, mais c'était le premier dans mon champ d'intérêt. Derrière tout ça, il y a Harry Harris, à Londres, qui me disait : « Ne lâche pas, mon vieux, tu es dans la bonne voie ».

Andrew Hoffman : C'est ironique… Vous êtes allé à Londres plutôt qu'à New York parce que vous vouliez travailler auprès des patients, et vous vous êtes rendu compte, à leur chevet, que le côté scientifique de la chose vous intéressait davantage.

Dr Charles Scriver : Voilà, vous avez tout compris.

Andrew Hoffman : Curieux paradoxe que ce cheminement de carrière : vous allez quelque part de votre plein gré dans un but déterminé et en raison de ce que vous trouvez là, vous retenez quelque…

Dr Charles Scriver : En fait, quand je suis arrivé à Londres, Charles Dent voulait que je fasse beaucoup plus de clinique que moi, je voulais en faire, parce que je voulais découvrir comment mesurer les acides aminés. En passant, Stan Moore – de l'Institut Rockefeller – venait assez souvent voir Charles Dent; c'est lui qui m'a appris à nettoyer la résine. Mes travaux l'intéressaient. Finalement, j'ai donc eu accès à l'expérience de Stan Moore dans le labo de Charles Dent, et j'ai pu étudier le métabolisme des acides aminés et approfondir l'idée des transporteurs, qui serait un jour indissociable du laboratoire de Charles Dent. Je pouvais me placer du côté scientifique du clinicien-chercheur en disant à Charles Dent que je ne voulais pas consacrer trop de temps à des tâches cliniques, que je voulais passer plus de temps au labo. J'ai en quelque sorte embrassé la carrière de clinicien-chercheur, ce que j'étais depuis le début, au fond.

Andrew Hoffman : Bon, nous en sommes à la page 7 de la transcription antérieure, et vous dites qu'il n'y a pas grand-chose passé la page 9. Nous en sommes déjà à 50 minutes d'entretien; si vous voulez faire une pause, nous pouvons…

Dr Charles Scriver : Nous sommes sur une belle lancée, non?

Andrew Hoffman : Oui, oui, c'est à vous de décider. De mon côté, ça va. Mais je veux simplement m'assurer que les réponses de cette entrevue vous conviennent mieux que celles de l'entrevue précédente. J'imagine que vous ne le saurez qu'en relisant les transcriptions, et c'est très bien comme ça.

Dr Charles Scriver : Nous avons parlé de ma famille, de l'école, de la médecine arrivée par hasard, de la formation rigoureuse plus poussée dont j'avais besoin, de mon désir ou non de faire de la recherche, de ce que m'ont apporté Ronald Christie, Charles Dent et John Beck, de l'influence qu'Alan Ross a eue sur mon parcours en m'incitant à aller élargir mes horizons à Boston, puis de ces deux rencontres extraordinaires. La première avec cet enfant épileptique et la deuxième avec l'enfant qui présentait une hématurie et était atteint du syndrome d'Alport. Puis de la pensée génétique et des expériences mendéliennes. Et enfin, de l'influence profonde que certains de mes mentors ont eue sur moi, Alan Ross, Harry Harris, Charles Dent.

Andrew Hoffman : Oui, alors je veux simplement faire le point. Je pense qu'il y aurait aussi la biochimie génétique par rapport à la génétique classique, mais ça arrive un peu plus tard, je crois.

Dr Charles Scriver : Oui, lorsqu'on parlera de la mise en commun de tout ça par l'entremise du CRM[1].

[1] Conseil de recherches médicales

Andrew Hoffman : Et le sujet est déjà bien couvert dans la transcription, je pense. Mais je le précise une fois de plus, c'est à vous de décider. J'ai la transcription et la première série de questions qui nous aurait menés à la page 7.

Dr Charles Scriver : Je pense qu'on peut dire sans se tromper que les techniques comme la chromatographie pour l'analyse enzymatique marquent le début d'une époque; à partir de ce moment, il est possible de savoir comment une mutation ou un gène perturbe le métabolisme.

Andrew Hoffman : Et c'est donc le point de rencontre entre la génétique et la chromatographie?

Dr Charles Scriver : C'est exact, la génétique et la biochimie. Donc, Garrod[2] avait parlé des erreurs innées du métabolisme et présenté les *Croonian Lectures* en 1908, mais les gens se sont dit : « C'est bien beau, tout ça, mais qu'est-ce que ça a à voir avec la médecine? ». Ça a pris 50 autres années avant qu'on en sache suffisamment en enzymologie – après tout, les enzymes n'ont fait leur apparition en médecine que dans les années 1930 – pour commencer à rechercher d'éventuelles déficiences enzymatiques à l'origine des erreurs innées du métabolisme que Garrod avait décrites.

En 1958, tout était en place. J'ai rédigé un article pour le *British Medical Bulletin* – après mon retour à McGill – où j'ai illustré à l'aide d'un graphique l'évolution des connaissances sur les erreurs innées du métabolisme – un terme probablement approprié – avec, si possible, des données sur la déficience enzymatique, et c'est une courbe de croissance logarithmique.

Andrew Hoffman : Un peu comme la création du savoir, finalement.

Dr Charles Scriver : Effectivement. L'existence des techniques de recherche a alimenté l'intérêt, éperonné la curiosité du chercheur, si bien que les connaissances se sont accumulées et ont fini par constituer la biochimie génétique humaine. Et Harry Harris est l'un…

Andrew Hoffman : Excusez-moi de vous interrompre, mais vous avez écrit un article sur la croissance de…

Dr Charles Scriver : Oui.

Andrew Hoffman : Vous rappelez-vous en quelle année?

Dr Charles Scriver : Je ne m'en souviens pas. C'était dans le *British Medical Bulletin*, probablement à la fin des années 1960.

Andrew Hoffman : Parce que cet article semble cadrer parfaitement dans ce que nous faisons actuellement, c'est-à-dire raconter l'histoire de ce domaine, visualiser son évolution au fil des ans.

Je ne sais pas si vous êtes au courant de ce travail. Alberto, par exemple, est l'expert de ce genre de graphique qui fait ressortir des grappes à des moments

[2] Archibald Garrod

	donnés, avec certains mots-clés. Ça ressemble énormément à ce que nous faisons.
Dr Charles Scriver :	Pouvons-nous faire un saut en avant et parler de ça maintenant?
Andrew Hoffman :	Bien sûr, si ça vous convient.
Dr Charles Scriver :	J'aimerais simplement donner suite à votre introduction. Comme vous le savez, j'ai été interviewé par l'historien des sciences Nathaniel C. Comfort. À la fin de l'entrevue, qui a duré un après-midi, une journée entière et une matinée, il m'a dit en me montrant un diagramme à flèches : « Voici votre carrière ».
Andrew Hoffman :	Ah oui, j'ai lu ça dans les autres transcriptions.
Dr Charles Scriver :	Inconsciemment, je parlais de diverses facettes de notre travail en génétique et en biochimie génétique; les articles publiés devenaient des points dans un réseau, étaient reliés à des pôles et rendaient compte de nos divers champs d'intérêt. C'était logique de créer un diagramme comme celui-là.
Andrew Hoffman :	Alors, c'est ce que vous faisiez dans les années 1960.
Dr Charles Scriver :	Non, pas dans les années 1960. Ces graphiques sont arrivés assez tard dans le portrait, mais il m'avait demandé de choisir huit à dix publications déterminantes. Je lui ai répondu que je ne pouvais pas faire ça, la publication majeure serait le pôle d'un ensemble de points connectés. Et c'est comme ça qu'est née l'idée du diagramme.
Andrew Hoffman :	Mais cet article que vous avez publié dans le *British Medical Bulletin*…
Dr Charles Scriver :	Serait l'un des premiers et portait sur la prise de conscience et l'évolution du savoir dans le métabolisme des acides aminés, les erreurs innées du métabolisme des acides aminés.
Andrew Hoffman :	C'est donc probablement plus ciblé que ce que vous faisiez, mais je pense que l'idée est exactement la même. Je pourrai vous les montrer plus tard, mais je vous avertis tout de suite, je ne suis pas un expert dans l'interprétation [de ces graphiques]. J'ai dû m'asseoir avec Alberto; il les utilise de temps à autre pour ses propres recherches. J'ai lu de ses articles, mais moi, je n'y vois qu'une série de grappes. Lui, il peut dire voici une grappe, en voici une autre. Mais nous y reviendrons. Maintenant que nous avons parlé…
Dr Charles Scriver :	Je ne vous ai pas raconté dans quelles circonstances je suis revenu à McGill.
Andrew Hoffman :	D'accord, racontez-moi ça. Alors, vous êtes à Londres…
Dr Charles Scriver :	Je suis à Londres et…
Andrew Hoffman :	Vous avez fait de belles découvertes et les avez exposées dans des articles.

Dr Charles Scriver : Et les six mois d'inactivité avaient été trop longs; c'était une merveilleuse période, vraiment palpitante. Je me rends compte que je ne vous ai pas parlé de ma femme. Nous nous sommes rencontrés à l'adolescence. Mon futur beau-père avait refusé de m'accorder la main de sa fille avant la fin de mes études de médecine.

Lorsque nous nous sommes mariés, en 1956, les invités étaient fort nombreux en raison de mes relations professionnelles, et je ne compte plus ceux qui m'ont dit : « J'étais certain que tu ne te marierais jamais. Je suis bien content pour toi! »

Ma femme a côtoyé la recherche universitaire dès l'enfance. Son père était radiologiste-chef à McGill, il avait participé de près à des trucs d'envergure, notamment le *Projet Manhattan*. Ma femme savait d'instinct ce qu'était la vie de chercheur.

En 1959, ou peut-être à la fin de l'hiver ou au début du printemps 1960, il était clair que pour montrer, données à l'appui, que l'injection de proline triplait l'aminoacidurie et valider ainsi mon hypothèse, il fallait que je fasse moi-même une bonne partie des analyses.

J'ai pensé doubler la vitesse recommandée pour les colonnes de Moore et Stein. Stan Moore m'a alors dit : « Tu viens de comprendre pourquoi on a recommandé 8 au lieu de 16 : c'était pour ne pas devoir se lever à 2 heures du matin pour changer le collecteur ». J'en ai donc parlé à ma femme et je lui ai demandé si elle était prête à accepter ça. Elle m'a dit : « Si c'est ce que tu dois faire pour démontrer ton hypothèse, je suis d'accord ».

Andrew Hoffman : Alors, vous avez opté pour la méthode qui exigeait que vous vous leviez à 2 heures du matin?

Dr Charles Scriver : C'est exact. Je lui ai aussi dit qu'en raison du nombre d'échantillons dont j'aurais besoin, nous ne pourrions pas rendre visite à son parrain en Norvège. Elle a soupiré profondément et m'a répondu que si c'était important pour ma carrière, nous pourrions toujours y aller plus tard; nous y sommes allés 20 ans plus tard. Et j'en garde de merveilleux souvenirs.

Toujours est-il que ma femme s'est montrée très compréhensive, et il me paraît fondamental de noter ça au dossier. Quoi qu'il en soit, nous avons fait un tas de choses, et tout ça fait partie des influences qui m'ont façonné.

Andrew Hoffman : Pendant combien de temps avez-vous dû mener cette expérience pour prouver votre hypothèse?

Dr Charles Scriver : J'ai utilisé les six mois dont je disposais pour l'acquisition des données et la rédaction de l'article à soumettre à l'American Society for Clinical Investigation. Alors, quand je suis revenu à Montréal, je pense que quelqu'un avait envoyé une lettre d'Angleterre pour dire que Scriver avait du potentiel.

C'est Alan Ross qui m'a reçu. À ce moment, j'avais décidé d'aller en pédiatrie plutôt qu'en médecine interne. La culture, les comportements et les personnalités me ressemblaient davantage en pédiatrie. John Beck a été déçu,

je crois, mais c'était clair comme de l'eau de roche : c'est la pédiatrie qui m'intéressait.

Et comme les problèmes de métabolisme se manifestent dans les premières années de vie, la voie de la pédiatrie était tout indiquée pour moi. C'est pourquoi biochimie génétique et pédiatrie vont souvent de pair.

On m'a nommé résident en chef en pédiatrie; un grand honneur. Mais je ne me plaisais pas dans ce rôle. Je vivais un conflit d'intérêts perpétuel. Mes fonctions de résident en chef me tenaient très occupé, mais moi, je voulais écrire. Et de fait, nous avons rédigé un article sur l'hyperprolinémie et le système de transport qui a été publié dans *Nature*, ce qui n'est quand même pas mal en début de carrière.

Quoi qu'il en soit, Alan Ross a été d'un grand soutien. Il me regardait et me disait : « Tu as l'air malheureux. Aimerais-tu avoir congé pour aller à Boston finir cet article avec Irwin Shafer et Mary Efron? » J'ai accepté.

Cette décision a donné lieu à un changement intéressant. À McGill, on s'est rendu compte qu'un seul résident en chef, ça ne suffisait pas. Je suis donc à l'origine du jumelage des résidents en chef.

Alan Ross a pensé qu'il serait bien que je sois candidat pour l'obtention d'une bourse Markle, octroyée par la Fondation Markle, qui plus tard allait offrir son soutien à Sesame Street. Cette bourse était la plus prestigieuse dans le monde universitaire. Je me suis donc retrouvé en lice pour une des 25 bourses versées à des médecins de partout en Amérique du Nord. La chance et ma bonne étoile m'ont permis d'en décrocher une. La Fondation espérait que je devienne directeur de département ou doyen. Les Markle voulaient couvrir l'Amérique du Nord de boursiers assis dans une chaise de doyen ou de directeur de département. Mais moi, ça ne m'intéressait pas. Je voulais continuer à faire ce que je faisais.

Andrew Hoffman : Cette bourse était-elle liée à un projet de recherche en particulier ou simplement à votre travail de chercheur en général?

Dr Charles Scriver : À mon travail de chercheur en général, à mes réalisations, etc. J'ai probablement déçu les Markle en ne devenant ni doyen, ni directeur; et si ça ne s'est pas produit, c'est parce que j'ai refusé les propositions en ce sens.

Mais Alan Ross était tout simplement brillant. Il a dit : « Maintenant que tu as ta bourse Markle, j'ai le devoir de te protéger pour que tu puisses l'utiliser à bon escient. Il a pris des mesures et des décisions cruciales comme chef de la pédiatrie, et ça m'a permis de poursuivre mes travaux. Au terme des cinq années de la bourse, j'avais une liste de publications très convaincante, et ma réputation de spécialiste en biochimie génétique humaine se bâtissait peu à peu. Je n'aurais pas pu y arriver sans la bourse Markle et sans Alan Ross, qui créait une zone tampon entre mes collègues et moi.

À un moment donné, on m'a dit que je devais faire de l'urgence comme tout le monde. J'ai dit à Alan Ross que j'étais disposé à le faire dans la mesure où les autres étaient disposés à venir me remplacer au labo, puisque je travaillais là

jour et nuit. Il a bien aimé ma réponse. Il en a parlé au groupe, puis est revenu me dire qu'apparemment, personne n'avait envie de venir me relever au labo. Ça réglait le problème.

Andrew Hoffman : Si je comprends bien, on n'était pas dans une logique d'enrichissement mutuel des compétences.

Dr Charles Scriver : Non, pas vraiment. Mais j'avais la chance d'avoir des collègues en or, qui semblaient comprendre ce que j'essayais de faire. Ils ne me faisaient pas la vie dure.

Andrew Hoffman : Dites-moi, quel poste Alan Ross occupait-il?

Dr Charles Scriver : Il était médecin-chef de l'hôpital et directeur de la pédiatrie à McGill, du volet recherche.

Andrew Hoffman : Ah, alors lorsqu'il parlait, on l'écoutait.

Dr Charles Scriver : Oui, exactement.

Andrew Hoffman : J'imagine que c'est bien d'avoir l'appui d'une personne comme lui quand on cherche à accomplir quelque chose.

Dr Charles Scriver : Exact. C'était un formidable mentor.

Andrew Hoffman : Donc vous êtes retourné à Boston et avez écrit cet article?

Dr Charles Scriver : J'y allais la fin de semaine pour la rédaction de l'article. Puis nous l'avons présenté, l'un à *Nature* et l'autre… l'autre était une description de cette famille porteuse du syndrome d'Alport, de l'hyperprolinémie et des deux troubles mendéliens, et cet article a été publié dans le *New England Journal of Medicine*.

Andrew Hoffman : Les deux articles portaient donc sur le cas de Francis?

Dr Charles Scriver : Oui.

Andrew Hoffman : Nous en sommes maintenant à votre relation avec Clarke Fraser. Je ne sais pas si vous souhaitez que nous en parlions.

Dr Charles Scriver : Oui, bien sûr.

Andrew Hoffman : C'est à vous de décider. Si les propos déjà recueillis vous suffisent, nous pouvons nous en tenir à ça.

Dr Charles Scriver : Je pense qu'il serait bien d'ajouter quelques précisions sur les débuts de cette relation. Lorsque je suis revenu à l'Hôpital pour enfants, tout le monde savait que la génétique m'intéressait. Clarke Fraser – que vous avez interviewé et qui, comme vous le savez, a créé une clinique de génétique à l'Hôpital de Montréal pour enfants, l'une des premières au pays – était reconnu comme un spécialiste en génétique médicale extraordinairement brillant, qui faisait avancer cette science et publiait beaucoup.

Les gens s'attendaient à ce que nous ne puissions pas travailler ensemble en raison de la compétition entre nous deux, mais ils avaient complètement tort. Nous adorions travailler ensemble. Ça allait tout seul, chacun se mêlait de ses affaires, et dans notre cas, le tout était vraiment supérieur à la somme des parties.

Andrew Hoffman : Pourquoi les gens avaient-ils cette impression?

Dr Charles Scriver : Parce que nous avions chacun une personnalité affirmée.

Andrew Hoffman : Vous aviez chacun vos façons de faire et y teniez mordicus… ou encore c'est comme ça que les gens vous percevaient?

Dr Charles Scriver : Ils se disaient que nous serions trop absorbés par nos propres travaux pour nous soucier de ce que l'autre faisait.

Andrew Hoffman : D'accord.

Dr Charles Scriver : Nous mettions sur pied un laboratoire de biochimie génétique humaine, et Clarke Fraser s'occupait de son programme de génétique médicale. Et à un moment donné, nous nous sommes rendu compte que nous avions le vent en poupe. Vous savez peut-être que McGill rend hommage au groupe. Le bruit courait que les cours de Fraser et de Scriver, c'était quelque chose. Personne ne voulait manquer ça; je vous le dis, la salle était tellement bondée que des gens s'assoyaient par terre pour laisser de la place aux autres.

Andrew Hoffman : C'était le cours sur la génétique humaine que vous donniez à la Faculté de médecine?

Dr Charles Scriver : Non, c'était à l'hôpital.

Andrew Hoffman : Ah, d'accord.

Dr Charles Scriver : C'était un genre de tournée, de tournée supplémentaire. Quelque chose de spontané qui a drôlement bien fonctionné.

Andrew Hoffman : Je vois.

Dr Charles Scriver : Ce sont des choses comme celles-là qui nous ont fait penser que nous devrions peut-être donner suite à l'invitation du Conseil de recherches médicales du Canada, qui souhaitait constituer des groupes aux intérêts communs. Nous avons donc soumis une demande en génétique médicale, qui englobait la biochimie génétique; à ce qu'on m'a dit, il y avait cinq demandes, je crois, et c'est la nôtre qui a été retenue. Les examinateurs du CRM nous ont dit que nos assises scientifiques solides avaient joué en notre faveur. Clarke s'intéressait à la tératologie, aux causes des malformations et des anomalies du développement, et faisait un travail formidable; quant à moi, je m'occupais de la biochimie génétique. Cet arrangement a été considéré comme acceptable.

L'une des choses que nous avons mises en place dans les années 1960 – voici encore une rétrospective. J'avais élaboré, avec la chromatographie, plusieurs

petites techniques qui nous ont permis de réaliser une étude chez 40 000 familles par dépistage chez les nouveau-nés. Nous voulions mettre au jour des erreurs innées du métabolisme avec cette nouvelle méthode et détecter ainsi une panoplie de troubles présents dans la population.

Et parce que nous croyions que le dépistage rapide pouvait ouvrir la porte au traitement, nous avons établi le Réseau de génétique médicale du Québec avec l'appui de Claude Castonguay, alors ministre de la Santé. À cette fin, nous avions aménagé une voie d'accès clinique qui se rapprochait beaucoup du régime de santé public. Les examinateurs du CRM ont vu là un élément qui distinguait notre demande de celle des autres. La personne qui avait rendu possible cet accès clinique – c'est d'ailleurs déjà dans votre transcription – est Carol Clow, une collègue qui a fait un tas de trucs intéressants.

Nous étions donc à moitié en régime public, nous faisions du dépistage, outil de première importance en génétique moderne. C'est…

Andrew Hoffman : Parlons-nous ici du test que vous avez mis au point?

Dr Charles Scriver : Oui.

Andrew Hoffman : De quoi s'agissait-il exactement?

Dr Charles Scriver : D'un test qui, grâce à la chromatographie, permettait de détecter les perturbations du métabolisme d'acides aminés pris individuellement.

Andrew Hoffman : À partir d'un échantillon d'urine?

Dr Charles Scriver : Oui.

Andrew Hoffman : Je vois.

Dr Charles Scriver : Et on prélevait beaucoup d'échantillons de sang. En fait, il y avait l'échantillon d'urine, mais aussi l'échantillon de sang prélevé chez le bébé avant sa sortie de l'hôpital.

Andrew Hoffman : Il semble donc que votre groupe se soit distingué grâce à cette voie d'accès clinique? Ça cadrait bien avec le reste de votre travail. Vous avez mentionné Carol Clow. Il y a une chose qui m'a frappé dans votre entrevue et dans d'autres lectures que j'ai faites à propos du groupe. Je m'écarte sans doute un peu du sujet et je m'en excuse, mais je trouve curieux qu'elle n'ait, semble-t-il, aucune formation scientifique en bonne et due forme.

Dr Charles Scriver : C'est vrai.

Andrew Hoffman : Mais elle n'était pas la seule qui s'acquittait de fonctions scientifiques dans votre groupe sans avoir de formation en sciences à proprement parler. Je ne sais pas si vous avez envie d'entrer dans les détails, mais il me semble curieux que ce groupe ait compté parmi ses membres des gens n'ayant pas de formation en sciences. Rappelons que c'est le groupe dont le financement

aurait été reconduit le plus longtemps dans l'histoire récente du CRM/IRSC[3] – il vient tout juste d'être démantelé, en 2009.

Dr Charles Scriver : Eh bien, je répondrai à cela en vous parlant de nous, mais aussi de McGill. Ce sont probablement mes parents qui m'ont appris que l'essence d'une personne était plus importante que ses diplômes. Mon amitié avec Carol Clow remontait au temps du Lower Canada College. J'ai également eu affaire à elle pour des raisons médicales pendant mes stages et ma résidence; par la suite, elle a vécu une tragédie : elle a perdu un enfant, un nourrisson mort subitement.

Il se trouve que ma mère était sur les lieux à ce moment-là pour accompagner Carol, et elle lui a donné, semble-t-il, de précieux conseils. Quelques mois plus tard, nous avons demandé à Carol si elle était disposée à venir nous prêter main-forte. Elle nous a dit que, oui, elle aimerait bien faire ça. Sa formation n'avait aucune importance à mes yeux.

Andrew Hoffman : Vous dites que vous avez eu affaire à elle pour des raisons médicales…

Dr Charles Scriver : Oh, un autre de ses enfants avait souffert de leucémie.

Andrew Hoffman : Ah, je vois.

Dr Charles Scriver : Et ma mère était chef de service pendant l'hospitalisation de l'enfant; c'est comme ça que j'ai appris sa mort. Carol est une femme intelligente qui n'a pas peur du travail. Elle et moi, ainsi qu'une ou deux autres personnes au labo, avons mené cette étude sur 40 000 familles pour déterminer si le dépistage néonatal pouvait permettre, par un diagnostic précoce et des interventions adéquates, de prévenir la maladie.

Évidemment, lorsque le dépistage sanguin révélait un problème, elle était très bien placée pour parler à la mère et calmer ses angoisses. Je lui ai confié ce travail en me disant que si je le faisais moi-même, je n'aurais plus beaucoup de temps pour la biochimie génétique. J'ai donc demandé à Carol si elle voulait parler aux mères. Elle m'a dit : « Oui, et je leur exposerai les faits, notamment lorsque je me sentirai dépassée ».

Nous venions donc d'ajouter la consultation génétique personnalisée et le volet « santé publique » aux activités du groupe.

Cette série d'événements a fait de Carol Clow l'instigatrice de la consultation génétique à McGill; elle a jeté les bases d'un nouveau programme, différent de celui de Clarke Fraser. C'est en grande partie grâce à Leonard Pinsky si la consultation génétique est devenue une matière académique en bonne et due forme à McGill. McGill a reconnu la valeur du travail de Carol et l'a promue au rang de professeure agrégée, alors qu'elle n'avait aucun des diplômes normalement exigés pour un poste comme celui-là.

Andrew Hoffman : Avait-elle un baccalauréat?

[3] Conseil de recherches médicales/Instituts de recherche en santé du Canada

Dr Charles Scriver : Non. Je pense qu'elle n'avait même pas d'attestation d'études secondaires, puisqu'elle avait dû couper court à ses études pendant la guerre en raison de difficultés familiales; c'est une femme remarquable qui a laissé sa marque.

Andrew Hoffman : C'était donc l'un des nouveaux programmes de consultation génétique issus du programme de dépistage en biochimie génétique?

Dr Charles Scriver : Au Canada, oui.

Andrew Hoffman : Oui. Et a-t-elle… J'imagine que je pourrais la trouver. Je ne pense pas que Christopher l'ai contactée au cours des…

Dr Charles Scriver : Je ne pense pas.

Andrew Hoffman : Je vais vérifier.

Dr Charles Scriver : Ce serait vraiment bien de l'interviewer.

Andrew Hoffman : Effectivement, ce serait bien de raconter l'histoire d'une femme qui, sans même avoir terminé son cours secondaire, a mis en place les services de consultation génétique au Canada. C'est pour le moins remarquable. Et, bien entendu, il y avait aussi tout un réseau autour de ça.

Si vous voulez bien me transmettre ses coordonnées, je verrai ce que je peux faire. Je ne sais pas si ça cadre dans notre budget; ces décisions ne relèvent pas de moi.

Dr Charles Scriver : Chose certaine, je vous recommande fortement de l'interviewer, parce que c'est notamment grâce à elle que nous avons gagné le concours.

Andrew Hoffman : Oui. Non, je sais. À vous écouter parler – et corrigez-moi si je me trompe – je comprends qu'elle était le visage de votre travail, puisque c'est elle qui communiquait avec les gens qui acceptaient de passer des tests ou d'en faire passer à leurs enfants.

Et probablement qu'à un moment donné… avez-vous publicisé le programme de dépistage après sa mise en place? Par exemple, nous vous proposons un test et du soutien, ou était-ce quelque chose qui arrivait après coup, après un examen de routine?

Dr Charles Scriver : Eh bien, en fait, je pense qu'on peut dire sans se tromper que nous n'aurions pas mis en place le Réseau de génétique médicale du Québec si nous n'avions pas eu la capacité d'interpréter les tests positifs et d'y donner suite par des services-conseils, puis par des traitements lorsque ces traitements étaient disponibles. Pour ça, nous avions besoin de gens comme elle. Elle a été un véritable modèle.

Andrew Hoffman : Je compte sur vous pour me fournir ses coordonnées, et c'est certain que je vais en parler au reste de l'équipe. Bon, nous sommes à peu près à mi-chemin dans… oui, nous devons être rendus à la page 11 à peu près.

J'ai quelques autres questions liées au contenu de la transcription. L'une a trait aux rapports du groupe avec Peter Hechtman et l'autre, aux problèmes de locaux, dont il a été question dans une lettre de 1988, puis brièvement ici. Mais ça me paraît important.

Dr Charles Scriver : Ça l'était.

Andrew Hoffman : Peut-être pourrions-nous approfondir un peu le sujet? Le groupe a été fondé en 1972. Et les deux noms qui figuraient sur la demande étaient le vôtre et celui du Dr Fraser.

Dr Charles Scriver : C'est exact, et nos collègues étaient Peter Hechtman et Renny Gold.

Andrew Hoffman : Gold, oui. Et donc…

Dr Charles Scriver : Et un peu plus tard, il y a eu David.

Andrew Hoffman : Oui. Mais pas au tout début.

Dr Charles Scriver : Parce qu'il était à l'étranger pour parfaire sa formation.

Andrew Hoffman : Oui, on attendait son retour. Ce sont les assises du groupe, et la subvention de cinq ans vous a menés à 1977.

Dr Charles Scriver : Oui. À l'époque, ces subventions de cinq ans étaient de l'or en barre, parce que vous n'aviez pas à entreprendre la rédaction d'un rapport d'étape immédiatement, à un moment où vous n'aviez somme toute pas grand-chose à dire.

Andrew Hoffman : Oui, bien entendu. Donc Peter Hechtman faisait partie du groupe au tout début. Dans votre première entrevue avec Christopher Canning, vous avez dit : « Il n'avait pas grand-chose, mais il posait de bonnes questions et faisait des choses intéressantes ».

En fouillant dans les archives, je suis tombé sur la réponse du CRM en 1977, et j'ai constaté que la productivité de Peter Hechtman pendant les cinq années précédentes préoccupait le Conseil. Je suis curieux de savoir… comme vous l'avez dit, une subvention de cinq ans, c'était de l'or en barre à l'époque, et j'imagine que les membres du groupe y tenaient comme à la prunelle de leurs yeux.

Je ne sais pas si vous pouvez vous rappeler cela, mais il me semble que ce genre de réponse – le fait qu'une personne avec laquelle vous avez collaboré plus ou moins étroitement ne soit plus considérée comme un membre du groupe par les personnes qui vous financent – ça doit changer la dynamique dans un groupe, non?

Dr Charles Scriver : Oui, je ne me rappelle pas s'il a entrepris avec nous la période de cinq ans suivante. Était-il là?

Andrew Hoffman : Je sais qu'il a fait partie du groupe plus tard. J'ignore s'il était là pour la deuxième période quinquennale, mais je sais qu'il a été là plus tard.

Dr Charles Scriver : Oui. Selon moi, il n'aurait pas été là plus tard s'il n'avait pas réussi à sortir de cette mauvaise passe. Par la suite, il a fait des choses pas mal intéressantes.

Andrew Hoffman : C'est ce que j'ai trouvé particulier. Il faisait partie du groupe au départ, il y a eu une sorte de rejet, puis il est revenu. Oui, c'est bien particulier.

Le dernier point dont j'aimerais parler est l'histoire de la lettre sur le problème de locaux et l'avenir du groupe. Je pense que le Dr Rosenblatt vous en a remis une copie avant votre entrevue avec Christopher Canning, à moins que vous ayez déjà eu un exemplaire de cette lettre, envoyée à bon nombre de vos collègues. Vous souvenez-vous de cette lettre?

Dr Charles Scriver : Je me rappelle du jour où Malcolm Brown est venu à McGill pour officialiser la création du groupe de génétique médicale du Conseil de recherches médicales. Ses conditions étaient les suivantes : nous ne verserons pas un sou à McGill tant que vous n'aurez pas de locaux dignes de ce nom où travailler.

Ses propos ont déclenché une véritable tornade au septième étage de l'Hôpital de Montréal pour enfants, qui servait alors d'entrepôt. Nous avons travaillé avec une firme d'architectes et avec une personne en particulier, Jim Malling. Ici encore, l'approche collaborative était de mise. Chaque jour, les principaux intéressés pouvaient donner leur avis sur l'utilisation optimale des locaux. Nous avons produit des plans d'aménagement pour cette zone de travail de 5 000 pieds. On connaît la suite; ces locaux nous ont servis pendant 25 ans.

Andrew Hoffman : Mais l'intégration ou l'existence du groupe de génétique médicale dans l'hôpital pour adultes également posait problème, il me semble…

Dr Charles Scriver : En fait, nos affaires marchaient rondement, à un point tel que les activités du groupe ont débordé le cadre de l'Hôpital pour enfants et de la recherche en pédiatrie. Et nous voulions que la génétique trouve sa place dans d'autres sphères des soins médicaux, de la formation en médecine et de la recherche. Et donc l'une des choses qu'a faites David Rosenblatt a été de militer pour l'aménagement de locaux de recherche à l'Hôpital Royal Victoria. Et ensuite, si je me souviens bien, nous avons voulu faire de même à l'Hôpital général de Montréal. Les rapports avec l'Hôpital général juif n'étaient pas évidents à l'époque. L'établissement voulait protéger son identité et ne voulait pas qu'on marche sur ses plates-bandes (du moins, c'est comme ça que je voyais les choses). Mais ce n'est plus comme ça aujourd'hui; l'hôpital recrute de nouveau à McGill, comme en témoigne l'embauche d'un de nos diplômés, Rod McInnes. Et il y a aujourd'hui une belle collaboration entre l'Hôpital général juif et McGill en génétique. Est-ce que ça répond à votre question?

Andrew Hoffman : Comme vous l'avez dit, les choses semblaient en voie de s'améliorer, mais le ton de votre lettre m'a semblé plutôt austère et j'y ai perçu une certaine inquiétude. C'était comme une lame à deux tranchants. La génétique gagnait en importance et les programmes se multipliaient dans d'autres services tout comme dans des établissements autres que l'Hôpital pour enfants, et ça, c'était une bonne chose. D'un autre côté, la source de financement risquait de se tarir en raison des modalités d'octroi, qui reposaient sur l'emplacement du groupe…

Dr Charles Scriver : Rafraîchissez-moi la mémoire, était-ce avant le Département de génétique humaine?

Andrew Hoffman : Le Département?

Dr Charles Scriver : Je veux dire quelqu'un dans les principaux…

Andrew Hoffman : La lettre date de 1988. Donc ce serait avant.

Dr Charles Scriver : Oui, fort probablement. L'inquiétude venait sûrement du fait qu'il fallait un point de référence en recherche, notamment pour assurer la cohérence des travaux; par contre, nous voulions que la génétique trouve sa place dans d'autres domaines, par exemple les soins aux adultes, l'obstétrique, etc. Alors, peut-être y avait-il apparence de conflit d'intérêts ou de tensions entre divers axes d'action, mais nous avons trouvé un *modus vivendi*, je crois. Je me souviens avoir débattu de la chose avec David Rosenblatt, qui se tirait fort bien d'affaire, et d'avoir plaidé pour qu'il y ait non seulement le Centre de génétique médicale – dont Leonard Pinsky était responsable – mais aussi le Département de génétique humaine. Je pense que nous avons réglé le gros du problème en optant pour cette solution.

Andrew Hoffman : Et j'ai l'impression que le financement a probablement évolué de façon parallèle, comme le concevait l'organisme subventionnaire… puisque le Département lui-même n'a jamais été financé par…

Dr Charles Scriver : C'est exact.

Andrew Hoffman : Par le groupe, le CRM ou les IRSC.

Dr Charles Scriver : Non, non, il était financé…

Andrew Hoffman : C'était le groupe lui-même.

Dr Charles Scriver : Oui. Et je tiens à souligner que le CRM ne s'intéressait pas uniquement à notre recherche, mais aussi à nos autres activités. « Parlez-nous de vos activités d'enseignement, des interactions avec vos étudiants. Comment vous perçoivent-ils? » Et donc Arno Motulsky, un grand nom en recherche, nous a dit : « Ce n'est pas à vous que je veux parler, messieurs, mais à vos étudiants. Je veux savoir ce qu'ils pensent de votre travail et s'ils estiment que ça fonctionne. »

Nous avons dû nous asseoir à côté de la porte et attendre dans une salle vide pendant qu'Arno et ses intervieweurs parlaient aux étudiants. L'information était conforme à leurs attentes et compatible – je ne sais pas si c'est avant ou après la création du Département – mais toujours est-il que c'était compatible avec un phénotype cohérent de ce que nous appelions le « groupe du CRM », qui était en fait un épicentre de formation et d'enseignement.

Andrew Hoffman : Alors, vous avez pu intégrer à tout ça des subventions de formation?

Dr Charles Scriver : Oui et ça aussi, c'était formidable. Grâce à ces subventions, le CRM nous a permis de recruter de très bons étudiants.

Andrew Hoffman : Et les bons commentaires de vos étudiants n'étaient pas étrangers à ça, j'imagine?

Dr Charles Scriver : Oui, et nous ne les avons pas payés!

Andrew Hoffman : Tant mieux s'il n'y avait aucun conflit d'intérêts. Nous en sommes donc à une heure et demie. Je pense bien avoir assez de matériel.

Dr Charles Scriver : Vous avez tout ce qu'il vous faut?

Andrew Hoffman : Je pense oui. Merci!

FIN DE L'ENTRETIEN

Reynold Gold, le 13 juillet 2010

Christopher Canning : Ici Christopher Canning en compagnie de Reynold Gold. Nous sommes le 13 juillet 2010. C'est un privilège pour moi de pouvoir m'entretenir avec vous de deux grands sujets portant sur la génétique humaine.

J'aimerais que nous abordions d'abord votre parcours universitaire, qui vous a permis de contribuer grandement à l'avancement de la génétique médicale au Canada et ailleurs dans le monde. Ensuite, et c'est le principal thème de l'étude, j'aimerais parler de votre participation au groupe de génétique médicale des IRSC[1] – anciennement le CRM[2] – auquel vous vous êtes joint au moment de sa formation en 1972 et dont vous êtes resté membre jusqu'en 1977, si je ne m'abuse.

Pour commencer, parlons un peu de vous, si vous le voulez bien. Pouvez-vous nous parler de votre lieu de naissance et de votre enfance?

Reynold Gold : Je suis né en Angleterre et j'ai obtenu un diplôme en sciences naturelles, qu'on appelle *Natural Sciences Tripos*, du Trinity College de l'Université de Cambridge. J'étais boursier du Trinity College, où j'ai fait mes études en sciences naturelles. J'ai obtenu un B.A. parce que le diplôme en sciences n'existe pas encore officiellement à Cambridge et que même les scientifiques reçoivent des diplômes en arts. J'ai ensuite obtenu un diplôme d'études supérieures en biochimie, dans le cadre du *Natural Sciences Tripos*, puis un diplôme en médecine, qui n'est pas l'équivalent d'un doctorat en médecine en Angleterre, mais qui m'autorise à pratiquer la médecine. Il s'agit en fait d'un baccalauréat en médecine et d'un baccalauréat en chirurgie.

J'ai finalement obtenu mon doctorat en génétique à McGill, juste avant de me joindre au groupe du CRM. Voilà en gros ma formation.

Christopher Canning : Où avez-vous passé votre enfance? Combien de temps êtes-vous resté au Royaume-Uni?

Reynold Gold : Je suis resté en Angleterre jusqu'à l'âge de 30 ans, et je suis arrivé au Canada en tant que briseur de grève.

Christopher Canning : Je crois que c'est pour cette raison que vous vous êtes rendu en Saskatchewan.

Reynold Gold : Exact.

Christopher Canning : Pouvez-vous nous parler de votre vie familiale? Avez-vous des frères et sœurs?

Reynold Gold : Je suis enfant unique. Mon père était fonctionnaire et il travaillait en contre-ingérence au sein du MI5 en Angleterre. Ma mère était femme au foyer. Elle était originaire d'Allemagne et issue d'une famille juive allemande qui possédait

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

une grosse entreprise d'articles en papier qui a été confisquée par Hitler. Ma mère a déménagé en Angleterre et a épousé mon père à la fin de la Première Guerre mondiale. Mon père faisait partie des troupes d'occupation. Ma grand-mère, elle, est arrivée en tant que réfugiée en 1939, juste avant le début de la guerre.

Donc, mon père était juif anglais et ma mère, juive allemande.

Christopher Canning : Quelle influence vos parents ont-ils eue sur vos études à partir de votre premier B.A. en sciences?

Reynold Gold : Ils m'ont toujours dit que mes études devaient être ma priorité. Ils ont eu une grande influence sur ma réussite intellectuelle. Plus tard, je me suis chicané avec mon père et il m'a coupé les vivres. Le Trinity College n'a pas pu me donner une bourse, parce que mon père faisait un bon salaire, mais il m'a accordé un prêt. J'ai donc pu poursuivre mes études grâce à ce prêt, que j'ai fini par rembourser, alors les choses se sont réglées.

Malgré tout, ma mère et mon père ont toujours insisté sur l'importance de la réussite intellectuelle. Je crois que c'est typique de bon nombre de familles juives de classe moyenne.

Christopher Canning : Revenons un peu en arrière avant de reparler de vos études supérieures. Quel genre d'élève étiez-vous, disons à la fin du primaire ou au secondaire?

Reynold Gold : J'ai fréquenté l'un de ces terribles pensionnats britanniques, et je détestais l'athlétisme. Pendant huit ans, j'ai dû m'astreindre à la pratique de sports qui ne me disaient rien qui vaille, mais dans l'ensemble, je réussissais bien à l'école, surtout dans les matières que j'aimais. Et j'ai fini par obtenir une bourse au Trinity College de l'Université de Cambridge, où les bourses sont très convoitées. Il y a 150 bourses pour environ 3 000 nouveaux étudiants. Seulement 5 % des nouveaux obtiennent une bourse. Je m'en suis donc plutôt bien tiré.

Christopher Canning : Pouvez-vous expliquer de quel type de bourse il s'agissait?

Reynold Gold : Il y avait une partie monétaire. Cette bourse me donnait 60 livres par année, croyez-le ou non. Il s'agit principalement d'un honneur puisque la somme attribuée était plutôt symbolique. C'est une reconnaissance que toutes les personnes au pays peuvent tenter d'obtenir. La concurrence était donc féroce pour cette bourse très convoitée.

Christopher Canning : Lorsque vous avez obtenu la bourse, saviez-vous déjà que vous alliez étudier à Cambridge ou bien avez-vous choisi cette université après avoir obtenu la bourse?

Reynold Gold : C'est la bourse qui a dicté mon choix. Je savais que j'irais à l'université, mais je voulais aller à Cambridge en raison de sa réputation. J'ai obtenu la bourse et j'y suis allé.

Christopher Canning : Étiez-vous au courant des recherches en génétique qui se faisaient à Cambridge à cette époque?

Reynold Gold : Non, mais j'étais à Cambridge lorsqu'on a découvert la structure de l'ADN.

Christopher Canning : Lorsque Watson et Crick…

Reynold Gold : Je n'étais absolument pas au courant de tout ça. C'est venu plus tard. Mais je connaissais Fisher, le grand statisticien spécialisé en génétique. J'avais déjà pris le thé avec lui, mais je n'étais pas au courant de ces travaux alors tout récents lorsque j'étais à Cambridge.

Christopher Canning : Lorsque vous avez commencé votre B.A. en sciences, aviez-vous déjà un intérêt pour la génétique ou juste pour la science en général?

Reynold Gold : Je m'intéressais à la génétique en raison du livre « *The Science of Life* » de Wells, Huxley et Wells, que j'avais lu quand j'étais plus jeune et qui m'avait beaucoup marqué. Ce livre donne beaucoup de détails sur la génétique, comme les découvertes de Mendel et les travaux de Morgan. La génétique m'intéressait beaucoup, mais bizarrement, je n'ai connu la structure de l'ADN et son fonctionnement que plus tard. J'avais un bon ami, Ian Shine, qui était également étudiant. Il a étudié en médecine avec moi à Cambridge, puis il est devenu médecin à Sainte-Hélène, où il a fait une étude auprès de cette population insulaire. C'était un contexte parfait pour des recherches en génétique, et il a commencé à étudier les maladies rares qu'on retrouvait sur l'île Sainte-Hélène. Au début de ma carrière, j'ai été médecin à bord d'un navire et je me suis rendu sur l'île. J'ai pu consulter ses travaux et je l'ai aidé à rédiger son livre sur la génétique de la population de Sainte-Hélène. Cette expérience a renforcé mon intérêt pour la génétique.

Christopher Canning : Quelles maladies étudiait-il à l'époque? Il s'agissait des premiers travaux en génétique des populations, n'est-ce pas?

Reynold Gold : Dans certains cas, il s'agissait de maladies courantes, mais comme on peut s'en douter, il y avait plusieurs maladies qu'on ne retrouvait qu'à Sainte-Hélène, comme des formes particulières de déficience intellectuelle et de nanisme. Je ne me souviens plus de tous les détails, ça fait longtemps que je n'ai pas consulté le livre auquel j'ai participé, mais j'étais vraiment fasciné par les recherches de mon ami. Il n'avait aucune formation en sciences, mais il avait un excellent sens de l'observation. Il avait des qualités innées d'observateur et il a fait une très très bonne étude génétique de la population de l'île. Comme je l'ai dit, je l'ai aidé à rédiger son ouvrage. Je n'étais pas du tout coauteur, mais Ian Shine a mentionné ma contribution.

Christopher Canning : Quel âge aviez-vous lorsque vous étiez sur ce navire?

Reynold Gold : J'étais médecin de bord dans un paquebot de ligne. J'ai fait ça pendant environ deux ans.

Christopher Canning : Comme un paquebot de croisière?

Reynold Gold : Pas exactement, les passagers n'étaient pas en croisière.

Christopher Canning : C'était un moyen de transport, bien entendu.

Reynold Gold : À cette époque, comme vous le savez sûrement, les gens prenaient le bateau comme on prend l'avion aujourd'hui; pas parce qu'ils voulaient jouer au bridge ou prendre des vacances, mais parce qu'ils voulaient se rendre quelque part. C'était donc un paquebot de ligne. Et les paquebots de croisière n'existaient pas vraiment dans ce temps-là.

J'ai donc été médecin de bord pendant deux ans pour l'Union-Castle Line, qui n'existe plus, mais dont l'activité principale était la livraison de courrier vers l'Afrique du Sud et le déplacement de fonctionnaires de l'Angleterre vers leur poste en Afrique du Sud et d'autres endroits en Afrique. C'est lors d'un de ces voyages que j'ai rendu visite à mon ami à Sainte-Hélène.

Ce sont toutes ces expériences qui ont nourri mon intérêt pour la génétique, plutôt que la découverte de la structure de l'ADN, qui a pourtant eu lieu pendant que je me trouvais à Cambridge.

Christopher Canning : Vous vous trouviez si près de là où la découverte s'est produite.

Reynold Gold : Oui, et la génétique m'intéressait en raison de son pouvoir parce que je me rendais compte qu'il s'agissait de la théorie atomique de la biologie, même si je n'étais pas au courant de la découverte de la structure de l'ADN.

Et pour vraiment connaître la biologie, il fallait étudier la génétique. C'était comme la physique des particules. C'était la physique des particules pour la biologie.

Christopher Canning : Il s'agissait des balbutiements de la physique en biologie?

Reynold Gold : Oui, en effet. Avec Delbrück, par exemple.

Christopher Canning : Donc, vous avez obtenu votre diplôme de médecine en 1958, c'est bien ça?

Reynold Gold : Oui.

Christopher Canning : Qui ne correspond pas exactement à un diplôme en médecine au Canada.

Reynold Gold : En fait, ce diplôme m'autorisait à pratiquer la médecine; c'est donc l'équivalent britannique d'un MD. D'ailleurs, aujourd'hui, je dis que je suis MD parce que lorsque je suis arrivé en Saskatchewan, j'indiquais clairement M.B.B. Chir. dans ma signature et tout le monde croyait que j'étais chiropraticien. J'ai donc remplacé mon titre par MD, ce qui est probablement l'un des rares cas de fraude commise par souci de clarté. [rires]

Je dis donc que je suis MD, même si ce n'est pas le cas, parce que j'ai le droit de pratiquer. J'ai l'équivalent britannique d'un MD. En réalité, il existe un MD britannique, mais il s'agit d'un doctorat en médecine. C'est un Ph. D.

Christopher Canning : Ce doctorat vous autoriserait à pratiquer?

Reynold Gold : Non, puisqu'il s'agit d'un doctorat (Ph. D.).

Christopher Canning : Lorsque vous avez obtenu votre diplôme en médecine, quel était votre domaine de spécialisation? La pédiatrie?

Reynold Gold : J'ai fait la formation en rotation habituelle, que l'on appelle *internship* en Angleterre. J'ai été résident en oto-rhino-laryngologie et en chirurgie générale pendant un an, puis j'ai fait un peu d'anesthésie. J'ai ensuite été médecin de bord. J'ai beaucoup aimé cet emploi, mais je n'ai jamais pensé en faire une carrière. C'était un emploi très plaisant pour un jeune homme pour une année ou deux, et j'ai acquis une bonne expérience médicale. Le médecin de bord n'a pas toujours bonne réputation. Pourtant, il doit accomplir beaucoup d'actes médicaux parce qu'il fournit des services à 500 membres d'équipage et 800 passagers. Quand vous devez prendre soin de 1 300 personnes, en haute mer, et que vous êtes le seul médecin, vous devez accomplir de vrais actes médicaux.

Christopher Canning : Vous étiez le seul médecin pour 1 300 personnes?

Reynold Gold : Sauf si l'un des passagers était médecin, oui, j'étais seul, avec une infirmière et un assistant médical. C'était tout.

Christopher Canning : Je crois que vous avez ensuite passé cinq ou six ans au Royaume-Uni avant de venir au Canada. C'est bien ça?

Reynold Gold : En fait, j'ai obtenu mon diplôme de Cambridge en 1958, et je suis arrivé au Canada en 1962, pendant la grève des médecins.

Christopher Canning : D'accord, nous y reviendrons. Avant que nous parlions de votre intérêt pour la génétique, pourriez-vous me dire si la génétique faisait partie de votre formation en médecine à l'époque? Étiez-vous intéressé par la génétique et la médecine?

Reynold Gold : Pendant ma formation en médecine, je n'ai pratiquement pas abordé la génétique. En fait, j'ai donné des cours en génétique médicale, surtout à des étudiants en médecine. Je leur ai enseigné plus de notions en génétique qu'ils en demandaient. Je commençais mon cours en disant : « Je suis censé vous dire qu'une compréhension approfondie de la génétique est essentielle à la pratique de la médecine, mais vous êtes beaucoup trop intelligents pour croire ça. »

Je poursuivais en disant aux étudiants : « Je ne vais donc pas vous dire ça, mais je vais vous dire qu'au cours de votre vie, la génétique révolutionnera la pratique de la médecine. » En passant, cette révolution n'a pas encore eu lieu, mais ça viendra dans les 20 ou 25 prochaines années. Je leur disais aussi : « Vous coûtez très cher, alors vous ne pouvez pas échouer. Seule une ignorance crasse vous fera échouer. La génétique est un sujet très intéressant, profitez-en. »

Mais pour résumer, il n'est pratiquement jamais question de génétique en médecine générale.

Christopher Canning : En médecine générale?

Reynold Gold : En fait, les généticiens vous diront que c'est très important. Tout le monde veut vendre sa salade, et les généticiens veulent qu'on parle des gènes, les néphrologues veulent qu'on parle des reins, et ainsi de suite. Tout ça va finir par changer.

Christopher Canning : Croyez-vous toujours que l'étude de l'ADN en tant qu'unité fondamentale de l'hérédité révolutionnera un jour notre façon de voir la médecine?

Reynold Gold : Absolument. Lorsqu'on a réussi le séquençage du génome, beaucoup de gens ont vu ça comme un sprint vers la ligne d'arrivée, alors qu'il s'agit plutôt d'un sprint vers la ligne de départ, vous voyez? Je crois que c'est Collins qui a dit… Disons que vous n'avez pas compris ça. Je ne connais pas grand-chose à la biologie, vous savez.

Christopher Canning : Plus je parle à des scientifiques, plus je comprends de choses. Je pense connaître les notions de base.

Reynold Gold : Voici un exemple. Supposons que nous ne savons pas comment les automobiles fonctionnent, mais que nous en voyons circuler. Cette machine est automotrice, elle émet un peu de fumée et elle fait un son strident de temps en temps. Nous voulons savoir comment elle fonctionne, mais nous n'avons pas le droit de la démonter. Nous ne possédons aucune pièce de rechange, mais nous avons une pile de schémas qui représentent toutes les pièces de l'automobile. Nous devons découvrir comment une automobile fonctionne simplement en consultant ces schémas. C'est là où nous en sommes en ce moment.

Christopher Canning : Lorsque vous avez commencé à travailler en génétique et en médecine, y avait-il des conflits entre les généticiens et les médecins généralistes?

Reynold Gold : Je ne pense pas. Vous voulez parler de conflits personnels?

Christopher Canning : Plutôt du point de vue des connaissances. Comme une petite guerre de territoire.

Reynold Gold : Non, pas du tout. Je ne crois pas. Malgré ce que disent certains chercheurs cliniciens, il y a des différences énormes entre la pratique de la médecine et la recherche, mais ce sont des différences culturelles, pas des conflits. Ce sont deux univers. Les chercheurs cliniciens vous diront que la fusion de ces deux univers est très productive. C'est parfois vrai, mais très rare. Nous en reparlerons.

Christopher Canning : D'accord.

Reynold Gold : Je ne pense pas que les médecins méprisent les chercheurs. Je pense que ce sont plutôt les chercheurs qui ont tendance à mépriser les médecins.

Christopher Canning : Est-ce que c'est pour ça que certaines personnes décident de porter les deux chapeaux en même temps?

Reynold Gold : Je crois qu'on peut diviser les personnes qui font de la recherche clinique en deux catégories : celles qui agissent par pure curiosité intellectuelle et celles qui

veulent ajouter des lignes à leur CV. J'estime qu'une très grande proportion de ce que nous appelons de la recherche clinique ne vaut pas grand-chose. Il y a beaucoup de choses inutiles, mais les médecins cliniciens et les chercheurs peuvent aussi avoir des interactions prolifiques.

Christopher Canning : Pouvez-vous me donner un exemple d'un domaine dans lequel vous estimez que les cliniciens et les chercheurs ont des échanges fructueux?

Reynold Gold : Je crois qu'en génétique humaine, l'exemple parfait est celui de la drépanocytose. Il y avait un seul gène et nous connaissions la protéine-cible. C'était l'un des rares cas où la protéine-cible était connue, parce que nous ne pouvions pas compter sur la protéomique et la génomique à l'époque. Ingram avait fait le séquençage des peptides, trouvé la substitution d'un acide aminé unique et déduit le remplacement d'un nucléotide.

C'est un bon exemple. Pauling et Ingram ont participé à cette découverte. Mais c'est un cas assez rare.

Christopher Canning : Il s'agit de découvertes de maladies mendéliennes monogéniques.

Reynold Gold : Exactement; parmi les premières. Et j'ai créé le cours de génétique biochimique. Je ne sais pas s'il existe encore. Est-ce que ce cours est toujours donné à McGill?

Christopher Canning : J'imagine que oui, mais je ne suis pas certain.

Reynold Gold : J'ai mis ce cours sur pied. Il était toujours donné lorsque je suis parti. La moitié du cours portait sur l'hémoglobine.

Christopher Canning : Nous allons reparler de sciences. Les aspects sociologiques et historiques des sciences m'intéressent beaucoup, mais pour l'instant, j'aimerais que nous parlions un peu plus de vous. Ça m'intéresse d'en savoir plus sur votre arrivée en Saskatchewan pendant la grève des médecins, en 1962. Pourriez-vous me parler de votre recrutement pour ce travail?

Reynold Gold : J'avais fini mes *internships*, ma résidence en anesthésie, et je savais que je ne voulais pas faire carrière en tant que médecin de bord. Mais je ne savais pas vraiment quoi faire. J'ai toujours eu un intérêt pour le milieu universitaire, mais je ne savais pas trop comment concrétiser ça.

Je faisais un peu de suppléance et de médecine générale lorsque j'ai reçu un appel de la Saskatchewan House de Londres. On m'a demandé si j'avais envie de partir pour la Saskatchewan en tant que briseur de grève. Ça me tentait beaucoup parce que j'avais toujours cru en une assurance maladie à payeur unique. Je croyais au National Health Service et j'estimais que ce modèle avait de l'avenir.

Christopher Canning : Pouvez-vous répéter ça?

Reynold Gold : Le National Health Service. J'étais membre du parti travailliste à Cambridge. J'étais un social-démocrate. Ça me semblait être une belle aventure, et la paie était très intéressante, alors je me suis lancé. Pour un jeune homme de 30 ans,

c'est une expérience exaltante de travailler pour une cause qui lui tient à cœur, surtout s'il défie ses aînés. Cette idée était très attirante.

Christopher Canning : Pouvez-vous me parler un peu plus de ce projet?

Reynold Gold : C'était au moment de la création de l'assurance maladie au Canada. Je me suis rendu là-bas et ce fut une période très passionnante.

Christopher Canning : Avec qui avez-vous travaillé pendant la grève?

Reynold Gold : En arrivant au Canada, je n'avais pas de collègues. Un représentant du gouvernement m'a accueilli et m'a conduit dans un motel miteux. Des espions du Collège des médecins ont fini par découvrir où moi et les autres briseurs de grève habitions, et ils nous ont demandé de rentrer chez nous. Nous ne comprenions rien à la situation. Ils nous ont invités à rejoindre les autres médecins qui faisaient la grève à titre d'invités. J'ai refusé. Ils nous ont amenés dans un immeuble du gouvernement, à Regina, où ils nous ont remis des billets de cent dollars.

Christopher Canning : Pour vous faire taire?

Reynold Gold : Non. C'était une première paie. On nous a dit que nous devions attendre d'avoir nos permis. En fait… Voulez-vous que je donne plus de détails à ce sujet?

Christopher Canning : Vous pouvez me donner autant de détails que vous le désirez.

Reynold Gold : D'accord. Tous les médecins anglais avaient le droit de recevoir automatiquement un permis en Saskatchewan grâce à une entente de réciprocité entre la Saskatchewan et l'Angleterre, qui permettait à chaque territoire d'accorder des permis aux médecins de l'autre territoire. Tous les détenteurs d'un diplôme de médecine anglais, dont moi, pouvaient recevoir un permis du Collège des médecins. Et le Collège prenait parti pour les grévistes, bien entendu. Il ne faut pas oublier qu'à cette époque, le Collège était à la fois un organe disciplinaire et un syndicat. Il y avait donc un certain conflit d'intérêts.

Il a donc retardé l'émission des permis et pendant ce temps, je restais à l'hôtel et j'étais payé par le gouvernement. Nous voulions travailler, et le gouvernement a émis un mandamus. Ou plutôt, il a demandé un mandamus, qui lui a été accordé, et les permis nous ont été remis. Ensuite, j'ai demandé à me joindre à la clinique médicale communautaire de Saskatoon, qui était mise sur pied par D^{r} Sam Wolfe, un type très charismatique qui enseignait la santé publique à l'Université de la Saskatchewan. Il était très courageux parce qu'il a abandonné son poste de professeur pour venir sur le champ de bataille. Il y avait deux médecins canadiens, lui et un psychiatre. Ces médecins faisaient preuve d'un courage énorme en s'opposant à tous leurs collègues.

Pour nous, c'était facile : nous ne connaissions personne. Mais pour les médecins canadiens, qui étaient parfois traités de communistes ou de mercenaires, c'était un sacrifice important.

Sam Wolfe a donc fait un sacrifice énorme. Il a formé un groupe de personnes de tous horizons; nous étions six. Il y avait le D^{r} Tulchinsky, médecin

généraliste, la Dr Mahood, psychiatre, et son mari, qui était un fier marxiste. Qui d'autre? Le Dr Langer, chirurgien, s'est joint à nous un peu plus tard. Sa participation était précieuse parce que les chirurgiens gagnaient très bien leur vie. Et malgré ça, il a accepté de faire partie de notre groupe. Et il était marxiste aussi. C'était un vrai révolutionnaire. Deux d'entre nous étaient communistes, mais pas moi.

Christopher Canning : Autoproclamés?

Reynold Gold : Ils étaient des marxistes autoproclamés, et quand ils se sont joints à nous, j'ai pu voir qu'ils appuyaient vraiment la philosophie communiste. Le Dr Langer a non seulement tenu tête à ses collègues, il ne s'en est même pas préoccupé parce qu'il disait que les médecins faisaient partie de la bourgeoisie et qu'ils étaient voués à l'extinction. [rires]

Il ne se préoccupait pas de ça, et il a accepté de travailler au même salaire que les autres membres du groupe. Il aurait pu gagner des centaines de milliers de dollars, même à l'époque, et il avait accepté de travailler pour un maigre salaire. Dans son cas, l'accuser d'être un mercenaire n'était pas du tout justifié. Cette accusation s'appliquait plus à nous, les médecins britanniques.

Christopher Canning : Combien de temps êtes-vous resté en Saskatchewan?

Reynold Gold : Cinq ans.

Christopher Canning : De 1962 à 1967?

Reynold Gold : Exactement, de 1962 à 1967. Vous voulez d'autres détails? Nous avons donc obtenu notre permis et nous avons commencé à travailler à l'hôpital. Puis, la question des privilèges hospitaliers s'est posée. Entre vous et moi, c'est possible d'être médecin généraliste sans avoir de privilèges hospitaliers, mais il faut généralement travailler dans un hôpital pour être médecin de famille. Mais ces privilèges sont avantageux, surtout dans une petite ville. Il y avait aussi des raisons politiques, et les hôpitaux ont refusé des privilèges hospitaliers à bon nombre d'entre nous.

Une commission royale sur les privilèges hospitaliers a donc été mise sur pied, sous la direction du juge Woods. Vous étiez peut-être déjà au courant de ça. J'ai témoigné devant cette commission pendant deux jours, parce qu'on m'avait refusé ces privilèges, et le Collège a été sommé de produire ses dossiers. La commission a révélé que des personnes avaient reçu des privilèges sur simple recommandation du directeur de l'hôpital et qu'elles étaient de bonne moralité. La commission a demandé une tonne de références, et le directeur de l'hôpital municipal a aussi dit, devant la commission, que ma formation était de la bouillie pour les chats. [rires]

Pendant son témoignage, un autre médecin a affirmé que ma formation ne m'avait pas permis d'acquérir les compétences nécessaires pour faire de la « médecine de prairie ». À la fin du processus, le juge Woods a affirmé qu'il était justifié pour moi de croire que la décision de ne pas m'accorder de privilèges hospitaliers était motivée par des considérations politiques. Et il a recommandé une révision de mon cas.

Le juge s'est montré très diplomate, et nous avons fini par avoir nos privilèges hospitaliers.

Christopher Canning : C'était vers la fin de votre séjour en Saskatchewan?

Reynold Gold : C'était au milieu. Je ne me souviens plus du moment exact. Cette période a été très divertissante.

Christopher Canning : J'imagine que pendant cette période politique divertissante, vous deviez réfléchir à la possibilité de retourner à l'université pour faire un doctorat ou autre chose?

Reynold Gold : C'est exact, vous avez vu juste. Je n'aimais pas vraiment pratiquer la médecine à l'époque et je vais vous dire pourquoi. Après avoir obtenu mon diplôme de sciences à Cambridge et avoir travaillé à l'hôpital universitaire de Londres, j'ai subi un choc culturel énorme parce que je suis passé d'un univers de connaissances établies à un monde dans lequel il y avait beaucoup d'incertitudes. C'est encore le cas aujourd'hui. Quand on parlait de médecine factuelle, il y avait beaucoup d'inconnu. Je trouvais la situation très inconfortable et lorsque je pratiquais la médecine, je n'ai jamais senti que je savais ce que je faisais d'un point de vue scientifique.

Christopher Canning : Vous avez toujours eu des bases scientifiques, même si vous étiez clinicien.

Reynold Gold : Exactement. J'étais un pur produit de la science. Autrement dit, j'ai toujours essayé d'aborder les choses avec une pensée scientifique. Je trouvais donc ma situation inconfortable. C'est au moment où j'ai voulu rentrer à la maison que j'ai parlé à mon ami Ian Shine, le gars avec qui j'avais travaillé sur un livre à Sainte-Hélène. Il m'a conseillé de sauter dans un avion et d'aller voir Clarke Fraser. J'étais marié à ce moment-là.

En passant, je devrais vous dire que pendant mon séjour en Saskatchewan, je n'ai pas été dérangé par les reproches de mes collègues. J'avais l'habitude de ça, et je dois dire que je m'attendais à être traité de cette façon. Ce qui me perturbait le plus, c'était le désert culturel dans lequel je vivais. Quand je suis arrivé à Saskatoon, il y avait deux salles de cinéma. L'une d'elles projetait *King Kong contre Godzilla* et l'autre, *Dracula au pensionnat pour jeunes filles*. Je me suis dit que Saskatoon pourrait vraiment profiter d'une transfusion culturelle. J'ai donc ouvert un café, le Louis Riel Coffee Shop, qui a attiré une foule de gens. C'est comme ça que j'ai rencontré celle qui allait devenir ma femme.

Elle faisait un doctorat en psychologie. Je donc suis allée à McGill avec elle. Elle a ensuite décroché un poste de professeur en psychologie à Concordia, et comme je l'avais appuyée pendant son doctorat, elle a fait la même chose pendant mon doctorat à McGill.

Christopher Canning : À ce moment-là, avez-vous demandé à travailler avec le Dr Fraser?

Reynold Gold : Oui. Je suis allée voir le Dr Fraser, et je lui ai dit que je m'intéressais à la génétique biochimique et moléculaire. Il m'a dit d'aller voir Charlie à ce sujet. Je suis donc allé voir Charlie.

Christopher Canning : Il devait faire de la tératologie et de la cytogénétique, non?

Reynold Gold : Il faisait de la génétique biochimique, et…

Christopher Canning : Il vous a donc dit d'aller parler au Dr Scriver?

Reynold Gold : Exact. Il m'a ensuite dit qu'il allait me prendre avec lui. J'ai donc suivi des cours pendant un an, ce qui m'a beaucoup surpris parce qu'on ne suit pas de cours pendant un doctorat en Angleterre. Si vous demandez à un superviseur au doctorat en Angleterre quels cours vous devriez suivre, il vous dira que vous êtes censé tout connaître, que vous devez trouver quelque chose de nouveau, et que si vous estimez devoir apprendre quelque chose, vous pouvez assister à n'importe quel cours de votre choix.

J'ai donc trouvé étonnant de devoir suivre des cours au doctorat.

Christopher Canning : Donc, à 35 ans et avec une expérience de médecin de bord et de militant politique en Saskatchewan, vous êtes de retour en classe à l'Université McGill.

Reynold Gold : C'est exact. Et j'ai adoré ça. Je me suis senti comme chez moi pendant mon doctorat. Il y avait une seule ombre au tableau. J'étais extrêmement maladroit et incapable de faire une expérience, ce qui était un handicap. Plus tard, grâce au groupe, j'ai pu mettre en pratique mes connaissances théoriques et faire faire les expériences par des personnes qui y arrivaient bien mieux que moi.

Christopher Canning : Voilà qui fait une belle transition vers mes questions au sujet du groupe. Nous avons fait une incursion dans votre passé intellectuel et politique, et nous sommes maintenant en 1972.

Reynold Gold : Oui, j'ai commencé mon doctorat en 1967.

Christopher Canning : Et vous l'avez terminé en 1970?

Reynold Gold : Je l'ai terminé en 1970. Je ne me rappelle plus ce que j'ai fait après mon doctorat. J'ai obtenu mon diplôme assez rapidement.

Christopher Canning : Je vois.

Reynold Gold : Il a dû s'écouler 2 ans et demi. J'ai obtenu mon doctorat en 1970 et le groupe a été formé en 1972.

Christopher Canning : En 1972. La demande a été faite au printemps 1972 et le financement a été obtenu à l'automne.

Reynold Gold : J'ai travaillé un peu aux urgences de l'Hôpital de Montréal pour enfants, mais je ne me rappelle plus quel statut j'avais.

Christopher Canning : En 1971, vous avez publié un article avec le Dr Scriver sur la composition des acides aminés qu'on retrouve dans les cheveux de différentes origines raciales.

Reynold Gold : J'avais complètement oublié cet article.

Christopher Canning : J'imagine que vous faisiez toujours des recherches avec le Dr Scriver avant ça ou au début des années 1970?

Reynold Gold : Je ne m'en souviens pas du tout. Je ne sais pas dans quel contexte j'ai rédigé cet article, ni même si j'étais étudiant à cette époque. Mais ce n'était pas au sein du groupe parce que le groupe n'existait pas à ce moment-là.

Christopher Canning : Vous avez donc travaillé avec le Dr Scriver. Vous avez fait votre doctorat avec lui. Au départ, vous vouliez travailler avec le Dr Fraser. Il s'agit là des deux membres fondateurs du groupe du CRM.

Reynold Gold : C'est exact.

Christopher Canning : Ils sont les fondateurs de ce projet.

Reynold Gold : Oui, ce sont les fondateurs.

Christopher Canning : Comment en êtes-vous venu à faire partie du groupe? Vous rappelez-vous avoir été invité à participer à leurs recherches ou à vous joindre au groupe?

Reynold Gold : Je pense que le Dr Scriver m'a simplement invité à me joindre au groupe et que j'ai accepté. La formation du groupe a été vraiment spéciale; à part Charlie [Scriver] et Clarke [Fraser], aucun d'entre nous n'avait une expérience solide. Qui étaient les premiers membres du groupe? Charlie, Clarke, Peter Hechtman et moi.

Christopher Canning : Peter Hechtman et David Rosenblatt se sont joints au groupe en 1975, mais ils étaient mentionnés sur la demande de 1972.

Reynold Gold : David Rosenblatt.

Christopher Canning : Son nom était indiqué sur la première demande, mais il se trouvait aux États-Unis et faisait sa formation postdoctorale à Boston.

Reynold Gold : Aucun de nous trois n'avait une expérience vraiment pertinente. C'était extraordinaire qu'ils nous intègrent à leur groupe alors que nous n'étions que des coquilles vides.

Christopher Canning : Vous rappelez-vous avoir rédigé cette demande de subvention?

Reynold Gold : Je ne pense pas l'avoir rédigée.

Christopher Canning : Il y a une longue liste de vos travaux en génétique de la kératine, et la première demande, dont j'ai une copie, renferme une longue description de cinq ou six pages de vos recherches dans ce domaine.

Reynold Gold : Je ne m'en souviens pas. J'avais produit un certain nombre d'articles, mais leur contenu scientifique était vraiment négligeable.

Christopher Canning : Eh bien, moi, je m'intéresse beaucoup à ça parce que votre nom était mentionné dans cette première demande de subvention.

Reynold Gold : Vous me parlez de choses que j'avais complètement oubliées.

Christopher Canning : C'est intéressant parce que la demande de subvention mentionnait vos travaux en tant que nouveau domaine de la génétique qui porte sur les kératines présentes dans les follicules pileux. Qu'est-ce qui était spécial à propos de votre recherche à ce moment-là? Quel effet cela a-t-il eu sur la formation du groupe? J'ai l'impression que le CRM a trouvé votre recherche intéressante parce que la demande mentionne aussi deux personnes qui n'ont pas obtenu la subvention. Margaret Corey…

Reynold Gold : J'avais complètement oublié Margaret. Je n'étais même pas au courant de ce refus.

Christopher Canning : Et Hy Goldman.

Reynold Gold : En fait, Hy Goldman n'était pas un scientifique. C'était un médecin très gentil, mais ça s'arrête là. C'était un homme très sympathique, et il était très actif dans la communauté juive, mais il n'était pas un scientifique. Il n'avait aucune idée de ce qu'est la science. Mais Peter Hechtman n'avait pas fait grand-chose lui non plus, n'est-ce pas?

Christopher Canning : Il venait tout juste de terminer son doctorat.

Reynold Gold : Et est-ce que David Rosenblatt avait fait quelque chose?

Christopher Canning : David Rosenblatt venait également de terminer son doctorat et il faisait ses études postdoctorales à Boston, aux États-Unis. Vous veniez tout juste de finir votre doctorat, David Rosenblatt était en train de faire son postdoctorat et Peter Hechtman venait également d'obtenir son diplôme.

Reynold Gold : Je ne me rendais pas compte que j'avais fait quelque chose de pertinent avant de me joindre au groupe. D'accord.

Christopher Canning : Qu'est-ce qui vous intéressait dans la génétique de la kératine, ou pourquoi était-ce intéressant dans un contexte de travail au sein du groupe? Vous en souvenez-vous? De toute évidence, il s'agissait de votre domaine de prédilection dans le groupe.

Reynold Gold : Je vais vous dire ce qui m'intéressait. En étudiant la kératine présente dans les cheveux, on s'aperçoit qu'il y a divers groupes de protéines riches en tyrosine ou en lysine, mais que chacun de ces groupes possède un très grand nombre de protéines individuelles. Comme les cheveux sont des tissus morts, ils ne sont pas très importants du point de vue biologique. Mais deux questions piquaient vraiment ma curiosité. Je me demandais entre autres pourquoi il y avait tant de protéines différentes au sein d'un même groupe. C'était une question théorique, bien sûr. Ensuite, comment se fait-il que la mutation d'une

protéine, comme nous l'avons découvert plus tard, faisait réduire le nombre de protéines. Comme je l'ai démontré avec Susie [Tenenhouse], la taille du groupe de protéines est réduite de moitié environ. Nous avons aussi travaillé avec les souris nude, et nous avons obtenu des résultats très précis avec ces souris de souches consanguines.

Christopher Canning : C'est le sujet d'un article que vous avez publié avec Susie Tenenhouse en 1976. J'ai ça ici.

Reynold Gold : Il y a eu quelques articles…

Christopher Canning : En génétique biochimique, oui.

Reynold Gold : La collaboration entre… Je m'éloigne du sujet un peu.

Christopher Canning : Nous pourrons y revenir.

Reynold Gold : Oui, j'y reviendrai. Je n'ai pas oublié ce que nous faisons. La collaboration avec Susie [Tenenhouse] a été fantastique parce que Susie était une expérimentaliste extraordinaire. La regarder faire une expérience, c'était comme regarder une artiste à l'œuvre. Elle travaillait avec beaucoup d'exactitude et de précision, et notre collaboration était un excellent exemple de travail d'équipe. Je ne sais pas si vous lui avez déjà parlé. Elle a fait des expériences que je n'aurais jamais pu faire moi-même parce que je suis très maladroit dans un laboratoire. Si je me charge d'une expérience, elle ne sera pas un succès, c'est certain. Il y a des gens qui ne sont pas doués pour les tâches manuelles, mais elle, elle était très douée.

Par contre, je ne sais pas ce qu'elle en dirait. Je pense que j'étais en mesure de lui proposer des expériences qu'elle n'aurait peut-être pas envisagées elle-même, mais je ne sais pas. Vous pourriez lui demander ce qu'elle en pense. J'ai trouvé des façons d'interpréter les données qu'elle n'aurait peut-être pas trouvées.

Nous avons donc marié nos compétences théoriques et expérimentales. Et j'ai rédigé l'article. Je ne suis pas trop mauvais comme rédacteur. Disons que je suis aussi bon rédacteur que mauvais expérimentaliste. [rires]

Christopher Canning : Je constate que Susie Tenenhouse participait à vos travaux, mais qu'elle ne s'est jointe au projet qu'en 1981. Que pouvez-vous me dire là-dessus?

Reynold Gold : Il y a une histoire derrière ça.

Christopher Canning : J'aimerais bien l'entendre, si ça ne vous dérange pas.

Reynold Gold : Laissez-moi d'abord vous expliquer pourquoi je m'intéressais aux kératines, puis je vous raconterai l'histoire concernant Susie. Tout d'abord, je voulais savoir pourquoi il y avait une foule de protéines très similaires, alors qu'il aurait pu y en avoir une seule. Les cheveux sont des tissus morts, alors pourquoi en avons-nous besoin? Ont-ils une utilité biologique? Deuxièmement, comment un seul gène pouvait-il moduler la quantité de protéines d'une même famille?

Christopher Canning : Des chaînes d'acides aminés?

Reynold Gold : En gros, la Bible dit : un gène, une protéine, alors qu'ici, on a un gène et environ douze protéines différentes qui diminuent de moitié. Je me suis donc dit que nous étions peut-être en présence d'un gène régulateur. Ça éveillait ma curiosité. Je ne sais pas si c'est ce qui intéressait le Dr Scriver, mais moi, ça m'intéressait.

Christopher Canning : À l'époque, que représentait un gène régulateur?

Reynold Gold : Nous savions comment les gènes étaient régulés dans les bactéries, avec l'opéron, par exemple. Nous savions déjà beaucoup de choses au sujet de la régulation des gènes dans les virus, mais nous ne savions rien sur la régulation des gènes chez les animaux d'espèces supérieures, et nous ne savions pas s'il y avait des opérons chez ces animaux. Nous ne pensions pas que c'était le cas parce que les gènes aux fonctions connexes ne se trouvent pas nécessairement près l'un de l'autre sur les chromosomes, comme dans les bactéries. Vous me suivez?

Ce que j'appelais un gène régulateur, c'est un gène qui commande la production d'une grande quantité de protéines. La notion était aussi vague que ça, et je me demandais s'il y avait un gène régulateur et comment il fonctionnait. Je n'en avais pas la moindre idée.

Finalement, je me suis rendu compte que la question était trop complexe. Je n'y ai toujours pas trouvé de réponse. À Toronto, nous avons analysé un problème semblable chez la souris atteinte de cataracte. Encore une fois, une famille de cristallines a été réduite par la mutation d'un gène. Nous avons donc décidé de nous intéresser à ce sujet puisque nous avions accès à d'excellents généticiens moléculaires. Lap-Chee Tsui a travaillé sur ce gène et a découvert qu'en fait, la mutation se produisait dans l'un des gènes, dans le codage de l'une des protéines de structure, dans une des cristallines gamma. À ce moment-là, nous nous sommes demandé « Pourquoi la mutation qui se produit dans un gène qui code pour un des gènes de la famille provoque-t-elle une réduction dans toute la famille? »

D'après ce que je sais, cette question n'a toujours pas de réponse. Pour revenir à l'histoire concernant Susie Tenenhouse…

Christopher Canning : Juste avant de me raconter cette histoire, pourriez-vous me parler un peu plus de vos travaux sur la kératine? Ils sont mentionnés sur la demande de 1972, mais on ne les revoit plus par la suite.

Reynold Gold : Qu'est-ce qui est mentionné dans la demande?

Christopher Canning : Votre intérêt pour la génétique de la kératine. De toute évidence, vous ne faisiez plus partie du groupe en 1977 et personne ne s'est intéressé à la génétique de la kératine par la suite.

Reynold Gold : En effet.

Christopher Canning : Pourquoi le groupe a-t-il cessé de s'intéresser à la génétique de la kératine? Y avait-il encore des questions sans réponse ou s'agissait-il d'un sujet trop vaste?

Reynold Gold : On peut penser à deux raisons. Tout d'abord, nous avions étudié le problème dans la mesure de nos connaissances et de la technologie que nous possédions. Pour pouvoir répondre à la question fondamentale, nous aurions eu besoin d'un type de génétique moléculaire qui n'était pas encore disponible. Ce qui m'amène à poser une autre question : « Pourquoi devrions-nous étudier la génétique humaine? » Mais c'est un autre sujet.

Ensuite, Susie Tenenhouse a commencé à travailler sur autre chose. En fait, Susie était l'adjointe de Charles Scriver. Elle s'est mise à s'intéresser à mes recherches en génétique et Charles Scriver ne lui a pas interdit de travailler avec moi, ce qui est tout à son honneur. Au contraire, il l'a encouragée à le faire si ça l'intéressait. Plus tard, elle a décidé d'orienter ses recherches vers le rachitisme lié à la carence en phosphate.

Christopher Canning : Le Dr Scriver travaillait déjà sur ce sujet, n'est-ce pas?

Reynold Gold : Oui. En plus, je commençais à m'intéresser à autre chose. Susie et moi avons donc interrompu nos recherches sur la kératine, en partie parce que Susie avait d'autres champs d'intérêt et en partie parce que je ne voyais pas comment faire évoluer le projet. Pourtant, lorsque je suis arrivé à Toronto, nous avons progressé grâce à une autre mutation. Mais nous n'avons pas élucidé le fonctionnement du gène.

Je me suis ensuite intéressé à l'aspect mathématique des tests de dépistage. Mon projet a pris de l'ampleur, et j'ai pu en tirer beaucoup d'articles parce que chaque fois qu'ils faisaient des tests de dépistage, ils utilisaient mes calculs – ou plutôt nos calculs. Mon nom s'est donc retrouvé dans un grand nombre d'articles.

Christopher Canning : Vous avez dit une chose intéressante tout à l'heure sur le fonctionnement du groupe. Vous vous occupiez davantage de l'aspect théorique des choses, alors que Susie était plus du côté pratique…

Reynold Gold : En gros, c'est ça.

Christopher Canning : Est-ce que Charles Scriver était aussi principalement un expérimentaliste?

Reynold Gold : Il était la force motrice du groupe.

Christopher Canning : Qu'en est-il de Clarke Fraser? Que faisait-il à l'époque?

Reynold Gold : Clarke Fraser est un homme génial. Je l'aime beaucoup. Il est authentique, très droit. J'aime beaucoup les gens qui ne se cachent pas derrière un masque. Il est le genre de personne qui vous pousse à vous dépasser intellectuellement. Il se dégageait de lui une très grande humilité, et je trouve ça remarquable. Même chose pour Lap-Chee Tsui; avez-vous entendu parler de lui? J'ai travaillé avec lui à Toronto. Je l'ai intéressé au problème des cristallines, mais il est surtout connu parce que c'est lui qui a isolé le gène de la fibrose kystique. Et il était comme Clarke Fraser. Quand il entrait dans le laboratoire, on aurait pu

croire qu'il était le technicien. Et pourtant, il était un scientifique célèbre. C'est admirable. C'est Charles Scriver qui est à l'origine de la formation du groupe. Bien entendu, il a demandé à Clarke Fraser de se joindre à lui parce qu'il était important dans le domaine de la génétique humaine. Ça n'aurait pas été une bonne idée de créer un groupe sans Clarke Fraser. Pourtant, il n'y avait pas beaucoup de liens entre leurs travaux respectifs. En effet, il s'intéressait aux anomalies congénitales chez les souris et chez les humains.

Finalement, il y avait une certaine interaction entre leurs travaux parce que c'est lui qui m'a suggéré de m'intéresser à la souris nude.

Christopher Canning : C'est Clarke Fraser qui vous a suggéré ça?

Reynold Gold : Oui. Il a coécrit l'article pour la revue *Nature* avec moi. J'ai ajouté son nom à l'article parce que la suggestion venait de lui et qu'elle avait été très fructueuse pour moi.

Christopher Canning : Parce que vous avez ainsi pu vraiment faire partie du groupe?

Reynold Gold : En fait, je faisais déjà partie du groupe, mais mes recherches m'ont beaucoup aidé à m'attaquer la question du gène lié à un grand nombre de protéines. C'est le sujet sur lequel j'ai travaillé avec Susie.

Christopher Canning : J'aimerais revenir sur les débuts du groupe. Comme vous êtes l'un des membres fondateurs, j'aimerais bien avoir votre point de vue. Mais juste avant, parlons de cette histoire concernant Susie Tenenhouse. Elle est arrivée en scène au début des années 1970, mais elle n'est devenue membre du groupe qu'au début des années 1980.

Reynold Gold : Nous parlons de Susie.

Christopher Canning : Oui, Susie Tenenhouse.

Reynold Gold : Elle est devenue chercheuse principale lorsque j'ai quitté le groupe.

Christopher Canning : Elle a participé à la demande de 1980 et a obtenu une subvention en 1981.

Reynold Gold : En tant que chercheuse principale? C'était donc à mi-mandat. Probablement la première ou la deuxième demande après mon départ?

Christopher Canning : La deuxième demande. Vous n'avez pas participé aux demandes de subvention de 1976 et de 1981.

Reynold Gold : Voici comment ça s'est passé. Susie était encore plus ou moins une adjointe, mais elle était une excellente expérimentaliste. Elle n'avait toutefois pas le statut de professeure et son statut d'adjointe à la recherche ne donnait pas de visibilité à ses recherches personnelles.

Charles Scriver n'était pas très bon pour faire progresser les gens. Il était excellent pour fournir des installations propices à la collaboration, mais pas pour aider les gens à avancer dans leur carrière. Vous voyez ce que je veux dire? Il n'a donc rien fait pour que Susie obtienne un poste permanent ou même

un poste de professeure menant à la permanence. Le mari de Susie, Alan Tenenhouse, que je connais très bien et qui est tout un personnage, était en poste à l'Hôpital général de Montréal. Il s'intéressait au métabolisme du calcium, ce qui avait un lien avec les travaux de Susie, et il a fini par dire à Charles Scriver : « Nous devrions faire quelque chose pour Susie. » Ce à quoi Charles Scriver a répondu : « Il n'y a rien que je puisse faire. »

Christopher Canning : Il a dit qu'il ne pouvait rien faire? Intéressant.

Reynold Gold : Je ne fais que répéter les propos d'Alan, qui lui a dit : « Ça suffit. Vous avez plus de pouvoir que n'importe qui d'autre à l'Université. Il suffit d'un mot de votre part pour que Susie obtienne un poste menant à la permanence. » C'est ce que Charles Scriver a fini par faire, et Susie a obtenu son poste.

Christopher Canning : Est-ce qu'elle a manifesté l'intérêt de travailler davantage avec le groupe lorsque vous avez publié des articles ensemble au milieu des années 1970?

Reynold Gold : Elle était de nature très douce et réservée, mais je savais qu'elle avait une volonté de fer. Elle était également ambitieuse, et j'ai l'impression qu'elle a mentionné son mécontentement à son mari, qui lui – comment dire – n'hésitait pas à exprimer ses opinions. Mais ce n'est qu'une déduction de ma part. Néanmoins, Alan m'a dit qu'il était allé voir Charles Scriver pour lui demander de faire quelque chose, sinon… et Charles Scriver l'a fait, même si, à mon avis, il aurait bien aimé la garder comme chercheuse principale et ne pas lui donner de coup de pouce pour qu'elle obtienne son propre poste.

Christopher Canning : Vous souvenez-vous du processus de demande de subvention? Le groupe a été créé seulement quelques années après que le CRM a commencé à reconnaître le statut de groupe. Et ce qui est intéressant, je trouve, c'est que le guide de présentation des demandes de subvention précisait que tous les membres du groupe devaient travailler au même endroit. Où les membres travaillaient-ils au début des années 1970?

Reynold Gold : Je pense que Charles Scriver devait prouver que nous avions des locaux adéquats pour la recherche. En fait, nous avions de très petits locaux, mais nous travaillions tous ensemble et nous avons fini par tous nous retrouver au même endroit. Même David Rosenblatt. Je crois qu'il est passé à autre chose un peu plus tard; je ne me rappelle plus. Mes souvenirs de cette époque sont un peu flous. Charles Scriver était enchanté. Par contre, je ne suis pas certain d'avoir rédigé une partie de la demande. Je l'ai peut-être fait, ou peut-être pas. Je ne m'en souviens pas.

Christopher Canning : Si vous aviez une copie de la demande sous les yeux, pourriez-vous me le dire?

Reynold Gold : Absolument. Je pourrais vous dire qui l'a rédigée parce que Charlie et moi, nous n'écrivions pas du tout de la même manière.

Christopher Canning : Je vous montrerai la demande un jour.

Reynold Gold : Et je pourrai vous dire qui l'a faite.

Christopher Canning : D'accord.

Reynold Gold : Je le saurais à ce moment-là. C'est possible que Charlie m'ait dit que nous allions rédiger une demande, mais je ne me rappelle pas si je l'ai fait. Désolé.

Christopher Canning : On m'a dit que pour les premières demandes, Charles Scriver et Clarke Fraser étaient responsables de la rédaction. Mais je ne sais pas si ça s'est passé comme ça dans votre cas.

Reynold Gold : Je ne m'en souviens vraiment pas, mais je pourrais vous le dire immédiatement si je voyais la section sur la kératine. Charlie et moi avions des visions très différentes de la façon d'écrire des documents scientifiques.

Christopher Canning : D'accord, je vous montrerai la demande la prochaine fois que nous nous verrons. Vous souvenez-vous des locaux que le groupe occupait? Il y avait des installations dans l'Hôpital de Montréal pour enfants. Un laboratoire a été aménagé un peu plus tard.

Reynold Gold : C'est bien ça. Au septième ou huitième étage, je crois. L'espace était restreint, et il n'y avait pas beaucoup de bureaux séparés. Je n'avais pas de bureau et Charlie en avait un petit. Clarke se trouvait à un bout et nous étions à l'autre bout. Nous avions seulement des paillasses. Les étudiants travaillaient avec nous, et nous occupions tous un espace très petit.

Christopher Canning : Vous faisiez des expériences à ce moment-là?

Reynold Gold : Oh oui! Nous avons fait beaucoup d'expériences dans cet endroit.

Christopher Canning : Aviez-vous des étudiants aux cycles supérieurs?

Reynold Gold : Oui, j'en avais plusieurs. J'en avais trois, et quand j'ai quitté le groupe, deux d'entre eux sont passés à un autre projet.

Christopher Canning : Pourriez-vous me parler de votre relation avec le Dr Scriver? Comment se sont déroulées les quatre ou cinq premières années? Comment était la relation entre lui et vous, mais aussi entre lui et le reste du groupe?

Reynold Gold : Il était le gourou.

Christopher Canning : Intéressant. Plus précisément, quel type de relation avait-il avec vous et avec l'ensemble du groupe? Quelle incidence cette relation avait-elle sur la dynamique du groupe, surtout dans les premiers temps après la formation du groupe?

Reynold Gold : Laissez-moi réfléchir. Au début, je l'admirais beaucoup pour ses compétences de gestionnaire. Je l'admirais parce qu'il excellait dans l'organisation des soins médicaux, surtout pour les maladies génétiques. Je trouvais ça intéressant parce qu'en Saskatchewan, j'avais participé à des recherches sur la prestation de soins de santé et que je m'intéressais beaucoup aux aspects logistiques, politiques et économiques de ce sujet fort intéressant.

C'était l'une de ses forces. Il était aussi un politicien hors pair. Par exemple, il a réussi à convaincre M. Steinberg d'ajouter de la vitamine D au lait, ce qui a produit des bienfaits énormes. J'ai donc été un grand admirateur pendant environ un an, puis j'ai commencé à me rendre compte de deux choses. Tout d'abord, il n'avait pas de grandes connaissances en sciences. Du moins, pas des sciences pures et dures. Ensuite, il était une sorte d'imposteur. Je le voyais donc comme un excellent politicien d'un côté, et comme un imposteur de l'autre. Je ne sais pas si d'autres personnes vous ont dit ça, mais c'est l'impression qu'il me donnait. Il se préoccupait beaucoup de son image. Lorsque vous travaillez en recherche clinique, vous pouvez être vraiment tenté de vous présenter comme scientifique auprès des médecins et comme médecin auprès des scientifiques. Et je dois avouer que je l'ai probablement fait moi-même parce que comme vous pouvez le voir sur mon CV, j'ai donné beaucoup de conférences. Mais lors de ces conférences, j'essayais d'insister sur le fait que nous ne savions pas grand-chose, par exemple, alors que Charles Scriver a beaucoup écrit pour ne rien dire. Il a écrit des trucs hallucinants, je ne sais pas comment décrire ça, du grand n'importe quoi. C'est étonnant qu'il ait réussi à faire publier ses articles.

Il attachait beaucoup beaucoup d'importance à son image. C'était évident qu'il se préoccupait du bien-être du groupe, mais je sentais qu'il se servait de ça pour asseoir sa réputation. C'est comme ça que je voyais les choses. Plus tard, comme je n'étais que professeur associé en biologie et en pédiatrie, j'ai dit à Charles Scriver que je voulais avoir un poste de professeur menant à la permanence. Je ne faisais pas cette demande pour des raisons financières, je n'avais pas de crainte à cet égard, mais plutôt par principe. Je voulais plutôt que mon statut soit reconnu. De toute façon, j'avais un salaire et je pouvais très bien gagner ma vie comme médecin. Ce n'était donc pas une question d'argent, même si Charles Scriver croyait le contraire. Il m'a dit : « Je ne suis pas professeur permanent moi non plus, tu sais. » Je me suis alors dit que cet homme, dont je n'avais jamais douté de l'intégrité jusque là, avait peur de la vérité parce qu'il avait une énorme capacité à croire ce qui faisait son affaire. C'est ce que j'ai pensé immédiatement. Je n'en revenais pas.

Christopher Canning : Wow. Ça s'est produit combien de temps après la formation du groupe? Environ deux ans?

Reynold Gold : Oui, environ deux ans. La première année, je trouvais que tout était parfait, puis après…

Christopher Canning : Vous veniez de finir votre doctorat, c'est bien ça?

Reynold Gold : Oui, je venais de finir mon doctorat, et il m'a accepté dans un groupe fantastique. Je dois bien le reconnaître. Je n'avais pas besoin de faire un postdoctorat, vous voyez? Je suis donc devenu chercheur principal directement, et je lui en suis reconnaissant. Je crois que c'était un aspect positif de ses talents de politicien. Alors, lorsqu'il m'a dit : « Je n'ai pas un poste permanent », je me suis dit qu'il se moquait de moi. S'il m'avait dit : « Je vais être franc avec toi. Ce sera très difficile, voire impossible. Si tu veux vraiment obtenir un poste permanent, tu devrais peut-être penser à aller ailleurs. Je ne pense pas que ça va arriver. C'est très improbable, mais si le groupe a de bons résultats, tu auras un bel avenir au poste que tu as présentement. Et si ça te

convient, tant mieux, sinon, je vais être honnête avec toi, je ne peux pas faire grand-chose. » J'aurais pu accepter la situation. En fait, je lui aurais dit que ça me convenait, mais quand il m'a dit : « Je n'ai pas de poste permanent moi-même », je suis resté sans voix.

J'ai soudainement vu clair dans son jeu, et ça m'a donné un choc. Je vais vous parler de la seule autre fois où j'ai eu un choc pareil. Lorsque j'étais étudiant en médecine, je jouais aux échecs avec un gars. C'était un gars très agréable et rationnel, et j'ai joué aux échecs avec lui pendant environ six mois. Nous prenions le thé et nous jouions aux échecs au YMCA. Il était étudiant. Un jour, pendant une partie d'échecs, il m'a dit « En passant, savais-tu que les analystes jungiens essayaient de me tuer? »

Je pensais qu'il faisait des blagues. Je me suis dit qu'il faisait des études en analyse freudienne et qu'il exprimait son désaccord. Je lui ai donc dit : « Ha Ha, très drôle! » Mais il m'a dit qu'il était très sérieux. Finalement, il était schizophrène, mais j'ai eu un choc. Je ne dis pas que Charlie est schizophrène, mais le choc…

Christopher Canning : Une prise de conscience?

Reynold Gold : Oui. Je me suis rendu compte qu'un homme que je croyais intègre ne l'était pas vraiment.

Christopher Canning : Wow. Et est-ce que cette prise de conscience a nui à votre relation avec lui?

Reynold Gold : Oh oui, oh oui, parce que j'avais vu clair dans son jeu et, d'une certaine façon, il le savait. Mais j'ai joué le jeu et je lui ai répondu « C'est terrible ». Je savais très bien qu'il avait un poste permanent. Je me suis demandé pourquoi il me disait un mensonge aussi évident. J'ai donc continué à jouer le jeu, et je lui ai dit : « C'est terrible parce que si toi, avec toutes tes réalisations, tu n'arrives pas à avoir un poste permanent, il n'y a à peu près pas d'espoir pour moi ». Et je lui ai dit : « Je vais écrire au doyen et lui demander si je peux espérer obtenir un poste permanent. Je vais lui demander dans quelle mesure il y a de l'espoir pour moi, puisque toi-même, tu n'as pas de permanence. Est-ce que j'ai un avenir à l'Université? » Charlie m'a simplement dit « Vas-y! »

Il ne croyait pas que j'allais le faire, mais je l'ai fait. J'ai écrit une lettre pour le doyen. J'ai dit à Charlie que j'étais ébranlé et que j'allais envoyer la lettre. Il m'a dit : « Fais comme bon te semble », mais il ne me pensait pas capable de le faire. J'ai donc envoyé ma lettre au doyen, et le doyen m'a répondu : « Évidemment qu'il a un poste permanent. » En fait, il a dit : « Ne vous inquiétez pas, il a un poste permanent. »

J'imagine que le doyen a écrit à Charlie, et Charlie était un peu nerveux lors de la réunion suivante, et il m'a dit : « Eh bien, je ne savais pas. Je ne savais pas que j'avais un poste permanent. » Et je me suis dit qu'il se moquait encore de moi. Il y a eu plusieurs autres incidents – je ne vous embêterai pas avec ça – et je me suis dit…

Christopher Canning : Est-ce que la situation avait des répercussions pour l'ensemble du groupe ou était-ce un problème uniquement entre vous deux?

Reynold Gold : C'était un problème entre nous parce que j'ai fait bien attention de ne pas faire de vagues. Je n'ai pas fait de crise, j'ai juste tenu mon bout. Et comme Clarke Fraser le dirait, il fallait simplement réfuter ses arguments un par un. C'est ce que j'ai fait. Je ne sais pas pourquoi il agissait comme ça, mais je ne suis pas le seul à penser ça.

Christopher Canning : Et bien sûr, vous travaillez tous au même endroit à ce moment-là et vous faites des expériences pour vos projets individuels qui profitent à tout le groupe.

Reynold Gold : En effet. Je crois qu'il aurait peut-être pu m'aider à obtenir mon poste permanent, comme il l'a fait pour Susie. Mais il a agi d'une façon pas très honnête.

Christopher Canning : Avec l'ensemble du groupe?

Reynold Gold : Avec moi. Mais je suis celui qui a mis le doigt sur le problème. Je pense que je suis un homme plutôt tolérant, mais si j'estime que quelqu'un n'est pas honnête avec moi, je durcis le ton. Si j'ai l'impression qu'une personne agit de façon non intentionnelle ou qu'elle risque de se montrer un peu irritable, je vais me retenir, mais si je m'aperçois qu'elle cherche à me nuire, je peux montrer les dents.

Christopher Canning : C'est ce que vous ressentiez à l'époque?

Reynold Gold : Oh oui! Mais je ne sais pas pourquoi il a agi comme ça. Notre relation ne se résumait pourtant pas à ça. Vous m'avez aussi demandé pourquoi je suis parti. Il faut savoir que Charles Scriver est un homme très étrange, pour plusieurs raisons. Laissez-moi d'abord revenir à l'époque où j'ai arrêté de travailler sur la kératine. J'ai laissé ce projet de côté pour les raisons que j'ai déjà mentionnées, mais aussi parce que j'ai commencé à m'intéresser aux tests de dépistage. Charlie avait élaboré une méthode de dépistage à deux tests. Il utilisait en fait deux méthodes et faisait un dépistage du statut de porteur de la phénylcétonurie et de la maladie de Tay-Sachs. J'ai lu ses documents, et je me suis rendu compte qu'il utilisait mal les données. D'un point de vue mathématique, son utilisation des données était totalement incorrecte. Je lui ai dit ce que j'avais constaté, et je lui ai aussi dit que j'allais rédiger un article. Il m'a répondu : « OK, pas de problème. »

Christopher Canning : Qu'elle était votre formation en mathématiques?

Reynold Gold : Je n'en avais pas vraiment. J'ai fait des mathématiques au secondaire, c'est à peu près tout. Mais j'ai une assez bonne maîtrise des notions de base en mathématiques. Je n'ai pas de formation officielle, mais il ne s'agit pas ici de mathématiques très compliquées. Je peux vous donner un exemple d'une mauvaise utilisation qu'il faisait des données. C'est un peu difficile à expliquer. Connaissez-vous un peu la théorie des probabilités?

Christopher Canning : À peine.

Reynold Gold : Je vais essayer de vous expliquer pourquoi l'utilisation qu'il faisait des données pouvait être vraiment dangereuse. Il cherchait à dépister l'état de porteur de la phénylcétonurie, et il faisait passer un test à des personnes prises au hasard,

qui avaient environ une chance sur cinquante d'être porteuses de la maladie. Il testait également les enfants sains de deux porteurs. Dans ce cas, la probabilité était de deux sur trois. Si l'enfant de deux porteurs obtenait les mêmes résultats que l'enfant d'une personne choisie de façon aléatoire, Charles attribuait la même probabilité aux deux enfants. Mais ce raisonnement est complètement faux parce que la probabilité est plus grande dès le départ, même si les résultats sont les mêmes. On peut calculer cette probabilité plus élevée à l'aide du théorème de Bayes. Il n'a pas du tout pensé à la probabilité dans son raisonnement. J'ai donc fait une analyse mathématique avec l'aide de quelques collaborateurs.

Christopher Canning : Au moment où il faisait ses tests de dépistage?

Reynold Gold : Non, après la publication de son article dans la revue *Nature*. Étonnamment, il a totalement accepté nos conclusions. Il n'a pas dit : « Je ne sais pas trop… » Il n'a rien contesté. En fait, il en a parlé à des visiteurs; ou plutôt, il a mal expliqué l'analyse parce qu'il ne la comprenait pas. C'était complètement absurde. Il était **quand même** coauteur de cet article!

On peut voir là de la tolérance et de la bienveillance, mais il faut savoir qu'il a accepté nos conclusions, même s'il ne les comprenait pas du tout. Je trouve que c'est étrange, très étrange. On pourrait dire que sa réaction démontre une grandeur d'âme, ce qui est le cas, mais cela cache aussi autre chose que je n'arrive pas à m'expliquer. On pourrait croire qu'une personne qui a publié un article dans *Nature* et qui se fait dire que sa théorie est complètement fausse aurait le réflexe d'affronter ses opposants. Mais il n'a pas eu ce réflexe parce qu'il ne maîtrisait pas le sujet.

Christopher Canning : Comment l'article s'est-il retrouvé dans *Nature*?

Reynold Gold : C'est Charles Scriver qui l'a fait publier.

Christopher Canning : Mais comment a-t-il fait si les calculs et les analyses de probabilité étaient discutables?

Reynold Gold : Les recherches en étaient à leurs débuts, et c'était une bonne idée. C'était une bonne idée d'avoir recours à deux tests, et j'imagine que la personne qui a lu l'article ne s'est pas attardée à l'aspect mathématique. Les revues publient beaucoup de choses et toutes sortes de choses. L'autre question importante qu'on pourrait se poser au sujet du groupe, c'est « qu'a-t-il réellement accompli? ». C'est une question intéressante. On peut évidemment dire qu'il a organisé le dépistage de maladies génétiques et la prise en charge des personnes atteintes. Et il a fait ça très très bien, et probablement mieux que n'importe où ailleurs dans le monde. Donc, si c'était là la raison d'être du groupe de génétique, on peut dire que le but a été atteint. Est-ce que le groupe a accompli suffisamment de choses d'un point de vue scientifique? Je ne crois pas.

Christopher Canning : L'ensemble du groupe?

Reynold Gold : Non.

Christopher Canning : Pendant les 37 années?

Reynold Gold : En fait, je ne sais pas vraiment ce qu'il a accompli. Il a rédigé un très grand nombre d'articles, mais combien de percées scientifiques vraiment importantes le groupe a-t-il réalisées? Je ne sais pas ce qui s'est passé plus tard. Êtes-vous au courant de découvertes? Je sais très bien qu'il ne s'est rien produit de marquant lorsque je faisais partie du groupe, ni dans mes travaux, ni dans ceux des autres. Nous n'avons pas découvert quelque chose comme le récepteur de l'antigène des lymphocytes T ou le rôle d'un gène dans une maladie quelconque.

Christopher Canning : Je vais vous lire un extrait de la demande de subvention de 1972. Voici ce que le groupe a indiqué comme buts de la recherche. Vous pourrez peut-être ensuite me dire ce qui a été réalisé. On dit que le groupe cherchait à établir l'origine des modes d'hérédité, à évaluer l'aspect génétique des maladies familiales autres que mendéliennes, à étudier la sensibilité génétique à la maladie et à poursuivre le travail en consultation génétique.

Reynold Gold : En fait, j'ai travaillé sur l'aspect mathématique de la consultation génétique. Je viens d'ailleurs de vous en parler. J'ai aussi mis au point une sorte d'algorithme mathématique. En tenant compte de données sur les membres d'une famille, du pedigree et de renseignements pertinents sur les membres de ce pedigree, on pouvait utiliser un algorithme pour calculer automatiquement les risques associés à chaque personne. Je crois que cette méthode est mentionnée dans ma demande sur la génétique clinique. Je pense que je peux donc dire que j'ai fait quelque chose en consultation génétique.

Christopher Canning : Et ce domaine semble avoir survécu depuis les années 1970. La consultation génétique est toujours un aspect important de la génétique médicale.

Reynold Gold : Oui, nous avons travaillé sur la consultation génétique. Continuons à parler des buts du groupe et je vous en dirai plus.

Christopher Canning : L'origine des modes d'hérédité?

Reynold Gold : Je pense que nous n'avons pas découvert grand-chose à ce sujet. Mais je n'en sais rien. Je ne suis pas au courant des articles qui ont été publiés après mon passage dans le groupe. Savez-vous s'il y a eu des articles à ce sujet?

Christopher Canning : C'est ce que nous tentons d'établir. C'est trop tôt pour que je puisse me prononcer sur ce que le groupe a découvert ou n'a pas découvert.

Reynold Gold : Nous avons constaté la perte d'une famille de protéines dans une maladie dominante. Mais ça ne nous éclaire pas vraiment sur l'origine. Ça nous dit qu'une chose s'est produite dans une maladie transmise sur un mode dominant, mais ça ne donne aucune indication sur le mécanisme. Mais je vous laisse continuer.

Christopher Canning : Plus précisément, vous avez fait des recherches sur la dysplasie ectodermique, n'est-ce pas?

Reynold Gold : Il s'agit d'une maladie héréditaire dominante.

Christopher Canning : Une maladie héréditaire dominante, et…

Reynold Gold : Et la souris nude. Quels sont les autres objectifs?

Christopher Canning : L'évaluation de l'aspect génétique des maladies familiales autres que mendéliennes.

Reynold Gold : Nous ne pouvons toujours pas faire ça, même avec les nouvelles techniques de génétique moléculaire. Pour l'instant, nous n'avons qu'effleuré ce sujet.

Christopher Canning : La morphologie des chromosomes.

Reynold Gold : Y avait-il des cytogénéticiens?

Christopher Canning : Pendant les premières années du groupe. Quand le groupe s'est formé, on a assisté au rapprochement de la cytogénétique et de la tératologie, avec le D^r^ Fraser, et de la biochimie, avec le D^r^ Scriver.

Reynold Gold : Le D^r^ Fraser ne fait pas de cytogénétique.

Christopher Canning : Si je ne me trompe pas, il s'intéressait à la cytogénétique et à la tératologie.

Reynold Gold : Vraiment?

Christopher Canning : Oui, dans les années 1950. Je crois qu'il a formé d'autres cytogénéticiens et qu'il a fait quelques recherches dans ce domaine.

Reynold Gold : Oui, c'est vrai. Vous avez raison.

Christopher Canning : Nous avons donc la cytogénétique, l'étude de la morphologie des chromosomes, ainsi que la biochimie et la pédiatrie. Ce sont les domaines qui sont mentionnés dans la première demande de subvention et qui définissaient le groupe à ses débuts.

Reynold Gold : Je ne pense pas que la pédiatrie puisse être considérée comme un objectif scientifique. C'est une spécialité de la médecine. Les travaux du groupe avaient des applications très pratiques qui gravitaient autour des soins associés aux maladies génétiques. On pourrait se demander pour quelle raison un groupe de génétique humaine a été créé. Je pense qu'un tel groupe aurait une plus grande raison d'être de nos jours. Voyons la question autrement. Pour étudier le fonctionnement des gènes et les mécanismes qui assurent la vie, il ne fallait pas étudier les humains. Du moins, pas à cette époque. Peut-être les souris, *E. coli* ou des virus. À ce moment-là, à cause des connaissances limitées en génétique humaine, il était très difficile de faire des découvertes scientifiques applicables à la santé humaine ou encore d'utiliser la génétique humaine pour repousser les frontières de la science.

Christopher Canning : Toutefois, à cette époque, la recherche en génétique humaine n'était pas nécessairement motivée par les résultats, mais plutôt par les possibilités. Et les débuts sont remplis de promesses.

Reynold Gold : C'est exact. Vous voyez, à l'époque, il était évident que ce n'était pas en faisant de la génétique humaine qu'on pouvait espérer faire avancer notre compréhension de la génétique. En gros, il y avait deux raisons d'étudier la génétique humaine : l'envie narcissique de faire de l'auto-contemplation et l'espoir de faire une découverte médicale.

Christopher Canning : Vous diriez qu'il s'agit là des objectifs de la génétique médicale à ses débuts?

Reynold Gold : Oui, en partie. Supposons que le directeur du Conseil de recherches médicales se demande pourquoi il veut créer un groupe de génétique humaine. Si je voulais en savoir plus sur les avancées fondamentales concernant les gènes, je ne m'intéresserais pas aux humains. On pourrait alors s'intéresser à la génétique humaine parce qu'on veut en savoir plus sur soi-même. Il n'y a rien de mal à ça, mais ça n'a rien à voir avec la science. L'autre raison serait parce que c'est pertinent d'un point de vue médical.

Mais à cette époque, l'espoir de faire une découverte fondamentale en génétique humaine était très mince. Aujourd'hui, je crois qu'il y a deux raisons d'étudier la génétique humaine, d'un point de vue scientifique. Tout d'abord, si on a le génome, et on connaît un très grand nombre de phénotypes et beaucoup plus de choses sur les phénotypes qui sont influencés par les gènes, donc, si on a une séquence de gènes complète et un immense répertoire de phénotypes, on a une bonne chance de pouvoir étudier le mécanisme des gènes. Et même dans ce cas, on ne peut pas faire beaucoup de chemin, même si les opinions divergent à ce sujet, mais ça va venir.

Ensuite, on peut vouloir essayer de trouver le fondement génétique de la conscience, parce que cette conscience de l'être humain, est en quelque sorte un phénomène fascinant d'un point de vue scientifique. Et si on arrive à découvrir pourquoi nous ne sommes pas des chimpanzés en comparant le génome du chimpanzé et celui de l'humain, on a les premiers éléments pour découvrir les différences génétiques qui font que nous avons une forme de conscience que les chimpanzés n'ont pas.

Vous avez peut-être entendu parler des régions accélérées humaines? Par des méthodes mathématiques et informatiques très complexes, nous avons réussi à cerner des régions du génome humain qui ont changé très rapidement par rapport à celui du chimpanzé depuis six millions d'années. Et dans ces régions, il y a des gènes dont on sait déjà qu'ils sont associés à la parole et à l'activité cérébrale. C'est très intéressant. Si on me demandait de mettre sur pied un groupe de génétique humaine, je m'intéresserais à ces deux aspects.

Christopher Canning : Ironiquement, vous me dites qu'un groupe de recherche en génétique humaine serait plus pertinent de nos jours qu'il y a 40 ans. Alors pourquoi le CRM a-t-il financé le groupe pendant 37 ans?

Reynold Gold : Je ne sais pas. Le savez-vous?

Christopher Canning : C'est ce que nous tentons de déterminer. Quelle est la raison à votre avis?

Reynold Gold : Vous devriez poser la question à la personne qui a pris cette décision. Je ne veux pas vous dire quoi faire, mais vous devriez aussi essayer de savoir

pourquoi ils ont mis fin au groupe. À tous les groupes en fait. J'aimerais bien le savoir. Savez-vous pourquoi ils ont fait ça?

Christopher Canning : Je n'en ai aucune idée, mais nous allons tenter de le découvrir. Par contre, c'est intéressant de savoir qu'au début des années 1970, Malcolm Brown, qui était directeur du CRM, était un ami des parents du Dr Scriver. C'est l'une des principales raisons pour lesquelles les gens de McGill se sont intéressés à la recherche collective au départ.

Reynold Gold : Décisions politiques

Christopher Canning : L'aspect politique n'est évidemment pas étranger à la création de ce groupe. Mais il y avait d'autres groupes à Montréal et ailleurs au Canada qui se penchaient sur d'autres disciplines scientifiques.

Reynold Gold : La question qu'on pourrait se poser, c'est « Est-ce une bonne chose d'avoir des groupes? » C'est une bonne question. Et je dirais que si on a affaire à des personnes très compétentes et qui travaillent dans des domaines différents, un groupe peut être très très productif. Mais s'il y a des éléments médiocres dans le groupe, la médiocrité se propagera. Un groupe renforce ce qui est déjà là, et dans notre groupe, je crois qu'il n'y avait aucun scientifique exceptionnel. Quand je pense à un bon groupe, je pense par exemple à l'Institut Périmètre à Waterloo. Je crois que c'est la première fois que le Canada commence à avoir une université de calibre mondial. À Waterloo. L'Institut Weizmann est un autre excellent exemple de groupe efficace.

Christopher Canning : Où est-il?

Reynold Gold : L'Institut Weizmann se trouve à Rehovot, en Israël. J'y ai enseigné il y a quelques années. C'est un bon exemple. C'est à peu près tout. Je crois avoir tout dit. Vous voulez savoir autre chose?

Christopher Canning : C'est super!

Reynold Gold : Depuis combien de temps discutons-nous?

Christopher Canning : Une heure et demie, ce qui est excellent.

Reynold Gold : J'ai pas mal tout dit. Mais j'aimerais vous parler de quelques idées. Ce n'est pas vraiment pertinent pour votre étude, mais j'ai eu une idée très très innovante. Je songe à écrire un article sur l'organisation des soins de santé. J'ai une idée très précise de ce qui doit être fait. Il doit n'y avoir qu'un seul payeur. Obama a eu beaucoup d'obstacles parce que c'est très difficile d'aller de l'avant s'il n'y a pas qu'un seul payeur. On peut faire comme en Suisse et s'en remettre aux compagnies d'assurance, mais en Suisse, ces compagnies sont très réglementées et n'ont pas le droit de faire des profits. Détail intéressant : même si elles ne sont pas autorisées à faire des profits, elles se livrent une vive concurrence entre elles.

Il faut donc désigner un payeur unique, puis faire en sorte que l'État finance des « organismes de gestion intégrée des soins de santé », les fameux « HMO », une invention des États-Unis. Ils sont très bien, même s'ils ont eu mauvaise

presse récemment. Autrement dit, vous regroupez tous les médecins et toutes les installations dont vous avez besoin pour traiter 500 000 personnes, par exemple. Vous rassemblez tous les psychiatres, économistes de la santé, infirmiers, psychothérapeutes, psychologues, omnipraticiens, pédiatres, chirurgiens esthétiques, bref, tous les spécialistes que vous voulez avoir dans votre groupe. Je pense que le nombre de personnes que peut traiter le spécialiste le plus souvent évalué est une bonne donnée de départ. Ensuite, les 500 000 personnes doivent se joindre à l'un de ces groupes de patients, puis le gouvernement dit à chaque groupe : « Nous voyons que vous avez un groupe de 500 000 patients, et les contribuables acceptent de payer 4 000 ou 5 000 dollars par personne pour l'assurance maladie. Voici deux milliards de dollars, bonne chance et à la prochaine! »

C'est aussi simple que ça. Et rapidement, les médecins découvriront que les infirmières praticiennes sont la meilleure invention depuis la roue. Et il faudra aussi mettre en place une formation en santé qui fonctionne, parce que ça permet de faire des économies, et éliminer tout ce qui ne fonctionne pas.

C'est ça qu'il faut faire parce que si le gouvernement ne peut pas décider, on peut compter sur un conseil d'administration composé de médecins, de gens d'affaires, d'économistes de la santé, de patients. Tous les revenus des fournisseurs de soins de santé sont mis en commun et si, par exemple, un conseil d'administration veut retenir un très bon médecin, il pourra le payer un peu plus. Et si un médecin n'est pas bon, le conseil ne se gênera pas pour refuser une augmentation, et le médecin partira. C'est comme ça qu'il faut procéder.

Je crois que c'est la façon de faire, mais aussi qu'il faut absolument faire ça parce que c'est la seule solution. Que pensez-vous de ça?

Christopher Canning : De toute évidence, vous en savez beaucoup plus que moi sur ce sujet.

Reynold Gold : Je vais écrire un article là-dessus.

Christopher Canning : C'est très intéressant. Écrivez-vous en ce moment?

Reynold Gold : Eh bien, j'écris cet article.

Christopher Canning : Super! Est-ce que je peux le lire?

Reynold Gold : Il n'est pas encore écrit. Mais je vais le soumettre au *Globe and Mail* comme article de fond.

Christopher Canning : Fantastique!

Reynold Gold : Je crois que c'est tout ce que j'avais à dire, à moins que vous…

Christopher Canning : Je crois que nous avons fait le tour de la question.

Reynold Gold : Vous avez d'autres questions?

Christopher Canning : Juste une question pour terminer. Avez-vous gardé contact avec certains membres du groupe? Je sais que vous avez déménagé à Toronto pour travailler de là-bas.

Reynold Gold : Exactement. J'ai fait des recherches et j'ai obtenu une permanence là-bas.

Christopher Canning : Pratiquiez-vous toujours la médecine à ce moment-là?

Reynold Gold : Non. Je ne pratiquais pas la médecine. Mais j'ai obtenu ma permanence. Ensuite, comme ma femme n'arrivait pas à trouver un emploi à Toronto – elle est professeure de psychologie – j'ai décidé de revenir à la maison et de rester avec ma famille en pratiquant la médecine. J'ai pris cette décision pour des raisons familiales, mais aussi parce que je ne pensais pas réussir à faire des découvertes aussi intéressantes que je l'aurais voulu.

Et puis, être professeur permanent, ce n'est pas si important quand on n'arrive pas à accomplir ce qu'on aimerait accomplir. Je ne faisais pas vraiment ce que je voulais faire en recherche fondamentale, et je ne pouvais pas faire ce que j'espérais faire. J'ai donc choisi de pratiquer la médecine à la place.

Christopher Canning : Je vois. Avez-vous gardé contact avec des membres du groupe? J'ai l'impression que vous et Susie Tenenhouse étiez…

Reynold Gold : Je l'ai revue au dîner. Par la suite, elle m'a envoyé un courriel parce qu'elle avait découvert qu'une chanteuse folk célèbre, son nom m'échappe… c'est une chanteuse connue mondialement… Toujours est-il que Susie venait de lire un livre dans lequel cette chanteuse folk disait que j'avais lancé sa carrière. Nous avions un café, le Louis Riel, en Saskatchewan. Des chanteurs folk venaient y chanter et on avait de grandes discussions sur Cuba à l'époque. Et il y avait cette serveuse dont j'ai oublié le nom. Ça me reviendra.

Christopher Canning : Une chanteuse folk canadienne?

Reynold Gold : Oui.

Christopher Canning : Joni Mitchell?

Reynold Gold : Oui, c'est ça! Joni Mitchell. Elle s'appelait Joni Anderson à l'époque. Elle était serveuse au Louis Riel.

Christopher Canning : Wow, Joni Mitchell était serveuse dans votre café?

Reynold Gold : J'avais complètement oublié ça. Dans son livre, elle dit qu'elle est venue passer une audition et que mes deux copropriétaires lui ont dit d'oublier ça, mais que j'ai dit : « Attendez, elle a quelque chose de spécial. » Je suis moi-même musicien, voyez-vous. J'ai donc insisté pour qu'on lui donne sa chance. Elle me décrit comme « un homme à lunettes et à l'accent d'Oxbridge qui conduit une Jaguar ».

Christopher Canning : Pas mal!

Reynold Gold : Toujours est-il qu'elle est très populaire et qu'elle me remercie d'avoir lancé sa carrière. Je suis certain que si je ne l'avais pas fait, quelqu'un d'autre l'aurait fait. J'ai donc envoyé un courriel à son agent pour lui dire que j'aimerais beaucoup la rencontrer. J'étais très content de cette marque de reconnaissance. Ensuite, j'ai eu une influence…

Christopher Canning : Sur la carrière de Joni Mitchell? Super!

Reynold Gold : Susie m'a donc envoyé ce courriel pour me parler de ce livre qu'elle venait de lire. J'ai aussi contacté Peter Hechtman pour l'inviter à souper, mais je n'ai pas eu de réponse. Mais je suis resté en très bons termes avec eux. Aucun problème de ce côté-là.

Christopher Canning : Voilà qui conclut notre entretien. Merci beaucoup d'avoir pris le temps de répondre à mes questions.

FIN DE L'ENTRETIEN

Dr Leonard Pinsky, le 21 juillet 2010

Christopher Canning : Nous sommes le 21 juillet 2010. Ici Christopher Canning en compagnie du Dr Leonard Pinsky. Dr Pinsky, je suis honoré de pouvoir m'entretenir avec vous de deux grands sujets en génétique humaine. J'aimerais d'abord que nous parlions de votre parcours universitaire, qui vous a permis de contribuer grandement à l'avancement de la génétique médicale au Canada et ailleurs dans le monde. Ensuite, et c'est le principal thème de mon étude, j'aimerais parler de votre participation au sein du groupe sur la génétique médicale des IRSC[1] – anciennement le CRM[2] – de McGill, dont vous avez été membre de 1981 à 1990.

Mais parlons d'abord de vous, si vous le voulez bien. Pouvez-vous nous parler de votre lieu de naissance, de votre enfance et de vos premières années d'école?

Dr Leonard Pinsky : C'est une véritable enquête!

Christopher Canning : Vous pouvez donner la quantité de détails que vous voulez.

Dr Leonard Pinsky : J'étais un peu spécial. [rires] Dès l'âge de 5 ans, environ, chaque fois qu'on me demandait ce que je voulais faire quand je serais grand, je répondais que je voulais être médecin. Pourquoi? Aucune idée. Il n'y avait pourtant pas de médecins dans mon entourage. J'ai grandi à une époque où il n'y avait pourtant pas une foule d'émissions de télévision qui se déroulaient dans un hôpital, comme aujourd'hui. Toujours est-il que je voulais être médecin.

Lorsque j'étais adolescent, un de mes amis s'est blessé pendant que nous jouions au touch-football dans la rue avec un ballon fait de chaussettes. Il a fait une mauvaise chute et s'est cassé la jambe. Je me souviens que j'étais si effrayé que je me suis enfui. Un peu plus loin, je me suis demandé pourquoi je courais. Je me suis dit : « Tu ne deviendras jamais médecin si tu te sauves ». [rires]

Voilà mes débuts en médecine.

Christopher Canning : Ou plutôt le moment où vous avez commencé à vous intéresser à la médecine.

Dr Leonard Pinsky : Oui.

Christopher Canning : Et où était-ce? Avez-vous grandi à Montréal?

Dr Leonard Pinsky : Oui, à Montréal.

Christopher Canning : Vous êtes né à Montréal également?

Dr Leonard Pinsky : Oui.

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

Christopher Canning : Et quel genre d'étudiant étiez-vous à l'école secondaire? Vous intéressiez-vous aux sciences à cette époque?

Dr Leonard Pinsky : Je peux vous répondre par une autre bonne anecdote.

Christopher Canning : Parfait, nous aimons les anecdotes.

Dr Leonard Pinsky : J'ai grandi dans un quartier particulier de Montréal. Il abritait la plupart des familles juives qui avaient immigré au cours des cinq, 10 ou 15 premières années du XIXe siècle, pendant une grande migration des familles juives vers New York et Montréal.

Christopher Canning : Étiez-vous un bon étudiant au secondaire?

Dr Leonard Pinsky : Je n'étais pas mal, mais je n'étais pas un cerveau non plus. Les sports étaient beaucoup plus importants pour moi.

Christopher Canning : Et comment étaient vos parents? Vous poussaient-ils à avoir de bons résultats?

Dr Leonard Pinsky : Non.

Christopher Canning : Non?

Dr Leonard Pinsky : Non. Mon père ne croyait pas qu'il avait un fils suffisamment bon ou spécial qui pouvait devenir médecin.

Christopher Canning : Je vois que vous êtes entré à McGill au début des années 1950.

Dr Leonard Pinsky : J'ai commencé mes études à McGill en 1952.

Christopher Canning : C'est ça. Dans quel programme?

Dr Leonard Pinsky : C'était une sorte de programme mixte parfait pour les personnes comme moi qui ne savaient pas si elles voulaient étudier en arts ou en sciences. Croyez-le ou non, McGill offrait un baccalauréat mixte, mais j'ai rapidement découvert que ce n'était pas pour moi et que j'allais beaucoup mieux réussir en sciences qu'en latin.

Christopher Canning : Je vois.

Dr Leonard Pinsky : À cette époque, les gens croyaient encore que pour être médecin, il fallait savoir rédiger des ordonnances en latin. [rires] Ça semble stupide, mais on peut constater que les choses ont bien changé. Les choses ont aussi beaucoup changé au cours de ma carrière. Nous sommes passés d'un monde où on croyait que les ordonnances se rédigeaient en latin à un monde où on prescrit ce qu'il est convenu aujourd'hui d'appeler des « traitements personnalisés » à des personnes qui souffrent d'une erreur innée du métabolisme.

Christopher Canning : Je vois.

Dr Leonard Pinsky : Nous observons aujourd'hui le résultat de cette révolution dans les domaines de la génétique et des sciences.

Christopher Canning : Oui.

Dr Leonard Pinsky : J'ai perdu le fil de ma pensée. Je voulais dire autre chose sur mes études secondaires, mais ça me reviendra peut-être.

Christopher Canning : Pas de problème. Vous avez donc obtenu votre baccalauréat en 1956. Un baccalauréat en sciences?

Dr Leonard Pinsky : C'est ça.

Christopher Canning : Et je vois que vous vous êtes ensuite inscrit en médecine.

Dr Leonard Pinsky : Oui. J'imagine que je devrais vous parler de mes années de premier cycle?

Christopher Canning : Oui, si vous le voulez bien.

Dr Leonard Pinsky : C'est très simple. Je suis entré à McGill en 1952. Je vous ai déjà dit que j'étais dans un programme mixte. J'ai rapidement su que la génétique serait mon sujet de prédilection. Avant 1955.

Christopher Canning : Avant Watson et Crick.

Dr Leonard Pinsky : Oui, c'est ça.

Christopher Canning : Je vois.

Dr Leonard Pinsky : Ça remonte à loin. McGill n'avait pas de programme de spécialisation en génétique avant que deux autres étudiants et moi exprimions au même moment un vif intérêt pour ce sujet.

Christopher Canning : Bien. Est-ce que ça se passait dans le Département de biologie à cette époque?

Dr Leonard Pinsky : C'était le Département de génétique.

Christopher Canning : Je vois.

Dr Leonard Pinsky : Plus tard, la génétique, la biologie et la zoologie ont fusionné, puis défusionné. Je ne me rappelle pas les dates exactes. Ce renseignement serait facile à trouver, si vous le voulez, mais je ne crois pas que ce soit important. Il faut juste savoir que la génétique a eu du mal à se faire connaître au sein de l'Université.

Christopher Canning : Alors, qu'est-ce qui vous a attiré dans la génétique clinique si personne ne s'intéressait vraiment à la génétique à McGill?

Dr Leonard Pinsky : C'est une excellente question, et je suis content que vous me la posiez. C'est l'une des rares choses que je me félicite d'avoir faites. Je ne sais pas comment j'ai fait, mais j'ai réussi à voir clair dans toute cette pile d'information accumulée jusqu'au milieu des années 1950, environ. J'ai compris que si une personne tombait malade alors que ce n'était pas le cas d'une autre personne exposée à la maladie, c'était probablement parce que ces deux personnes avaient des

différences génétiques.

Christopher Canning : Comme c'était avant la visualisation de la structure de l'ADN, vous vous disiez que la maladie était héréditaire?

Dr Leonard Pinsky : C'est exact. Je ne suis pas en train de vous dire que j'avais déduit que l'ADN renfermait de l'information génétique et qu'elle pouvait expliquer pourquoi une personne tombait malade et une autre personne non. Je ne dis pas que je savais que l'ADN était la clé, mais que je savais qu'il y avait quelque chose de nouveau.

En fait, je ne savais pas vraiment. J'avais une intuition qu'il y avait quelque chose comme l'ADN qui produisait les effets que j'avais constatés.

Christopher Canning : Avec qui travailliez-vous à ce moment-là? Qui d'autre s'intéressait à la génétique et à la possibilité qu'elle puisse s'appliquer à la médecine humaine?

Dr Leonard Pinsky : Nous n'étions que trois. Que trois : un, deux trois! Il y a eu trois personnes dans le premier programme spécialisé en génétique, et l'année suivante, une autre personne très importante est arrivée. C'est tout ce dont je me souviens avec certitude. Et ces personnes étaient vraiment remarquables.

L'une d'elles était David Rimoin, qui a réalisé des choses vraiment admirables dans le domaine de la génétique humaine et médicale. Je n'entrerai pas dans les détails, mais je peux vous dire qu'il est devenu célèbre.

Il y avait une deuxième personne, qui a poursuivi sa formation en obstétrique et en gynécologie, et il y avait moi. Une quatrième personne est ensuite arrivée en deuxième année. Il s'agissait de Dorothy de Montmorency, qui a fait de remarquables réalisations en cytogénétique humaine.

Christopher Canning : Parlons maintenant de vos années d'études en médecine. Vous avez terminé votre baccalauréat dans ce programme mixte de biologie et d'arts, puis vous êtes entré à la Faculté de médecine. À cette époque, vous commenciez donc à vous intéresser à la génétique et à son utilisation en médecine humaine. Quelle place la génétique a-t-elle prise dans votre formation en médecine?

Dr Leonard Pinsky : Eh bien, lorsque je suis entré à la Faculté de médecine en 1956, l'ADN était déjà un sujet chaud.

Christopher Canning : Évidemment.

Dr Leonard Pinsky : Les progrès ont été rapides et auraient été accomplis avec ou sans moi; on a vite vu le rôle possible de l'ADN et de l'ARN, entre autres.

Pendant ma formation en médecine, j'ai touché à la génétique en passant tous mes étés à travailler avec Clarke Fraser. Je me suis demandé si la génétique n'était pas la clé de bien des problèmes de santé dans le monde, et j'en suis devenu de plus en plus convaincu au fil du temps.

Christopher Canning : D'après mes recherches, vous avez obtenu votre diplôme en 1960. Pendant vos dernières années d'études, vous avez publié un article très intéressant sur

une approche génétique de la médecine globale.

Dr Leonard Pinsky : C'est exact.

Christopher Canning : Vous étiez jeune; vous deviez avoir 24 ou 25 ans.

Dr Leonard Pinsky : Effectivement.

Christopher Canning : Qu'est-ce qui vous a incité à écrire cet article? On dirait presque une déclaration sur la nécessité d'intégrer la génétique à la médecine.

Dr Leonard Pinsky : C'est vrai. Et ce n'est pas qu'une impression. Je pensais avoir tout compris.

Christopher Canning : Je vois ce que vous voulez dire.

Dr Leonard Pinsky : Je pensais avoir trouvé la solution aux grands problèmes de santé dans le monde. Je voulais attirer l'attention du milieu médical et je voulais convaincre les autres que j'avais raison. J'ai donc recueilli toute l'information, ce qui n'était pas une sinécure pour un étudiant en troisième et quatrième années de médecine. En réalité, j'ai publié deux articles intitulés *Genetic Approches to Comprehensive Medicine*. Le deuxième article traitait de pathologie moléculaire et portait le sous-titre *Prevention*.

Christopher Canning : En fait, je vois que l'article *Genetic Approches to Comprehensive Medicine – Prevention* a été publié en premier.

Dr Leonard Pinsky : C'est bien ça.

Christopher Canning : Ce fut votre premier article, publié en 1959. Puis il y a eu *Genetic Approches to Comprehensive Medicine – Molecular Pathology*, qui est paru en 1960.

Dr Leonard Pinsky : C'est ça.

Christopher Canning : Vous souvenez-vous de ce que vous avez ressenti au moment de la publication? Ça devait être palpitant pour un jeune étudiant en médecine?

Dr Leonard Pinsky : Oui, très palpitant. Tout d'abord, les quelques personnes qui ont lu les articles les ont trouvés très bons, ce qui m'a fait vraiment plaisir. Et je me souviens que Clarke Fraser avait été très élogieux. Que dire de plus?

Christopher Canning : La génétique médicale en était encore à ses débuts. Qu'est-ce qui vous intéressait le plus en génétique? Je ne vous demande pas de les énumérer par ordre d'importance, mais quels sujets vous intéressaient? La biologie des cellules somatiques, la culture cellulaire ou la biochimie, par exemple? Tous ces sujets étaient dans l'air du temps.

Dr Leonard Pinsky : À ce moment-là, mes études en médecine étaient terminées et j'avais des décisions à prendre. J'ai décidé de me spécialiser en pédiatrie, parce que j'avais souvent entendu dire que lorsqu'on voulait avancer en médecine universitaire, il ne fallait pas commencer par un sujet comme la génétique. Il était préférable d'opter pour la pédiatrie, par exemple.

J’ai donc choisi la pédiatrie, en partie parce que j’aimais bien travailler avec les enfants et en partie par stratégie, comme je l’ai dit tout à l’heure. Ensuite, je me suis progressivement dirigé vers la génétique.

Christopher Canning : Et j’imagine que c’est pour ça que vous vous êtes retrouvé à l’Institut Lady Davis.

Dr Leonard Pinsky : Non.

Christopher Canning : Ça, c’est un peu plus tard.

Dr Leonard Pinsky : Beaucoup plus tard.

Christopher Canning : Parfait. Nous y reviendrons.

Dr Leonard Pinsky : Nous y reviendrons très rapidement. J’ai fait une résidence d’un an à l’Hôpital général juif. C’était une résidence par rotation classique. J’ai ensuite passé un an à l’Hôpital de Montréal pour enfants, puis ma femme et moi avons déménagé. Je me suis marié au début de ma résidence par rotation, et ma femme étudiait alors en médecine. Le meilleur moment pour un déménagement était à la fin de sa deuxième année de médecine, et à la fin de ma première année de pédiatrie, pendant ma résidence.

Nous avons donc déménagé à Philadelphie. Ma femme est allée à la Temple Medical School, et moi, à l’hôpital pour enfants Saint Christopher, à Philadelphie. C’est un bon hôpital, même s’il est moins connu que le Children’s Hospital of Philadelphia, qui est associé à l’Université de Pennsylvanie. Donc, encore une fois, à la fin de ma deuxième année à Philadelphie…

Christopher Canning : C’était en quelle année?

Dr Leonard Pinsky : En 1964. Tout ça va s’éclairer dans une minute.

Nous avions une autre décision à prendre. Ma femme terminait ses études en médecine, et c’est à ce moment-là que j’ai bifurqué vers les sciences. J’ai choisi de m’intéresser à la génétique des cellules somatiques humaines à l’Université du Michigan, sous la supervision de Robert S. Krooth.

Christopher Canning : Vous vous êtes donc joint au groupe de génétique des cellules somatiques au Département de génétique humaine de l’Université du Michigan, ce qui est intéressant dans la mesure où l’Université avait déjà un Département de génétique humaine à cette époque.

Dr Leonard Pinsky : À l’époque, peu d’universités avaient un Département de génétique, de génétique humaine ou de génétique médicale, peu importe le nom qu’on lui donnait. Aux États-Unis, il y en avait un au Michigan, un au Wisconsin, un à Seattle, un à Washington et peut-être un autre. Le seul autre département en Amérique du Nord était celui de Clarke Fraser, à l’Université McGill.

Christopher Canning : Qui, techniquement, n’était pas un département à cette époque. C’était une unité.

Dr Leonard Pinsky : Oui. On leur donnait différents noms. Je n'arrive pas à me souvenir de tous les noms. Il y avait aussi un groupe à l'Hôpital des enfants malades de Toronto, qui était dirigé par Peggy Thompson. Elle n'était pas médecin, mais elle a beaucoup apporté à la génétique médicale au Canada, à ses débuts.

Elle a joué un rôle dans l'histoire du développement de la génétique médicale au Canada, mais son importance n'est pas tellement grande. J'espère que mes propos ne seront pas publiés. [rires]

Son rôle n'est pas aussi grand que d'autres, dans le monde de la génétique au Canada. Mais il faut préciser que Peggy Thompson et son mari ont coécrit ce qui est, je pense, le premier manuel de médecine humaine qui a connu du succès, à juste titre. Et ce manuel a été publié au Canada.

Christopher Canning : D'accord.

Dr Leonard Pinsky : J'espère juste que Peggy ne sera pas trop fâchée.

Christopher Canning : Vous étiez donc au Michigan, en 1965 et 1966, et vous êtes retourné à l'Hôpital général juif en 1967.

Dans quelle mesure votre expérience au Michigan vous a-t-elle donné envie de créer votre propre Centre de génétique humaine à McGill, qui n'a vu le jour qu'à la fin des années 1970? À votre retour du Michigan, et pendant votre collaboration avec Clarke Fraser, pensiez-vous que McGill avait besoin d'une unité plus directement liée à la génétique médicale?

Dr Leonard Pinsky : Le travail de Clarke Fraser était déjà directement lié à la génétique médicale. Mais voilà où ça devient intéressant. Pour une raison que je ne m'explique toujours pas, je trouvais qu'il était important d'aider l'Hôpital général juif à devenir un hôpital universitaire à part entière pour la Faculté de médecine de McGill. Et j'estimais que si j'allais à l'Hôpital général juif pour lancer un programme de génétique, j'atteindrais ce but.

C'est ce qui m'a poussé à choisir Montréal. J'ai reçu beaucoup d'offres d'écoles de médecine au Canada et aux États-Unis, mais j'ai décidé de revenir à Montréal. Et quand je suis revenu, j'avais dans mes bagages les compétences et les connaissances nécessaires en génétique des cellules somatiques.

La génétique des cellules somatiques est l'étude des mécanismes génétiques qui touchent la physiologie ou la pathologie au moyen de cellules produites en éprouvettes plutôt qu'*in utero*.

Christopher Canning : Est-ce à ce moment-là que vous avez commencé à vous intéresser à la génétique des récepteurs des androgènes?

Dr Leonard Pinsky : Oui.

Christopher Canning : Vous avez donc étudié la biologie des cellules somatiques et la culture de cellules, et vous vous êtes principalement intéressé aux différences sexuelles et aux récepteurs des androgènes, c'est bien ça?

Dr Leonard Pinsky : C'est ça. Je voudrais juste préciser que j'ai été la première personne à Montréal à cultiver des cellules somatiques diploïdes humaines dans le but d'étudier les maladies génétiques qui touchent ces cellules, ce qui ne me semblait pas très important à l'époque, mais qui est intéressant du point de vue historique.

Christopher Canning : Bien.

Dr Leonard Pinsky : J'ai commencé à travailler comme chercheur indépendant en 1967. Je pense que c'était en 1967.

Christopher Canning : Au moment où vous étiez directeur du laboratoire de génétique cellulaire à l'Hôpital général juif?

Dr Leonard Pinsky : Oui. Je crois que c'est l'année où j'ai obtenu ma première subvention du CRM. C'était un octroi par concours.

Christopher Canning : Est-ce que vous dirigiez votre propre laboratoire à cette époque?

Dr Leonard Pinsky : Oui. Et les recherches que j'ai faites sur l'insensibilité aux androgènes, au début, sont les premières recherches faites entièrement à Montréal à l'aide de cultures de cellules somatiques diploïdes.

Christopher Canning : En 1970, vous avez publié l'article intitulé « Enzymatic Differences in Cultured Fibroblasts » dans la revue *Nature*. Cet article est-il lié à vos recherches?

Dr Leonard Pinsky : Oui, mais le titre de l'article est plus long.

Christopher Canning : En effet. Je n'ai gardé que la première partie du titre.

Dr Leonard Pinsky : Pouvons-nous y jeter un coup d'œil?

Christopher Canning : Oui, vous pouvez regarder votre CV. De toute évidence, c'est lié aux recherches dont vous m'avez parlé.

Dr Leonard Pinsky : J'imagine que c'est le moment idéal pour parler de mes publications.

Christopher Canning : Absolument. Parlez-nous du contenu de votre CV.

Dr Leonard Pinsky : Je suis en train de parler avec Christopher de mes premières publications sur la génétique des cellules somatiques pour mettre l'accent sur la vérité historique de certains de mes travaux.

Si vous regardez la publication numéro 12 dans mon CV, vous verrez que mon premier article qui parlait de mes recherches sur la génétique des cellules somatiques remonte à l'époque où j'étais à l'Université du Michigan, où j'étudiais la génétique des cellules somatiques humaines avec Bob Krooth. Cet article a été publié dans la célèbre revue *The Proceedings of the National Academy of Sciences* (PNAS) en 1967, c'est bien ça?

Christopher Canning : Vous ne connaissiez personne d'autre qui faisait des recherches semblables à Montréal?

Dr Leonard Pinsky : Personne.

Christopher Canning : Je vois.

Dr Leonard Pinsky : C'était en 1967. Le deuxième article a également été publié dans PNAS en 1967. Il s'agissait de publications très importantes, dont nous n'aurons peut-être pas le temps de parler, mais je vais vous dire pourquoi elles sont importantes.

Christopher Canning : Oui, vous pourriez me dire brièvement pourquoi vous estimez qu'elles sont importantes.

Dr Leonard Pinsky : Pour l'instant, je vais avancer encore un peu.

Christopher Canning : D'accord.

Dr Leonard Pinsky : Continuons avec les articles 14 et 15. Regardez l'article 15. Reconnaissez-vous certains noms?

Christopher Canning : Bien sûr. Vous avez publié avec Hy Goldman et Charles Scriver.

Dr Leonard Pinsky : C'est exact. C'était en 1970. Il s'est donc écoulé environ trois ans avant que le reste du monde, y compris mes collègues, s'intéresse à la génétique des cellules somatiques.

Christopher Canning : Évidemment, le Dr Rosenblatt est arrivé avec des recherches similaires quelques années plus tard, n'est-ce pas?

Dr Leonard Pinsky : Oui, très similaires et très bonnes. Mais quelques années plus tard.

Christopher Canning : À cette époque, il faisait ses recherches postdoctorales aux États-Unis. Il est revenu en 1974 ou 1975. Vos recherches à Montréal datent donc de six ou sept ans avant l'arrivée du Dr Rosenblatt?

Dr Leonard Pinsky : Oui, je crois que c'est bien ça.

Christopher Canning : Parfait. Ça nous ramène à la fin des années 1960 et au début des années 1970, au moment où le groupe du CRM a commencé à se former.

Dr Leonard Pinsky : Oui.

Christopher Canning : Vous ne vous êtes pas joint au groupe avant la fin des années 1970 ou le début des années 1980, mais quelles relations entreteniez-vous avec les membres du groupe en 1972? Avez-vous entendu parler de la formation de ce groupe, et quelle était votre relation avec les Drs Scriver et Fraser et avec les premiers membres du groupe comme Peter Hechtman et Renny Gold? Que pouvez-vous me dire sur ces personnes et sur vos liens avec elles?

Dr Leonard Pinsky : C'est une bonne question, mais une question beaucoup plus difficile que les autres questions sur les années 1970 auxquelles j'ai répondu jusqu'à présent et pour lesquelles je pouvais donner plus de détails. Mais dans l'ensemble, c'est clair comme de l'eau de roche. Ma première allégeance allait à l'Hôpital

général juif. L'Institut Lady Davis pour la recherche médicale était déjà construit et j'étais en quelque sorte son premier chercheur employé.

Christopher Canning : Je vois.

Dr Leonard Pinsky : Ils n'ont pas construit l'institut pour moi, mais ils l'ont construit pour attirer des personnes comme moi. J'ai été le premier à recevoir une offre d'emploi de l'Hôpital général juif et de son institut de recherche, le Lady Davis. On m'a aussi offert un poste de professeur et de superviseur pour la résidence en pédiatrie. Au début de cette période, j'ai joué tous ces rôles en même temps.

J'entretenais des liens très étroits avec les gens de l'Hôpital de Montréal pour enfants. J'ai participé à plusieurs programmes de recherche collaborative avec les chercheurs de l'Hôpital de Montréal pour enfants et d'autres établissements.

Ces liens se sont resserrés lors que j'ai commencé à travailler à l'Hôpital de Montréal pour enfants une fois par semaine, habituellement le vendredi, comme pédiatre, généticien et dysmorphologiste. Je rencontrais des patients aux prises avec des anomalies morphologiques ou métaboliques, entre autres, et je faisais des tournées de génétique. Cette période a été importante dans ma carrière. J'avais le meilleur des deux mondes. Je réalisais la plupart des choses que je voulais faire à l'Hôpital général juif. Je contribuais beaucoup à la capacité de l'hôpital d'être un hôpital universitaire à part entière. Et, en même temps, j'occupais des fonctions de dysmorphologiste, *et cetera*, à l'Hôpital de Montréal pour enfants.

Christopher Canning : Vous dites donc que vous apportiez votre contribution à la fois comme médecin en exercice et comme chercheur, et que vos recherches avaient une incidence directe sur les patients?

Dr Leonard Pinsky : Exactement. C'est à ce moment-là que je me suis intéressé de plus près à l'insensibilité aux androgènes.

Christopher Canning : Comme nous abordons le sujet, pouvez-vous me dire brièvement ce que cela signifiait à l'époque? Les troubles du développement sexuel chez les garçons et les filles, c'était bien l'objet de vos recherches, n'est-ce pas?

Dr Leonard Pinsky : Oui, mais sous un certain angle. Je n'étudiais pas l'ensemble des problèmes de développement sexuel chez l'humain. J'ai commencé à m'intéresser au sujet très simplement. Je voulais savoir si je pouvais trouver une expression du problème que certaines personnes atteintes d'insensibilité aux androgènes présentaient. Je me demandais si je pourrais déterminer qu'une cellule était capable de réagir ou non au stimulus des hormones sexuelles mâles, et si je pourrais voir cette différence dans la culture en monocouche de cellules somatiques diploïdes. En quelque sorte, je suis retourné à ce qui m'avait conduit vers la génétique des cellules somatiques.

Christopher Canning : Est-ce que c'est ce type de recherche qui vous a amené à travailler avec le groupe du CRM?

Dr Leonard Pinsky : Oui, précisément.

Christopher Canning : Bien.

Dr Leonard Pinsky : Je n'ai jamais été très bon avec les dates.

Christopher Canning : Votre nom est indiqué sur une demande de 1980.

Dr Leonard Pinsky : Est-ce que c'était la première fois?

Christopher Canning : C'était la première fois. Vous êtes devenu directeur du groupe en 1981, après la demande de 1980.

Dr Leonard Pinsky : Je vois, parfait.

Christopher Canning : À cette époque, vous deviez travailler avec Peter Hechtman, David Rosenblatt, Charles Scriver et Susie Tenenhouse, mais pas avec Clarke Fraser, qui était à Terre-Neuve temporairement.

Dr Leonard Pinsky : C'est le genre de détails dont j'ai du mal à me souvenir. À cette époque, on m'a invité à me joindre au groupe et à devenir codirecteur, ou quelque chose du genre. De toute évidence, mes travaux étaient importants pour la viabilité et le succès du groupe. Je laisse aux autres le soin d'en juger, mais chose certaine, je n'aurais pas été invité à me joindre au groupe si je n'avais rien eu à lui apporter.

Christopher Canning : Croyez-vous que vous n'avez pas été invité plus tôt parce que vous étiez à l'Institut Lady Davis et non à l'Hôpital de Montréal pour enfants?

Dr Leonard Pinsky : J'en doute.

Christopher Canning : Je ne veux pas trop m'avancer, mais comme le Dr Scriver l'a dit, dans les années 1980, il était important que tout le monde travaille au même endroit. Le CRM voulait aussi que les chercheurs travaillent dans les mêmes installations.

Dr Leonard Pinsky : Je ne me rappelle pas les détails, et ce n'est pas important, mais à différents moments, on m'a invité à me joindre au groupe de génétique de l'Hôpital de Montréal pour enfants et à quitter l'Institut Lady Davis et l'Hôpital général juif. C'est normal que des gens changent d'allégeance. Mais je n'ai jamais jugé que je devais le faire. J'estimais qu'il était plus important d'essayer de faire reconnaître l'Hôpital juif comme un hôpital universitaire à part entière que de changer d'hôpital.

Christopher Canning : Bien entendu, vous avez finalement rejoint le groupe en 1981. Vous rappelez-vous comment se déroulaient les travaux au sein du groupe? Quel était le ciment du groupe?

Dr Leonard Pinsky : C'est une question difficile. Je suis certain qu'il y avait de nombreuses discussions impromptues entre collègues au cours d'une journée, ces brefs échanges qu'on oublie, mais qui sont si précieux.

J'ai sûrement manqué quelque chose en ne travaillant pas à proximité de cinq, six, sept, huit collègues avec lesquels j'avais de grandes affinités intellectuelles.

Christopher Canning : La distance physique provoquait en quelque sorte une distance intellectuelle?

Dr Leonard Pinsky : Oui. Par contre, je ne peux pas dire qu'au quotidien j'avais l'impression que mon travail progressait moins vite parce que je ne travaillais pas dans les mêmes locaux que le groupe de l'Hôpital de Montréal pour enfants. Et je n'ai pas souffert parce que je ne restais pas à l'écart. Je trouvais beaucoup d'occasions de communiquer avec eux, et j'étais toujours le bienvenu dans leur groupe.

Christopher Canning : Comment les choses se passaient-elles à l'époque? Aviez-vous des réunions de groupe? Vous souvenez-vous d'avoir assisté à des réunions au cours des huit années pendant lesquelles vous avez participé au projet?

Dr Leonard Pinsky : Les seules réunions dont je me souviens sont les rares réunions officielles, organisées pour des raisons administratives, je suppose. Mais il y avait peut-être d'autres réunions régulières dont je n'étais pas au courant. [rires] Je ne peux pas vous en dire plus.

Christopher Canning : J'ai trouvé un document très intéressant daté de 1987. Vous faisiez toujours partie du groupe à ce moment-là. De toute évidence, c'est après la création du Centre de génétique humaine. Le Dr Scriver a écrit une lettre indiquant que le groupe devait adopter une approche plus axée sur la génétique moléculaire. Vous rappelez-vous les conversations qui ont eu lieu vers le milieu des années 1980, alors que la biologie moléculaire commençait à prendre plus de place parce que le Dr Scriver semblait avoir toujours peur que le groupe n'obtienne plus de financement si la biologie moléculaire n'attirait pas de nouveaux membres? Vous souvenez-vous de ça?

Dr Leonard Pinsky : Je ne me rappelle pas les détails, mais nous étions fort probablement inquiets à l'époque. Laissez-moi réfléchir. Vous avez dit 1987?

Christopher Canning : Oui, 1987.

Dr Leonard Pinsky : À ce moment-là, je ne crois pas que nous pensions devoir nous concentrer sur la biologie cellulaire. Mais je ne peux pas en dire plus.

Christopher Canning : D'accord.

Dr Leonard Pinsky : Je pense à quelque chose, mais ça vient un peu plus tard. Je me souviens que lorsque nous avons commencé à nous intéresser à la biologie moléculaire, le groupe de génétique de McGill se sentait à l'écart parce qu'il n'était pas fort en cartographie génétique. La biologie moléculaire est arrivée et a accaparé tout le monde, sauf une demi-douzaine de personnes.

Christopher Canning : Vous avez dit avoir travaillé avec le Dr Clarke Fraser pendant les premières années, mais quelles étaient vos relations avec les Drs Fraser et Scriver pendant le projet et pendant que vous étiez à Montréal?

Dr Leonard Pinsky : J'étais toujours le bienvenu, et cette ouverture était importante pour moi. J'ai souvent vu des lettres de recommandation qu'ils écrivaient à mon sujet. Plus tard, j'ai commencé à écrire des lettres de recommandation ou de mise en candidature pour eux. Les rôles avaient changé et je faisais des blagues à ce

sujet.

Christopher Canning : Revenons un peu en arrière. Vous rappelez-vous avoir participé à la demande de 1981? Vous rappelez-vous l'avoir présentée? Je me demande qui préparait les demandes. J'ai posé la question à plusieurs personnes, et je crois que la tâche de rassembler les profils de recherche et les CV revenait habituellement au directeur. Vous rappelez-vous comment ça fonctionnait?

Dr Leonard Pinsky : Je me souviens juste que pour des questions de budget, il devait y avoir un certain lien entre les besoins budgétaires d'une personne A et ceux d'une personne B. Souvent, ce n'était pas logique d'avoir des budgets distincts pour un même type de dépenses. On regroupait donc les besoins de plusieurs personnes dans un budget conjoint. C'est tout ce dont je me souviens.

Christopher Canning : Ça semble être un processus très compliqué. Les demandes avaient des centaines de pages.

Dr Leonard Pinsky : Au départ, le nombre de pages n'était pas limité pour les demandes de subvention individuelle du CRM. Mais plus tard, au début des années 1990 je crois, les demandes de subvention ne devaient pas avoir plus de 10 pages, ou quelque chose comme ça, et il fallait respecter les paramètres. Mais je me souviens qu'en 1987 ou 1986, j'ai rédigé des demandes de subvention du CRM qui ressemblaient à des livres.

Christopher Canning : On dirait des livres, en effet.

Dr Leonard Pinsky : Il y avait 40 ou 50 pages, et à cette époque [rires], quand on faisait une faute de frappe… Et il n'y avait aucun moyen de photocopier les pages… C'est difficile à croire. Une seule erreur, et il fallait recommencer.

Christopher Canning : Comment ça va? Cette entrevue n'est pas trop longue?

Dr Leonard Pinsky : Ça va bien.

Christopher Canning : Ok, parfait.

Dr Leonard Pinsky : Mais il commence à faire noir ici.

Christopher Canning : En effet. Il y a un orage qui approche.

Dr Leonard Pinsky : Nous pourrions allumer une lampe.

Christopher Canning : C'est bon. J'ai de la lumière près de cette fenêtre.

Dr Leonard Pinsky : Certain?

Christopher Canning : Sur la demande de 1987, on dit que le groupe avait atteint un certain niveau d'érudition interdisciplinaire en combinant la cytogénétique, la génétique des cellules somatiques, la biochimie, la génétique physiologique, la génétique clinique et la génétique des populations. C'est une question très vaste, mais pouvez-vous m'expliquer ces liens? Comment ces disciplines se sont-elles combinées, et le groupe a-t-il réussi à aborder de façon interdisciplinaire ces

différents aspects de la génétique?

Dr Leonard Pinsky : Je crois pouvoir répondre à la question de mon point de vue de directeur du Centre de génétique humaine et de directeur, le temps d'un mandat, du Département de génétique humaine, où travaille David Rosenblatt. Je ne pense pas avoir participé à des discussions stratégiques sur le besoin de créer une plus grande interaction entre les différentes branches de la génétique que vous venez d'énumérer.

Je n'ai rien à ajouter d'intéressant à ce sujet. Peut-être que j'aurai d'autres réponses plus tard. Mais quand j'étais directeur du Centre de génétique humaine, ce que j'ai été pendant 15 ans, je crois…

Christopher Canning : De 1979 à 1994?

Dr Leonard Pinsky : Oui. J'ai eu beaucoup d'occasions d'apporter des changements ou de faire avancer les choses, si vous voulez. Ce n'est pas très important, mais il est intéressant de savoir que les relations n'étaient pas très bonnes entre Clarke Fraser et le Département de génétique original et les personnes qui ont plus tard formé le Département de biologie.

Les autres biologistes et généticiens ne se sont donc jamais rapprochés du travail de Clarke Fraser. Lorsque je suis devenu directeur du Centre de génétique humaine, j'ai travaillé très fort et je pense que j'ai réussi à nous réconcilier, nous, les spécialistes en génétique humaine, avec les autres généticiens du Département de génétique ou du Département de biologie. J'ai beaucoup travaillé et mes efforts ont quand même porté leurs fruits.

Christopher Canning : Est-ce que c'est ce que vous aviez en tête lorsque vous avez participé à la création du Centre de génétique humaine en 1979?

Dr Leonard Pinsky : Oui.

Christopher Canning : Ou bien avez-vous eu ce résultat parce que le Centre existait? Ou était-ce une combinaison des deux?

Dr Leonard Pinsky : C'est une bonne question, mais je ne sais pas comment y répondre.

Christopher Canning : Revenons à la première partie de ma question. Quelle était votre intention lorsque vous avez créé le Centre de génétique humaine en 1979?

Dr Leonard Pinsky : J'ai effectivement reçu ce mandat.

Christopher Canning : Pensiez-vous que toutes ces branches de la génétique et de la médecine humaine pourraient profiter du regroupement des scientifiques, des médecins, des pédiatres et des autres personnes intéressées? Croyez-vous que c'est ce qui s'est produit avec le Centre?

Dr Leonard Pinsky : D'un côté, nous avions du mal à attirer du sang neuf dans nos groupes parce que nous n'avions pas assez d'argent. Nous avons présenté une foule de demandes de financement, mais très souvent, ça ne marchait pas. Nous pensions que c'était principalement parce que nous n'étions pas un

département.

Christopher Canning : Vous ne pouviez pas subventionner un programme de maîtrise? Une maîtrise en génétique, par exemple?

Dr Leonard Pinsky : Pas au début, mais nous avons fini par pouvoir le faire. C'est l'une des choses que nous avons réussi à faire. Notre succès dans ce domaine a coïncidé avec une explosion des besoins en chercheurs.

Christopher Canning : Je vois que vous avez quitté le groupe en 1990? Pourquoi? Et vers où vos recherches se sont-elles orientées à partir de là?

Dr Leonard Pinsky : À mon grand regret, mon poste et celui de deux autres membres du groupe n'ont pas été financés par le CRM en 1990. Les raisons qu'on nous a données pour ce refus de financement étaient totalement fausses.

Christopher Canning : Pouvez-vous me dire quelles étaient ces raisons?

Dr Leonard Pinsky : Bien sûr. Dans le groupe d'évaluateurs externes nommé par le CRM, il y avait un jeune homme – je ne sais pas où il est maintenant – qui était un jeune employé ou peut-être même un étudiant postdoctoral dans le laboratoire où l'on étudiait la biologie des androgènes, et où on l'étudie encore, je crois. Je ne devrais pas nommer la personne qui réalise ces études actuellement, mais ça serait facile de découvrir de qui je parle parce qu'il est le seul à faire ça et qu'il dirige le groupe d'étude sur la génétique du métabolisme des androgènes au Canada. En bref, cet étudiant postdoctoral a été envoyé par le CRM, et le rapport qu'il a rédigé, et que j'ai lu, était négatif et contenait de fausses affirmations, ou alors les éléments favorables n'avaient pas été pris en considération.

Le financement a donc été refusé et, au même moment, le travail du Dr Fraser a été stoppé. Je crois qu'une troisième personne a été touchée, mais je n'en suis pas certain.

Christopher Canning : Je crois qu'il n'y avait que vous deux. Ce fut le dernier mandat du Dr Fraser et votre dernier mandat.

Dr Leonard Pinsky : Il n'y avait pas une troisième personne?

Christopher Canning : Pas que je sache, mais je ne peux pas en être certain.

Dr Leonard Pinsky : D'accord.

Christopher Canning : À l'époque, il devait y avoir le Dr Rosenblatt, Rima Rozen, le Dr Scriver, le Dr Skamene et Harriet Tenenhouse. Il semble que le CRM avait changé d'orientation?

Dr Leonard Pinsky : Je dirais simplement que je me suis fait couper l'herbe sous le pied par une personne qui est restée en arrière-plan, mais qui menait le bal. Je ne pourrai jamais le prouver, mais j'ai vraiment le sentiment que nos recherches étaient concurrentielles à l'échelle internationale et que les critiques de cette personne, qui répétait simplement les mots de son chef, nous ont nui.

Christopher Canning : On dirait que vous vous rappelez bien cette période.

Dr Leonard Pinsky : Ce fut un moment sombre dans ma vie. J'ai récupéré ma subvention du CRM une ou deux années plus tard, et je l'ai conservée jusqu'à ma retraite en 1999.

Christopher Canning : Fantastique.

Dr Leonard Pinsky : Je l'ai récupérée en 1991, je crois.

Christopher Canning : Je vois.

Dr Leonard Pinsky : Et je l'ai conservée pendant huit ou neuf ans.

Christopher Canning : Quelle incidence votre départ a-t-il eue sur vos relations avec les autres membres du groupe?

Dr Leonard Pinsky : Tout d'abord, je dois dire que je n'allais pas bien du tout. J'étais triste et ma santé et mon ego en ont souffert. Cette épreuve a été difficile pour ma famille également. C'est très dur lorsqu'on vous enlève injustement quelque chose dans laquelle vous aviez mis tout votre cœur. Que dire d'autre?

Christopher Canning : J'aimerais terminer avec quelques questions théoriques générales. Vous pouvez répondre comme vous le désirez. À votre avis, quelles sont les avancées les plus importantes en génétique médicale principalement attribuables aux travaux du groupe du CRM?

Dr Leonard Pinsky : Comparé à quoi?

Christopher Canning : À la génétique médicale en général. Qu'est-ce que ce groupe a produit, à votre avis?

Dr Leonard Pinsky : Je n'ai pas préparé de réponse à cette question. J'espère que ce que je vais dire sera clair.

Christopher Canning : Comme je vous l'ai dit, nous pouvons sauter cette question.

Dr Leonard Pinsky : Oui, s'il vous plaît.

Christopher Canning : Aimeriez-vous que je passe à une autre question?

Dr Leonard Pinsky : Oui. Laissons cette question mijoter un petit peu.

Christopher Canning : À votre avis, à quoi tient la longévité du groupe?

Dr Leonard Pinsky : Ça, c'est facile. Et je crois qu'elle est liée à la question précédente. Vous disiez?

Christopher Canning : Pourquoi le groupe a-t-il eu une vie si longue? Il s'agit du projet de recherche subventionné qui a duré le plus longtemps dans le secteur de la médecine et dans l'histoire du Canada.

Dr Leonard Pinsky : Pourquoi mettre fin à un projet qui a du succès? [rires]

Christopher Canning : Ça me ramène à la première question : comment mesure-t-on le succès pour assurer la survie d'un projet?

Dr Leonard Pinsky : Je savais bien que les choses allaient se corser à la fin. Je suis certain, et je crois que c'est une vérité universelle, que si une ou deux personnes, j'allais dire un ou deux hommes, mais il peut très bien s'agir de femmes, donc si une ou deux personnes très douées et connues s'associent à votre groupe dès le début, c'est dans la poche! C'est presque garanti. Clarke Fraser a eu le génie de poser une question qui, aujourd'hui, a l'air fort simple. Dans ce cas, si on injecte une quantité X d'hydrocortisone à une souris d'une certaine souche et la même quantité d'hydrocortisone à une souris d'une autre souche, le pourcentage de la substance tératogène absorbée sera nettement différent chez les deux souris. Je précise ici que l'hydrocortisone est un médicament et n'est habituellement pas tératogène.

Mais si vous en injectez trop à des souris de souche consanguine, vous obtiendrez des souris qui auront une fente palatine. Le Dr Fraser a eu l'idée de dire « Je vais étudier la génétique de la sensibilité à l'hydrocortisone et produire des souris qui ont une fente palatine, puis déterminer quelle est la meilleure souche de souris ». Personne ne l'avait fait avant.

Un dicton était affiché sur la porte de mon bureau. Il disait quelque chose comme « Quand vous aurez tout fait, les autres diront qu'ils connaissaient déjà la réponse ». Ça ne disait pas exactement ça, mais vous voyez l'idée. Et c'est vrai dans ce cas. Aujourd'hui, ça semble tellement simple. Mais quand il l'a fait, c'était révolutionnaire. Il y a 15 ou 20 ans, on acceptait à peine le fait qu'on pouvait utiliser des facteurs génétiques pour déterminer la prédisposition à des anomalies congénitales, alors qu'aujourd'hui, ça va de soi.

Christopher Canning : Je vois.

Dr Leonard Pinsky : Voici donc la première partie de ma réponse. Je m'en sors mieux que je l'aurais cru. Pour bâtir un département ou un groupe qui marche, il faut faire appel à des vedettes dès le départ et suivre leurs traces. Le Dr Scriver est arrivé par la suite. Il est aussi une vedette, dans un autre domaine. Ça n'avait pas été fait auparavant. Personne n'avait essayé.

D'autres personnes auraient pu découvrir ce que Clarke Fraser a découvert. Ce n'était pas comme si le monde entier attendait qu'il fasse cette découverte. Même chose pour le Dr Scriver. Tout le monde attendait que des erreurs innées soient découvertes, mais lui, il les a trouvées, les a étudiées et les a caractérisées. Il était également un orateur hors pair. Que demander de mieux? Je suis prêt à gager que vous n'entendrez pas cela très souvent, mais pour moi, c'est la vérité. Pourriez-vous lui dire que je le considère comme une véritable vedette?

Christopher Canning : C'est enregistré à jamais.

Dr Leonard Pinsky : Oui, c'est vrai.

Christopher Canning : Je pense que c'est une excellente conclusion à notre entretien. Si vous êtes

d’accord.

Dr Leonard Pinsky : Oui.

Christopher Canning : Merci beaucoup de m’avoir accordé de votre temps, Dr Pinsky.

FIN DE L’ENTRETIEN

Dr Emil Skamene, le 5 août 2010

Christopher Canning : Nous sommes le 5 août 2010. Ici Christopher Canning en compagnie du Dr Emil Skamene. Dr Skamene, je suis honoré de pouvoir m'entretenir avec vous de deux grands sujets qui touchent la génétique humaine.

J'aimerais d'abord que nous parlions de votre parcours universitaire, qui a contribué à l'avancement de la génétique médicale au Canada et dans le monde. Ensuite et surtout, j'aimerais en savoir plus sur votre participation au groupe de génétique médicale des IRSC[1], anciennement le CRM[2]. Mais parlons d'abord de vous, si vous le voulez bien. Pouvez-vous nous parler de votre lieu de naissance et de votre enfance?

Dr Skamene : Je suis né en 1941, en Galicie qui, à l'époque, faisait partie de l'Europe. Rattachée successivement à plusieurs États, surtout au XXe siècle, la Galicie comptait une très importante population juive et, avant la guerre, appartenait à la Pologne. Quand je suis né, elle faisait partie de l'Union soviétique (à cause du tristement célèbre pacte germano-soviétique) et subissait l'invasion allemande et le programme nazi d'extermination des Juifs, l'Holocauste. On m'a fait sortir clandestinement de Galicie à l'âge de 18 mois pour m'envoyer chez mes parents adoptifs, à Prague. C'est ainsi que j'ai eu la vie sauve. J'ai ensuite vécu à Prague de 1941 à 1968, où j'ai fait mes études. J'y ai notamment obtenu un diplôme en médecine de l'Université Charles et un doctorat de l'Académie des sciences de Tchécoslovaquie. J'ai quitté la Tchécoslovaquie en 1968, pendant l'invasion par la Russie et d'autres pays du pacte de Varsovie. Je ne voulais pas rester dans un pays occupé. Je suis allé aux États-Unis, où j'ai fait deux années d'études postdoctorales à l'Université Harvard, à Boston. J'ai ensuite été recruté par l'Université McGill.

Christopher Canning : Bien. Avant de parler davantage de votre formation postdoctorale à Harvard, pouvez-vous nous en dire un peu plus sur vos études en médecine dans la République tchèque?

Dr Skamene : Oui, mais à l'époque, on parlait encore de la Tchécoslovaquie.

Christopher Canning : Oui, bien sûr, la Tchécoslovaquie. Parlons-en un peu. Vous avez d'abord obtenu votre diplôme en médecine?

Dr Skamene : Oui, j'ai été admis à la Faculté de médecine à 17 ans. À l'époque, le programme durait six ans, comme c'est généralement le cas aujourd'hui en Europe. J'ai obtenu mon diplôme à 23 ans. Pendant mes études en médecine, je faisais déjà de la recherche, d'abord en biochimie, puis en immunologie. Je me suis ensuite inscrit à un programme que l'on pourrait comparer à un doctorat, le « programme du candidat en sciences », à l'Académie des sciences de Tchécoslovaquie, plus précisément à l'Institut de microbiologie et d'immunologie.

Christopher Canning : Dites-moi, quelle importance a eu la génétique dans votre formation médicale?

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[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

À l'époque, était-il courant d'étudier cette discipline en Tchécoslovaquie?

Dr Skamene : Non. Les programmes d'études, comme tout le reste, étaient sous le contrôle des Russes. Selon la ligne du parti, c'était le milieu qui commandait l'évolution, et les caractères issus du milieu étaient transmissibles par voie héréditaire. C'est ce qu'on appelait la « doctrine de Lyssenko », du nom du biologiste soviétique qui était ministre de l'Éducation sous Staline. La génétique était officiellement bannie de l'Union soviétique, mais, comme c'est toujours le cas dans de telles situations, un mouvement clandestin s'est organisé.

Christopher Canning : S'agissait-il vraiment d'un mouvement clandestin? De toute évidence, on enseignait la génétique dans les universités, mais le faisait-on dans la clandestinité?

Dr Skamene : Tout à fait, particulièrement dans le cas de la génétique mendélienne et de la génétique morganienne. Mais j'ai reçu une solide formation en génétique grâce à des professeurs géniaux qui nous faisaient goûter à ce fruit défendu le soir, dans des cafés, chez eux ou dans leurs laboratoires. C'était palpitant pour nous, notamment parce que c'était interdit. Certains de ces professeurs ont été congédiés de l'Université et persécutés, comme le voulait alors la règle dans tous les milieux.

Christopher Canning : Lisiez-vous les articles scientifiques publiés en Amérique du Nord ou dans d'autres parties de l'Europe?

Dr Skamene : Non, en tout cas, pas lorsque j'étais étudiant en médecine. Je ne pouvais ni lire ni parler l'anglais; ma langue seconde était le russe.

Christopher Canning : Après avoir obtenu votre diplôme en médecine, avez-vous suivi des cours de génétique pendant votre formation ultérieure?

Dr Skamene : Très peu.

Christopher Canning : La génétique médicale existait-elle en Tchécoslovaquie à l'époque?

Dr Skamene : Non.

Christopher Canning : Alors, d'où vous est venu cet intérêt pour la génétique et la médecine, si ces deux disciplines étaient si peu populaires dans votre pays?

Dr Skamene : Comme je le disais plus tôt, il y avait de multiples conférences et travaux de laboratoire hors programme et clandestins, non seulement en génétique, mais également dans d'autres disciplines médicales et scientifiques, comme la psychiatrie. Je participais à ces activités dans les domaines de la biologie, de la biochimie et de la génétique, et c'est là que j'ai rencontré deux ou trois professeurs absolument fantastiques.

Leurs explications étaient très claires et permettaient de comprendre l'influence de l'environnement sur le phénotype. Si l'on ne connaît pas les fondements de la génétique, il est très difficile de comprendre ce phénomène et de l'accepter. Grâce à leurs enseignements, tout était beaucoup plus clair. J'ai décidé que je voulais approfondir ces connaissances en laboratoire.

Christopher Canning : Et vous en avez fait le sujet de votre recherche postdoctorale?

Dr Skamene : Oui, et ça reposait en grande partie sur l'application et la connaissance de la génétique.

Christopher Canning : Absolument. C'était donc, à l'époque, la rencontre de la théorie de l'évolution de Darwin et de la génétique mendélienne?

Dr Skamene : Tout à fait.

Christopher Canning : Dans quelle mesure le gouvernement tchèque était-il favorable à la génétique? Pouvez-vous m'en dire un peu à ce sujet? La situation a-t-elle changé après votre départ? Parce que j'ai remarqué que vous aviez reçu plusieurs distinctions de l'Académie des sciences de la Tchécoslovaquie.

Dr Skamene : L'ancienne Tchécoslovaquie (qui, avant sa dissolution au début des années 1990, regroupait la République tchèque et la Slovaquie) est maintenant une région pleinement démocratique, aux frontières ouvertes, et membre à part entière de l'Union européenne.

Christopher Canning : À quel moment le changement s'est-il produit en Tchécoslovaquie?

Dr Skamene : Il est très difficile d'imaginer le contrôle qu'exerçait alors l'État sur la vie des gens. On pourrait comparer cela au régime autocratique actuel en Arabie saoudite, qui souhaite bannir les appareils BlackBerry par crainte de ne plus pouvoir contrôler la pensée des citoyens.

Vous savez, la génétique entrait en conflit avec la doctrine communiste et n'était tout simplement pas enseignée. Les manuels de biologie ne comportaient aucune section traitant spécifiquement de génétique.

Christopher Canning : Vous parlez de… Quand avez-vous fait… [Inaudible]

Dr Skamene : Lorsque je faisais mon doctorat, de 1964 à 1968, les choses étaient déjà un peu différentes : plusieurs pays du bloc communiste de l'Europe de l'Est (la Hongrie, la Pologne, la Tchécoslovaquie) avaient alors à leur tête des dirigeants qui, bien que communistes comme leurs prédécesseurs, permettaient une certaine libéralisation du régime (par exemple, le fameux « Printemps de Prague », de 1966 à 1968, quand Alexander Dubček était au pouvoir). L'invasion des armées russes a toutefois mis fin à ces mouvements de libération.

Christopher Canning : Parlait-on de génétique, de ce qui se passait ailleurs dans le monde, ou était-ce un sujet tabou?

Dr Skamene : À ce moment-là, la génétique est sortie de la clandestinité et les notions de biologie qu'on enseignait étaient très différentes. Malheureusement, cela n'a pas duré longtemps. Ainsi, en Tchécoslovaquie, 1968 a marqué le retour à la noirceur, à la répression et au totalitarisme, et tout ça a duré pendant encore 21 ans.

Christopher Canning : C'est alors que vous avez décidé d'aller à Harvard pour votre formation postdoctorale. Aviez-vous une raison particulière pour […]?

Dr Skamene : Oui. Ma thèse de doctorat ne portait pas vraiment sur la génétique, mais plutôt sur le développement du système immunitaire : c'était la génération de la diversité. D'ailleurs, on enseignait à l'époque que le système apprenait à lutter de diverses façons contre les attaques du milieu à force d'être exposé à de multiples bactéries, virus et cellules cancéreuses.

Christopher Canning : Du milieu, tout simplement?

Dr Skamene : Oui. Puis, en examinant une classe d'anticorps pour ma thèse, je me suis rendu compte que toute l'information sur la diversité existait déjà dans la lignée germinale. Deux de mes articles, qui en apportaient la preuve expérimentale et reposaient sur les recherches réalisées pour ma thèse de doctorat, ont été publiés dans la revue *Nature*, chose inimaginable à l'époque.

Christopher Canning : Oui, en Tchécoslovaquie.

Dr Skamene : Mais j'ai été très privilégié de faire mon doctorat auprès de Milan Hasek comme superviseur, un véritable génie en sciences. Il a failli recevoir un prix Nobel!

Christopher Canning : En immunologie?

Dr Skamene : Oui, en immunologie, pour sa découverte d'une tolérance immunitaire. Je vais sans doute m'écarter un peu du sujet de notre entretien, mais ce que je vais vous raconter est vraiment intéressant et révélateur. Le Pr Hasek était l'un des directeurs fondateurs d'un institut de biologie et de génétique expérimentales où j'ai fait de la recherche pour mon doctorat. L'institut a connu un essor considérable, car le directeur était un communiste convaincu qui avait pu obtenir un important financement de l'État et jouissait d'une entière liberté de recherche scientifique. Milan Hasek a fait une découverte fondamentale révolutionnaire sur la tolérance immunitaire, mais le biologiste lyssenkiste qu'il était toujours a erré complètement en interprétant les conséquences de cette découverte. Ses observations expérimentales étaient, en revanche, robustes et sans précédent. Peter Medawar (un Anglais) a reçu le prix Nobel pour cette découverte et a reconnu publiquement le travail de Milan Hasek (et mentionné son interprétation erronée des résultats) dans son discours de remerciement.

Christopher Canning : Très intéressant, ce regard sur les dessous du prix Nobel. C'est une tout autre histoire, je suppose.

Dr Skamene : Où en étions-nous?

Christopher Canning : Vous nous parliez de vos publications.

Dr Skamene : En effet. J'ai donc publié dans la revue *Nature* et, bien sûr, lorsque vous publiez quelque chose dans *Nature*, vous devenez quelqu'un. Tous les lecteurs de *Nature* ont tout de suite pris connaissance de mes articles, dans les pays occidentaux, s'entend. Et, vous savez, l'exode des cerveaux vers les États-Unis et d'autres pays était aussi important qu'aujourd'hui. Alors, dans les mois qui ont suivi, j'ai commencé à recevoir des lettres d'institutions des États-Unis et

d'Europe occidentale, qui m'invitaient à faire des études postdoctorales. J'ai accepté l'offre de Harvard, où je devais commencer mes études le 1er octobre 1968.

En août 1968, j'ai soudainement réalisé que je ne pourrais pas aller aux États-Unis en raison de l'invasion soviétique et de l'occupation subséquente de la Tchécoslovaquie. J'ai quand même réussi à franchir la frontière. J'ai « survécu » pour la deuxième fois de mon existence.

Christopher Canning : Où êtes-vous allé?

Dr Skamene : En Allemagne. Ma mère, qui était médecin, était extrêmement brillante. Certains de ses patients vivaient près de la frontière germano-tchèque et m'ont laissé passer.

Christopher Canning : Votre mère était médecin elle aussi [Inaudible]?

Dr Skamene : Oui. Ma mère [adoptive] était professeure de médecine à Prague.

Christopher Canning : Votre intérêt pour la médecine vous vient sans doute de votre mère?

Dr Skamene : J'avais 16 ans à la fin de mes études secondaires. J'étais un bon étudiant. Je ne savais pas ce que je voulais faire dans la vie. Mais une brillante femme juive m'a dit que je devais étudier la médecine. Alors, je l'ai fait. Si elle m'avait dit que je devais étudier le droit, je serais avocat aujourd'hui.

Christopher Canning : Et vous voilà ici, devant moi.

Dr Skamene : Oui. Lors de l'entrevue d'admission à la Faculté de médecine, j'ai raconté des histoires, j'ai affirmé que j'avais toujours aimé la médecine et voulu devenir médecin, mais, en fait, je répondais aux souhaits d'une personne qui me connaissait mieux que je me connaissais moi-même.

Christopher Canning : Alors, à quel moment avez-vous réalisé que c'est ce que vous vouliez faire dans la vie? À quelle étape de votre parcours?

Dr Skamene : J'ai adoré ça dès le début. C'était si différent de l'école secondaire. C'était tellement intéressant que j'ai su tout de suite que j'avais fait le bon choix.

Christopher Canning : J'aimerais en savoir plus sur Harvard, où vous avez passé deux ans. Quel était l'objet de vos recherches? Vos travaux portaient-ils encore sur l'immunogénétique?

Dr Skamene : Oui, mes travaux portaient toujours sur l'immunogénétique. À Harvard, j'ai été profondément influencé par Henry Winn, un formidable généticien de la souris. C'est là que je me suis converti à l'immunologie et à la génétique de la souris.

Christopher Canning : Vous avez donc plusieurs publications sur l'immunologie de la souris à votre actif?

Dr Skamene : Oui, j'ai publié plusieurs articles sur le sujet au cours de cette période. Après deux ans à Harvard, j'ai été nommé adjoint de recherche et j'ai soumis une

demande de subvention aux [National Institutes of Health]. J'ai présenté cette demande en mon nom et en celui des professeurs, soit les Prs Russell et Winn. Comme il s'agissait d'une demande de subvention très importante, des représentants des National Institutes of Health sont venus visiter nos installations.

Christopher Canning : Lesquelles?

Dr Skamene : Mon laboratoire à Harvard, au Massachusetts General Hospital. Plusieurs scientifiques se sont présentés sur les lieux et ont examiné notre milieu de travail, notamment pour s'assurer que nous étions en mesure de réaliser les travaux décrits. Je crois qu'ils ont organisé cette visite en raison du caractère inhabituel de cette demande. En fait, je crois qu'ils ont été surpris qu'un chercheur à Harvard depuis moins de deux ans puisse soumettre une demande de cette qualité.

Christopher Canning : Je vois.

Dr Skamene : Ils se sont donc présentés sur les lieux. Parmi les visiteurs se trouvait Phil Gold, de l'Université McGill, immunologue de renommée mondiale et membre de divers comités des National Institutes of Health. Il faisait donc partie de l'équipe de visiteurs. La visite s'est bien passée et nous avons obtenu la subvention. Mais Phil a fait une chose généralement interdite dans un tel contexte. Il m'a remis sa carte de visite et m'a dit « Appelez-moi à mon hôtel ».

Je l'ai donc appelé et nous avons mangé ensemble. Il m'a dit que j'avais fait du bon travail, puis m'a demandé ce que je voulais faire de ma vie. Il a ajouté : « Ne perdez pas votre temps à Harvard, venez travailler à McGill ». Nous avons ensuite parlé de la possibilité de combiner exercice de la médecine et recherche, ce qui m'intéressait beaucoup. Le Pr Russell, directeur de notre département à Harvard, n'était pas chaud à l'idée que j'obtienne un permis d'exercice de la médecine aux États-Unis pour pouvoir faire à la fois de la médecine et de la recherche. Il souhaitait que je dirige les laboratoires de recherche au sein du département.

Christopher Canning : Visiblement, il appréciait la qualité de votre travail de chercheur.

Dr Skamene : Oui, mais pendant notre conversation, j'ai demandé à Phil [Gold] comment tout cela pourrait fonctionner au Canada. Lui-même exerçait les deux professions. Il m'a répondu qu'une fois au Canada, je me verrais confier diverses tâches et on m'offrirait la possibilité de passer mes examens et d'obtenir mon permis d'exercice de la médecine. C'était drôlement tentant..

Il m'a demandé de venir à McGill le temps d'une courte visite. Vous savez quoi? J'ai beaucoup aimé l'endroit et l'équipe de la Division d'immunologie. Phil Gold m'a dit : « Écoutez, si vous venez à McGill, vous aurez tout de suite un poste d'adjoint de recherche, comme à Harvard, et nous nous organiserons pour que vous puissiez faire vos stages cliniques et vos résidences, passer vos examens et obtenir votre permis d'exercice. »

Christopher Canning : Très intéressant. J'aimerais maintenant que nous parlions de votre travail au sein du CRM. Nous sommes en 1972, année de formation du groupe. Il est

alors composé de Charles Scriver, Clarke Fraser, Reynold Gold, David Rosenblatt et Peter Hechtman. Saviez-vous sur quoi portaient leurs travaux en génétique ou vous en teniez-vous surtout à l'immunologie?

Dr Skamene : Je m'en tenais surtout à l'immunologie, mais en fait, j'avais déjà obtenu une deuxième subvention pour étudier les déterminants génétiques de la prédisposition aux infections. J'avais entendu parler des généticiens de McGill que vous venez de mentionner, mais j'ignorais tout du groupe du CRM. Je savais que ces scientifiques s'intéressaient à ce que j'appellerais aujourd'hui les caractères mendéliens ou monogéniques. Leurs travaux portaient sur les malformations du nouveau-né; ils excellaient en biochimie génétique appliquée notamment à la maladie de Tay-Sachs. Vous savez, la théorie « un gène, une maladie ».

Christopher Canning : Comme la phénylcétonurie.

Dr Skamene : Laissez-moi vous parler d'un autre problème où la théorie « un gène, une maladie » entre en jeu, d'accord? Alors que j'amorçais mon propre projet de recherche à McGill, j'ai décidé d'étudier quelque chose qui, à l'époque, était tout nouveau. J'ai découvert que certaines lignées pures de souris étaient très prédisposées aux infections, alors que d'autres y étaient résistantes. J'ai commencé à élever des souris pour étudier le mode de transmission des gènes de résistance ou de prédisposition d'une génération à l'autre. Mais je n'ai jamais observé de caractère monogénique : c'était vraiment très compliqué.

Christopher Canning : D'accord. Alors, vous travailliez avec des systèmes multigéniques plutôt qu'avec des phénotypes monogéniques?

Dr Skamene : Oui, les caractères monogéniques étaient pour moi sans intérêt, puisqu'ils ne s'appliquaient pas à mes travaux sur les variations immunologiques héréditaires.

Bien sûr, j'avais entendu parler des généticiens de l'Hôpital pour enfants – j'assistais à leurs conférences. Ils ont commencé à s'intéresser à mes propres recherches et m'invitaient à leurs conférences et à leurs tournées. Dans les années 1990, les organismes subventionnaires fédéraux ont mis sur pied le Réseau canadien des centres d'excellence, et le groupe de généticiens de McGill (particulièrement Charles Scriver et Roy Gravel) a été le fer de lance d'un des centres d'excellence en génétique. Comme on exigeait que la recherche en génétique ait des applications concrètes dans des problèmes de santé importants, il était très difficile de créer un centre axé sur des caractères monogéniques, comme la phénylcétonurie.

Ils ont donc recruté des scientifiques dont les travaux en génétique avaient une portée plus générale. Le Dr Scriver m'a invité à me joindre à eux, ce qui, bien sûr, était pour moi un immense privilège. Je suis donc devenu l'un des chercheurs principaux du Centre d'excellence en génétique. C'est à cette époque, je crois, qu'on avait besoin de sang neuf dans le groupe de génétique du CRM et ils m'ont demandé de me joindre à eux. Je crois que Rima Rozen s'est également jointe au groupe. Ses travaux portaient sur les déterminants génétiques du…

Christopher Canning : Métabolisme des folates?

Dr Skamene : Oui, le métabolisme des folates. Si je ne m'abuse, Roy Gravel a également été recruté à la même époque.

Christopher Canning : Donc, en 1990, le groupe était composé de Clarke Fraser, David Rosenblatt, vous-même, Harriet Tenenhouse, Charles Scriver, Rima Rozen et Roy Gravel.

Dr Skamene : Oui.

Christopher Canning : Vous avez donc été recruté en 1990, mais nous n'avons pas encore mentionné qu'en 1988, vous aviez mis sur pied votre propre Centre de recherche sur la résistance de l'hôte. Comment en êtes-vous venu à créer ce centre et quelle en était la composition? Était-ce une des raisons pour lesquelles le groupe a voulu vous recruter?

Dr Skamene : Je suis sûr que oui. À mon centre de l'Hôpital général de Montréal, on utilisait des outils génétiques chez la souris pour comprendre les mécanismes de la résistance à divers agents infectieux, dont *Listeria*, les mycobactéries, *Plasmodium* et la salmonelle. Lorsque nous avons commencé à élucider certains aspects génétiques et immunologiques de cette résistance, je me suis rendu compte qu'il nous fallait élargir notre équipe de scientifiques et recruter notamment un biochimiste, un microbiologiste, un épidémiologiste, un statisticien et un pathologiste. Heureusement, je disposais des ressources nécessaires pour recruter tout ce beau monde. Nous nous sommes donc retrouvés, au début des années 1990, avec l'un des premiers centres de recherche véritablement multidisciplinaires à la Faculté de médecine. Essentiellement, mes scientifiques enseignaient dans divers départements de la Faculté de médecine, mais les laboratoires de l'Hôpital général de Montréal étaient leur port d'attache en recherche. Nos travaux allaient bon train, et nous commencions à obtenir des subventions substantielles, qu'il s'agisse de subventions individuelles, de centre ou de programme. Nous recevions un très bon soutien financier, et c'est encore le cas aujourd'hui.

L'Hôpital général de Montréal a alors ajouté trois étages de recherche au Pavillon Livingston : le premier pour moi, le deuxième pour le Dr Aguayo et ses recherches en neurologie, et le troisième pour l'hébergement des souris.

Comme j'avais réussi à mettre le Centre sur pied, à obtenir le financement et à créer l'ensemble de cette infrastructure, les gens qui souhaitaient mettre en place un centre multidisciplinaire ont commencé à s'intéresser à moi. J'ignore pourquoi exactement, mais Charles Scriver m'a déjà appelé pour me demander si j'accepterais de devenir membre du groupe du CRM en génétique.

Christopher Canning : Vous me devancez. Depuis 1988, vous travailliez au Centre sur la résistance de l'hôte et vous commenciez à être connu. Vous étiez de toute évidence bien établi et en 1989, vous recevez cet appel : on vous invite à entrer dans la danse pour la demande de 1990. Comment vous êtes-vous senti lorsque vous avez reçu cet appel du Dr Scriver? Que vous a-t-il dit et quelle était sa motivation?

Dr Skamene : Je ne m'en souviens pas très bien, mais vous devez comprendre que la vie de chercheur est faite de relations, de liens et d'appartenance à des groupes et à

des réseaux, virtuels ou physiques. Il n'est pas nécessaire d'abandonner un groupe pour se joindre à un autre. J'étais dans une période féconde. Je ne me souviens pas exactement de ce que Charles m'a dit, mais je suis certain qu'il m'a parlé de mes stratégies expérimentales pour la dissection des caractères multigéniques en une série de caractères monogéniques en interaction les uns avec les autres. En me recrutant, il pourrait sortir du cadre strictement monogénique, certes extrêmement important, mais d'un point de vue pratique, ces caractères ne touchent qu'une infime partie de la population.

De mon côté, je m'intéressais à un problème de taille avec lequel des populations et des continents devaient composer et, sur le plan scientifique, je n'avais pas la réputation de Charles Scriver ou de Clarke Fraser. J'avais des projets qui les intéressaient beaucoup, car ils permettaient de jeter un nouveau regard sur des maladies courantes de l'adulte. Je suis persuadé qu'ils savaient, en me recrutant, que je n'avais pas l'étoffe d'un Nobel, mais que mon expertise s'inscrivait dans le prolongement naturel des travaux du groupe du CRM. Comme les chercheurs sont presque entièrement financés par les deniers publics, ils doivent sans cesse expliquer au grand public que leurs recherches permettront un jour d'aider quelqu'un. De ce point de vue, c'était très intéressant de dire que nos travaux permettaient de comprendre comment on contracte la tuberculose.

Christopher Canning : Oui. Fait intéressant, vous ne faisiez pas partie de ce groupe en 1987, mais il […]

Dr Skamene : Je n'étais pas membre du groupe.

Christopher Canning : Non.

Dr Skamene : Parfait.

Christopher Canning : En 1987, [Charles Scriver] a fait parvenir une lettre au groupe pour l'informer qu'il devait accorder plus d'importance à la génétique moléculaire. Il semble donc, comme vous le mentionniez, que ce léger coup de barre s'imposait pour que le groupe aille au-delà des caractères monogéniques. Il semble que tous les astres étaient alignés pour que le groupe fasse appel à une personne comme vous.

Dr Skamene : Oui, mais je ne me souviens pas de tous les détails. L'organisation des sciences repose en grande partie sur l'opportunisme. Charles Scriver et moi éprouvons beaucoup d'affection l'un pour l'autre.

Christopher Canning : J'allais justement vous demander… Quel genre de collègue était-il lorsque vous avez commencé à travailler avec le groupe?

Dr Skamene : Il était un véritable dieu, mais il demeurait très, très gentil et ouvert aux suggestions. Il était animé d'un esprit vif et critique, et il interagissait beaucoup avec nous.

Christopher Canning : À l'époque, on parlait beaucoup de l'importance, pour les chercheurs du groupe, de travailler au même endroit. Le CRM voulait que les gens soient regroupés dans le même centre de recherche et puissent ainsi mieux

collaborer. On craignait d'ailleurs que le CRM n'accorde aucun appui financier au groupe. Vous souvenez-vous de ces conversations sur le regroupement des chercheurs? Vous travailliez à l'Hôpital général de Montréal, alors que la plupart de vos collègues se trouvaient à l'Hôpital de Montréal pour enfants.

Dr Skamene : Je me souviens très bien de ces conversations. Nous nous étions informés auprès du CRM, qui ne voyait aucun inconvénient à ce que nous travaillions dans des centres différents si nous pouvions lui prouver qu'il s'agissait là d'une formule gagnante. Les scientifiques sont souvent regroupés virtuellement et non géographiquement – et je parle ici de ma vie à McGill.

Christopher Canning : Les chercheurs sont dispersés dans plusieurs établissements.

Dr Skamene : C'est ce que j'ai découvert lorsque j'ai été nommé directeur scientifique de l'Institut de recherche du CUSM[3], poste que j'ai occupé de 1998 à 2008. J'ai été le premier à assumer ces fonctions. Lorsque le CUSM m'a recruté, j'ai demandé les clés de l'Institut au chef de la direction. Il m'a répondu : « Quel institut? Il n'y a pas d'institut. » J'étais devenu le directeur scientifique de quelque 1 000 chercheurs qui travaillaient dans 65 laboratoires dispersés sur l'ensemble du campus du CUSM [l'Hôpital général de Montréal, l'Hôpital Royal Victoria, l'Hôpital de Montréal pour enfants et l'Institut thoracique]. Pour rencontrer mes chercheurs, je devais me rendre dans 65 endroits. Je réussissais à le faire une fois par année, parce que ces visites s'ajoutaient à toutes mes autres tâches de directeur.

La proximité géographique est très importante. La construction récente d'immeubles à McGill ainsi que l'aménagement d'un nouvel établissement central qui abritera l'Institut de recherche du CUSM au cœur de Montréal auront certainement une influence extrêmement positive sur la productivité des chercheurs et la qualité de la vie scientifique. Il n'y a rien de mieux que de travailler coude à coude avec ses collègues ou de prendre un café avec eux. En hiver, même s'ils se trouvent à quelques minutes seulement de votre lieu de travail, vous ne sortez pas pour aller les voir.

Christopher Canning : Si vous ne travailliez pas tous dans le même immeuble, qu'en était-il de la collaboration au sein du groupe pendant les quatre années de votre mandat? Avez-vous publié avec d'autres chercheurs? Qu'est-ce qui a contribué à l'essor du groupe selon vous?

Dr Skamene : En fait, j'étais pour ainsi dire laissé à moi-même. Nous travaillions un peu avec Harriet [Susie] Tenenhouse. J'étudiais l'ostéoporose chez la souris ainsi que le rhumatisme, mais notre collaboration n'était pas assez importante pour que nous rédigions des articles avec son groupe. Il s'agissait plutôt d'une collaboration à distance.

Christopher Canning : Selon la demande de subvention, vos travaux portaient sur les macrophages, n'est-ce pas?

Dr Skamene : Oui.

[3] Centre universitaire de santé McGill

Christopher Canning : Génial. Vos travaux ont ensuite porté sur les réponses génétiques aux parasites, soit le génome du parasite par rapport au génome de l'hôte?

Dr Skamene : C'est bien ça.

Christopher Canning : Et je suppose que vos travaux sont présentés ainsi dans la demande. Comment ce type de recherche pouvait-il aider un groupe de chercheurs spécialisé en génétique médicale?

Dr Skamene : Je peux difficilement expliquer avec précision la dynamique du groupe. Vous savez, il n'est pas nécessaire de réaliser des expériences ensemble pour s'enrichir mutuellement. Chaque fois que le groupe se réunissait, j'étais exposé à des concepts scientifiques que je n'avais jamais réellement étudiés et, de leur côté, mes collègues prenaient connaissance de mes travaux. Nous mettions également sur pied des séminaires pour les étudiants, alors mes étudiants assistaient aux réunions du CRM organisées pour eux.

Très franchement, mon apport a contribué à changer l'image du groupe, qui semblait s'intéresser désormais à des domaines médicalement et socialement plus importants. C'était très intéressant pour moi, car le groupe disposait de nombreuses ressources intellectuelles, mais également de banques de tissus et de cellules qui m'étaient très utiles. Toutefois, du point de vue de la recherche, il s'agissait surtout de stimulation intellectuelle plutôt que d'avantages concrets.

Christopher Canning : Très bien. Vous souvenez-vous d'avoir préparé une demande pour ces travaux? Vous souvenez-vous si le Dr Scriver vous avait demandé de préparer cette demande, car, à la lumière de certaines discussions, c'était le directeur qui soumettait la demande.

Dr Skamene : J'ai préparé tellement de demandes de subventions dans ma vie. C'est toujours le directeur qui prépare ces demandes. J'en ai préparé beaucoup à titre de directeur de divers groupes, mais en tenant toujours compte des commentaires des membres de l'équipe.

C'est pourquoi je suis presque certain qu'on m'a demandé de contribuer à la préparation de la demande, et, si ma mémoire est bonne, de grandes parties de ce que nous présentions étaient retenues, mais d'autres étaient supprimées lorsque le contenu était trop technique et qu'il devenait impossible de l'intégrer. Toutefois, je ne me souviens pas d'avoir préparé cette demande de subvention en particulier.

Christopher Canning : Je comprends, cela fait déjà longtemps. Dans l'ensemble, quelle était la dynamique du groupe? Comment fonctionnait-il? De toute évidence, ses chercheurs connaissaient beaucoup de succès à titre d'auteurs, de conférenciers et de participants à des séminaires. Vous souvenez-vous de la dynamique du groupe?

Dr Skamene : Le Dr Scriver était une figure dominante. Clarke Fraser était présent, mais pas autant que Charles Scriver. J'ignore si Roy Gravel était là à l'époque.

Christopher Canning : Non, il est arrivé lors de la demande de subvention suivante, en 1994.

Dr Skamene : Il s'est joint à nous par l'intermédiaire des Réseaux de centres d'excellence.

Christopher Canning : Bon, j'imagine que Rima…

Dr Skamene : Rima jouait un rôle de plus en plus important au cours des présentations, mais je précise une fois de plus que je ne pouvais juger de la dynamique du groupe ni des interactions entre ses membres à l'Hôpital pour enfants.

Christopher Canning : Bien sûr.

[Inaudible]

Dr Skamene : Pas de problème, c'est la vie.

Christopher Canning : Oui, c'est intéressant. Sans vouloir insister, vous vous êtes joint au groupe pendant quatre ans, et vos travaux étaient très différents de ceux des autres membres. Tous les autres chercheurs étudiaient la phénylcétonurie, le métabolisme des folates ainsi que les vitamines B_9 et B_{12}, alors que vous vous penchiez plutôt sur l'approche multigénétique. Je trouve cela très intéressant.

Dr Skamene : Un seul mandat, n'est-ce pas?

Christopher Canning : Un mandat en 1994, oui.

Dr Skamene : J'imagine que j'ai fait ce que l'on attendait de moi et ce que j'estimais important. Quant à mon travail au sein du groupe, ce n'était pas une priorité dans ma vie. Même que, lorsque vous m'avez appelé pour me demander une entrevue, j'ai dû consulter mon curriculum vitæ pour me souvenir des dates et des personnes visées.

Christopher Canning : Et de toute évidence, l'âme du groupe, c'était le Dr Rosenblatt, non? Il était là depuis 37 ans. Lui et Charles Scriver – il était [inaudible].

Dr Skamene : Oui. Je n'ai pas publié un seul article avec le groupe.

Christopher Canning : C'est intéressant. Puis-je vous demander pourquoi vous n'êtes pas resté avec le groupe en 1994?

Dr Skamene : Probablement parce qu'on ne m'a pas demandé de participer. Ou peut-être parce que grâce à l'arrivée de Roy Gravel et d'autres chercheurs, le groupe pouvait désormais faire de la recherche en génétique davantage axée sur la médecine.

Christopher Canning : D'accord. Par la suite, en 1994, Gravel, Malo, Nadeau, Shoubridge, Rosenblatt, Rozen, Scriver et vous avez présenté une demande. Votre nom figurait sur cette demande, mais vous avez quitté le groupe cette année-là. Vous en souvenez-vous?

Dr Skamene : Je suis désolé. Ils travaillaient tous en harmonie, mais je ne me suis jamais senti chez moi à cet endroit. Mon port d'attache a toujours été l'Hôpital général de Montréal.

Christopher Canning : Bien sûr. Vous avez passé quelques années à l'Hôpital pour enfants, avez apporté votre pierre à l'édifice, enrichi votre formation et poursuivi votre route.

Dr Skamene : C'est bien ça.

Christopher Canning : D'accord. J'aimerais maintenant vous poser quelques questions d'ordre général. Selon vous, et je pose la même question à tous, quels sont les facteurs qui ont contribué à la réussite du groupe du CRM de 1972 à 2009?

Dr Skamene : Qu'entendez-vous par « réussite »? S'agit-il de renouvellement ou d'autre chose?

Christopher Canning : C'était ma deuxième question. Comment définit-on la réussite en science? On pourrait mesurer la réussite par la longévité du groupe ou par ses découvertes. Quelles découvertes du groupe ont, d'une façon ou d'une autre, contribué à l'avancement de la génétique médicale, de la biochimie et de la biologie moléculaire? Comment mesure-t-on la réussite de ce groupe en particulier ou des groupes en général?

Dr Skamene : Vous savez, les temps changent et les critères de réussite sont maintenant différents. On nous pose beaucoup plus souvent les questions que vous venez de me poser. On nous demande notamment en quoi nos travaux sont utiles pour le commun des mortels. À l'époque, on mesurait la réussite à la hauteur du financement que vous obteniez en dehors du groupe. Le groupe devait recueillir des fonds pour des installations conjointes, qui, dès lors, n'auraient pas à être payées à même les subventions. Il devait également disposer de banques d'échantillons pour lesquelles il ne pouvait puiser dans les subventions de fonctionnement et payer le coût des réunions, etc.

Pour ce qui est de la véritable réussite scientifique, je crois que le groupe avait la formidable capacité de recueillir des fonds pour la recherche. Je ne me rappelle pas le montant, mais c'était un certain montant par personne. Ses membres ont également publié de nombreux articles importants. Je ne vous dirai pas lesquels – je crois que vous connaissez déjà certaines répercussions, sur la santé publique, du traitement conçu par Charles Scriver. La prévention des maladies métaboliques a permis de montrer au monde, et notamment aux politiciens, l'importance de la génétique médicale. Si vous trouvez le gène défectueux, vous pouvez corriger le problème. Nous en avons eu la preuve dans le cas de la phénylcétonurie et de quelques autres maladies, mais nous avons toujours dit que cette approche était possible et serait adoptée pour toutes les autres maladies après 2010.

Cette hypothèse ne s'est pas encore concrétisée. Ainsi, nous pouvons rechercher les gènes associés au cancer du sein, mais nous ne sommes pas passés de la théorie à la pratique. Les oncogènes connus ne sont qu'un élément de l'architecture multigénique du cancer, et il nous faudra encore de 10 à 20 ans avant de bien la comprendre. À l'heure actuelle, les véritables retombées de cette médecine multigénique sont beaucoup moins importantes qu'elles ne l'ont été dans le cas de la phénylcétonurie, où la présence d'un gène muté codant pour une enzyme particulière permet de poser un diagnostic formel chez l'enfant. Cette découverte était très, très importante.

Nous n'avons pas encore élucidé le mystère de la génétique du cancer du sein ou des maladies cardiaques. Les travaux de mon équipe ont contribué à accroître notre capacité à mettre au jour la vulnérabilité aux infections, avant même l'exposition aux agents infectieux, mais nous ne sommes pas encore en mesure de déterminer qui doit être vacciné ou non.

Toutefois, tant les scientifiques que les profanes savent maintenant, grâce aux travaux du groupe du CRM et, bien sûr, d'autres chercheurs, que nous pouvons connaître notre bagage génétique et trouver, manipuler et utiliser aux fins de diagnostic et de traitement les gènes et les voies biochimiques qu'ils régissent.

On ne saurait sous-estimer le rôle du groupe, qui offrait un cadre d'apprentissage exceptionnel. Une véritable armée de titulaires de doctorats et de maîtrises peut en témoigner. La situation économique du groupe lui permettait de choisir ses étudiants et de les soutenir financièrement de façon beaucoup plus stratégique.

Christopher Canning : Selon vous, exerce-t-on davantage de pression sur les chercheurs pour qu'ils prouvent l'efficacité de la recherche médicale, ou la recherche fondamentale constitue-t-elle une fin en soi?

Dr Skamene : Vous, vous le savez, mais la plupart des gens l'ignorent. Laissez-moi vous donner un exemple : nous avons publié les résultats de travaux de recherche fondamentale sur la découverte d'un gène qui régit la vulnérabilité ou la résistance aux infections mycobactériennes en 1982. Il a fallu plus de 30 ans de dur labeur et de multiples thèses de doctorat pour qu'on lève le voile sur l'expression phénotypique de ce gène au niveau organismique, tissulaire, cellulaire, moléculaire et structural. Aujourd'hui, en 2010, nous pouvons enfin affirmer connaître des processus analogues importants sur le plan médical chez l'humain et moduler la réponse de l'hôte en faveur de l'hôte.

Il n'y avait que peu d'exemples dans le groupe de recherches de nature à changer véritablement la vie des gens, mais je crois que cela ne se serait pas produit sans le groupe, parce que ces découvertes sont des signaux qui montrent la route vers d'autres réalisations. Le groupe a-t-il fait des recherches qui, sans lui, n'auraient jamais été réalisées? Franchement, probablement pas. Mais il a contribué à enrichir la vie universitaire, et ça, c'est notre raison d'être. Nous avons des étudiants et nous voulons changer les choses. Nous voulons susciter des débats; c'est pourquoi le groupe est très important. Si nous devons présenter une demande tous les quatre ans, nous pouvons faire valoir le nombre d'articles publiés. Il est très difficile de déterminer, à partir de la demande, le nombre d'articles que vous auriez publiés si vous n'aviez pas obtenu ce financement. Comme je l'ai mentionné, on recrute des gens et on change de perspective. On en a fait bon usage. Les gens pourraient dire la même chose de mon centre. Les occasions sont nombreuses, mais nous devons prendre tous les moyens à notre disposition pour obtenir le plus de ressources possible. Si Charles Scriver ne l'avait pas fait, quelqu'un d'autre en aurait profité. Alors, aussi bien en profiter.

Christopher Canning : Parfait. Une dernière question : je sais que vous devez nous quitter, mais savez-vous pourquoi le CRM ou, maintenant, les IRSC, ne financent plus les

groupes? Avez-vous une idée à ce sujet? Avez-vous participé aux travaux d'autres groupes subventionnés par le CRM ou les IRSC? Savez-vous pourquoi ces organismes ont cessé de verser des subventions?

Dr Skamene : Je crois qu'avec les dernières ressources, ils se sont dit qu'il s'agissait d'un groupe de personnes fantastiques et que les sommes octroyées étaient fantastiques. Ce n'est certainement pas le chercheur qu'ils souhaitaient soutenir financièrement; au contraire, ils veulent financer un […]. Pour ma part, je crois que ce n'est pas la bonne façon de faire, mais c'est ainsi que procèdent toutes les grandes organisations ici et aux États-Unis. Elles souhaitent financer maintenant la recherche thématique et les projets de mégascience. Elles préfèrent utiliser leur argent ainsi plutôt que d'appuyer les groupes de recherche fondamentale.

Christopher Canning : Ça pose problème, à mon avis. Sans recherche fondamentale, à quoi servira la recherche thématique si nous misons uniquement sur la mégascience?

Dr Skamene : La mégascience… Si un étudiant vient me voir et me demande s'il peut étudier la couleur des ailes d'un moustique – motif scientifique valable à l'appui – je vais y penser, mais je ne lui opposerai pas un refus catégorique. Le milieu compte suffisamment d'acteurs pour que la recherche continue d'évoluer. La recherche fondamentale occupe une place importante à McGill; ici, la tradition est bien ancrée, ce qui n'est pas le cas dans toutes les institutions. Une chose est sûre : pas une seule découverte nobélisée n'est le fruit de la recherche thématique et appliquée. Tous les chercheurs qui ont réalisé des découvertes importantes étaient des fondamentalistes mus par la curiosité.

Christopher Canning : Merci beaucoup de m'avoir accordé de votre temps.

FIN DE L'ENTRETIEN

P^r Peter Hechtman, le 30 septembre 2010

Christopher Canning : Nous sommes le 30 septembre 2010. Ici Christopher Canning en compagnie du P^r Peter Hechtman. Professeur Hechtman, je suis honoré de pouvoir m'entretenir avec vous de deux grands sujets qui touchent la génétique humaine.

J'aimerais d'abord que nous parlions de votre parcours universitaire, qui a contribué à l'avancement de la médecine génétique au Canada et ailleurs dans le monde. Ensuite – et surtout, pour les besoins de notre étude – je m'intéresse à votre participation au groupe sur la médecine génétique des IRSC[1] – anciennement le CRM[2] –, dont vous avez fait partie dès la première année de sa constitution, en 1972, si je ne m'abuse, jusqu'en 1987.

P^r Hechtman : C'est exact.

Christopher Canning : Mais parlons d'abord de vous, si vous le voulez bien. Où êtes-vous né et où avez-vous passé votre enfance?

P^r Hechtman : Je suis né à Brooklyn, à New York, et j'ai fréquenté l'école secondaire à Englewood, au New Jersey. J'ai obtenu un diplôme de premier cycle en biochimie à l'Université McGill, avant de décrocher une maîtrise dans cette même discipline à l'Université du Minnesota. C'était en 1966. Puis je suis revenu à McGill, où j'ai fait mon doctorat en compagnie de Charles Scriver, au Département de médecine expérimentale, comme on l'appelait à l'époque. Je suis par la suite retourné aux États-Unis et j'ai passé deux ans à la Faculté de médecine Albert-Einstein à titre de boursier de recherche postdoctorale, où j'ai collaboré avec le D^r Richard Soffer et étudié l'enzymologie.

Christopher Canning : Excellent! Avant de parler de vos recherches postdoctorales et du début de votre carrière, j'aimerais savoir dans quelle mesure la réussite scolaire était importante aux yeux de vos parents.

P^r Hechtman : Il était hors de question pour eux que je n'aille pas à l'université. Mon père nourrissait de grandes ambitions scientifiques dans sa jeunesse, plus précisément en physique. Mais la Grande Dépression l'a finalement poussé à se diriger vers autre chose. J'ai donc été investi de la mission de réaliser son rêve, sauf qu'au moment de mon entrée à l'université, le domaine scientifique de pointe n'était plus la physique, mais bien la biochimie; du moins, c'est l'impression que j'avais. J'ai donc décidé de m'y consacrer.

Christopher Canning : Intéressant… Vous étiez en quelque sorte à la rencontre de la biologie et de la physique.

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

Pr Hechtman : Eh bien, ce n'était pas parfaitement clair à ce moment-là, mais j'étais persuadé que la biochimie allait pouvoir répondre à toutes les questions d'ordre biologique.

Christopher Canning : Et quelles étaient vos ambitions durant vos études au premier cycle? Les sciences vous intéressaient-elles déjà?

Pr Hechtman : Je crois qu'il n'y a jamais eu de doute : j'allais faire carrière en sciences.

Christopher Canning : D'accord. Et vous n'avez suivi aucune formation en médecine, n'est-ce pas?

Pr Hechtman : C'est exact.

Christopher Canning : Alors, qu'est-ce qui vous a amené à vous consacrer à la médecine ou à la génétique médicale au début de votre parcours?

Pr Hechtman : Bien… À un certain moment, il est devenu évident que pour faire carrière en biologie, il fallait miser sur les domaines d'activité qui offraient des applications pratiques. Entre l'agriculture et la médecine, c'était la médecine qui offrait les horizons les plus vastes. C'est dans ce domaine qu'on pouvait espérer trouver le plus d'emplois et de débouchés.

Christopher Canning : Quand vous avez commencé à travailler en génétique et en biochimie, la médecine vous intéressait-elle déjà?

Pr Hechtman : Non, j'avais une idée très erronée du travail des médecins. Je croyais qu'il se limitait à offrir des soins aux patients. Puis plus tard, je me suis rendu compte que tout comme moi, les médecins rédigeaient des articles sur leurs patients, et que j'aurais probablement été mieux rémunéré pour le faire si j'avais étudié en médecine. Mais je n'avais pas encore compris ça à l'heure des grandes décisions.

Christopher Canning : Comment en êtes-vous venu à rencontrer le Dr Scriver et à collaborer avec lui durant votre doctorat?

Pr Hechtman : C'était une affaire personnelle à l'époque… Pendant la première année de notre mariage à peu près, mon épouse et moi ne pouvions vivre ensemble, car elle n'avait pas été admise en médecine à l'Université du Minnesota, où moi, j'étudiais. Dès lors, il était clair que je devais retourner à McGill. J'ai donc écrit à quelques amis à l'Université pour leur demander de me suggérer un directeur de thèse… et ils m'en ont proposé quelques-uns.

Christopher Canning : Au Canada ou à McGill précisément?

Pr Hechtman : À McGill, en fait, comme je vous le mentionnais, mon épouse étudiait à la Faculté de médecine de McGill à l'époque.

Christopher Canning : D'accord.

Pr Hechtman : Mes amis m'avaient donc recommandé certaines personnes à l'Université, et je suis venu en rencontrer quelques-unes. Je crois que j'ai rencontré le Dr Scriver à un congrès de la Fédération à Atlantic City.

Et c'est lui qui m'a paru le plus sympathique.

Christopher Canning : Connaissiez-vous son travail avant d'envisager de venir vous installer à Montréal?

Pr Hechtman : Non, mais il m'a parlé d'un problème qu'il tentait de résoudre. Il s'agissait de carences enzymatiques vitaminodépendantes, c'est-à-dire des patients qui présentaient des carences enzymatiques traitables au moyen de fortes doses de vitamines, tout particulièrement la vitamine B_6. Et il avait élaboré une théorie sur le mécanisme à l'origine de ce problème. Selon lui, une nouvelle mutation qui toucherait le site de liaison du cofacteur dérivé de la vitamine pourrait diminuer l'affinité de l'enzyme pour le cofacteur vitaminique. Donc, si on pouvait charger ces cellules de grandes quantités de ce cofacteur, on pourrait améliorer un peu le fonctionnement de l'enzyme et ainsi faire passer l'activité résiduelle de 1 % à 4 %, ce qui pourrait être suffisant pour obtenir un effet clinique.

Puis je me suis demandé si je ne pourrais pas utiliser des bactéries…

Christopher Canning : En quelle année était-ce?

Pr Hechtman : C'était autour de 1966, durant mes démarches pour poursuivre mon doctorat à McGill en compagnie du Dr Scriver. Quoi qu'il en soit, j'ai proposé d'opter pour une approche biochimique afin de vérifier son hypothèse relative aux mécanismes des erreurs innées du métabolisme vitaminodépendantes en concevant une bactérie mutante qui comporterait ce même type d'anomalie métabolique.

Christopher Canning : Très intéressant.

Pr Hechtman : Il a aimé l'idée et m'a donné l'occasion de la mettre à l'essai. Finalement, je ne suis pas parvenu à confirmer ni à infirmer l'hypothèse du Dr Scriver, mais j'avais en main d'intéressantes bactéries mutantes, qui m'ont permis d'explorer un autre domaine de recherche auquel il se consacrait à fond : le transport des acides aminés.

Christopher Canning : Bien.

Pr Hechtman : Je me suis donc servi de ces mutants pour réaliser ma thèse de doctorat, auprès du Dr Scriver, sur le transport des acides aminés dans la bactérie.

Christopher Canning : Formidable! Et quelle a été votre relation avec le Dr Scriver au cours de votre doctorat et dans les années qui ont suivi? Comment était-il à titre de superviseur, notamment? Il était déjà un scientifique de renom et visait des objectifs extrêmement ambitieux, n'est-ce pas?

Pr Hechtman : Oui. Assez rapidement, je me suis dit qu'il en menait un peu trop large. Il voulait parvenir à mettre la science au service du traitement de troubles médicaux. Certes, sa maîtrise de la recherche fondamentale était supérieure à celle de la majorité des médecins, mais je ne crois pas qu'elle était suffisante pour qu'il supervise des étudiants au doctorat en recherche fondamentale. J'avais donc l'impression d'être un peu laissé à moi-même. Cependant, il a su bien m'orienter vers d'autres sources de soutien. Par exemple, j'ai passé six mois ici [au Département de génétique humaine] à apprendre à travailler avec des agents mutagènes en compagnie d'une personne vers qui il m'avait orienté pour superviser cette partie de mes travaux.

Christopher Canning : Cette recherche est-elle à l'origine de votre participation au groupe à ses débuts? Je vois que vous avez obtenu votre doctorat en 1970, avant de retourner aux États-Unis pour y poursuivre vos études postdoctorales. À ce moment-là, saviez-vous que vous reviendriez, ou que vous alliez être invité à vous joindre au groupe à titre de fondamentaliste?

Pr Hechtman : Non, je l'ignorais. Je croyais que les États-Unis m'offraient bien plus d'occasions, que j'avais hâte de saisir, et j'espérais pouvoir y mener une carrière universitaire. Mais mes études postdoctorales se sont révélées ardues. Et disons que je me suis retrouvé beaucoup plus dépendant de mes amis de Montréal que je l'aurais souhaité, vu que mon superviseur d'études postdoctorales se montrait peu enclin à m'aider.

Christopher Canning : Et c'est ce qui vous a convaincu de revenir à Montréal?

Pr Hechtman : Oui.

Christopher Canning : Et comment vous êtes-vous retrouvé sur la première demande de subvention du groupe auprès du Conseil de recherches médicales du Canada?

Pr Hechtman : Eh bien, il [le Dr Scriver] m'a fait une offre, la seule que j'avais, en fait.

Christopher Canning : Je vois. Et quelle était cette offre? Que vous a dit le Dr Scriver?

Pr Hechtman : Tout simplement qu'il formait le groupe.

Christopher Canning : D'accord.

Pr Hechtman : Et que je pourrais en faire partie.

Christopher Canning : Pourriez-vous nous raconter l'histoire de la formation du groupe? Selon vous, pourquoi les Drs Scriver et Fraser voulaient-ils former un groupe?

Pr Hechtman : Comme je me trouvais aux États-Unis durant une bonne partie du travail de planification, je ne peux pas vous en dire bien plus à ce sujet. En fait, je dirais… ce n'est pas moi qui ai rédigé les propositions de recherche auxquelles j'ai fini par collaborer; c'est le Dr Scriver.

Christopher Canning : Oui, je l'avais entendu également de la part du Dr Reynold Gold, qui ne se souvenait pas d'avoir rédigé sa partie de la première demande du groupe, en 1972. Donc, vous n'avez pas rédigé cette demande?

Pr Hechtman : Non, pas celle-là. J'ai pour ainsi dire adhéré aux propositions formulées par le Dr Scriver.

Christopher Canning : D'accord, et qu'avez-vous ressenti par rapport à cette situation? Étiez-vous tout simplement heureux de vous joindre au groupe?

Pr Hechtman : Je dirais que oui. Je souhaitais obtenir un emploi, et on m'en offrait un.

Christopher Canning : Intéressant. Alors vous êtes revenu à Montréal en 1972, puis le groupe a été fondé. Où étiez-vous situés à l'époque? Pourriez-vous nous décrire l'endroit?

Pr Hechtman : La première année a été plutôt difficile, car nous étions au deuxième étage de l'Hôpital de Montréal pour enfants, dans le laboratoire où j'avais fait mon doctorat. On nous avait laissé entendre qu'on allait nous aménager des locaux dans l'ancienne maison de soins infirmiers. Ça s'est fait, mais au bout d'un an seulement. La première année, donc, j'étais quelque peu isolé, ici même, au Département de génétique humaine. En fait, j'occupais le local tout juste de l'autre côté du couloir.

Christopher Canning : Est-ce que le lieu de travail représentait un problème pour le groupe à ce moment-là? Parce que je comprends que les modalités de la subvention stipulaient que les membres du groupe devaient tous travailler au même endroit, conformément aux critères de la recherche collaborative.

Pr Hechtman : Au cours de l'année initiale ou des premières périodes de subvention, oui, la situation était préoccupante. Mais, plus tard, notamment lorsque le Dr Pinsky, dont le laboratoire se trouvait à l'Hôpital général juif, s'est joint au groupe, ces règles ont été assouplies, et le groupe a été pour le moins décentralisé.

Christopher Canning : En effet. J'aimerais vous poser quelques questions au sujet des autres membres du groupe à l'époque. Quel était le rôle de tous ces gens : les Drs Fraser, Scriver, Gold et plus tard Rosenblatt? Quelle forme prenait cette collaboration? Comment chaque membre a-t-il contribué à la formation du groupe?

Pr Hechtman : Peut-être que certains détails échappent à mon souvenir, mais je vous dirais que nous menions chacun nos propres programmes de recherche. Certes, nous partagions les locaux, le matériel et l'équipement lourd de base, et nous nous consultions sur différents aspects techniques, mais il y avait très peu de chevauchement entre mes travaux de recherche et ceux du Dr Rosenblatt, par exemple. Il élaborait notamment des cultures tissulaires, expertise qu'il semblait avoir acquise à Boston et sur laquelle mes travaux en sont venus à reposer grandement. Mais en définitive, ce n'était qu'un simple partage de ressources.

Christopher Canning : Et le Dr Gold?

Pr Hechtman : Le Dr Gold… Ce qu'il faisait?

Christopher Canning : Oui.

P[r] Hechtman : Disons qu'il n'avait pas un caractère facile… Je ne suis pas certain de vouloir m'étendre sur ce sujet.

Christopher Canning : Je comprends. À l'époque, il se consacrait à la génétique de la kératine, n'est-ce pas?

P[r] Hechtman : C'est exact. J'ai toujours été sceptique face aux résultats préliminaires sur lesquels il a fondé son hypothèse. Néanmoins, il a soulevé certaines questions qui avaient probablement échappé à nos leaders au moment de former le groupe. Par exemple, notre salaire était entièrement payé à même la subvention du groupe, vous comprenez? Mais il s'agit là d'une source de financement précaire. Les plus jeunes d'entre nous ne s'en faisaient pas trop avec ça au départ, mais le D[r] Gold, lui, était plus âgé que nous.

Christopher Canning : Si je ne m'abuse, il devait être dans la quarantaine à ce moment-là?

P[r] Hechtman : Oui, et je ne sais trop quelles promesses on lui avait faites, mais il nous a annoncé pratiquement dès le départ qu'il n'allait pas se contenter indéfiniment d'un financement incertain. Il voulait être un employé de l'Université, avoir un salaire stable et un poste de professeur au sein d'un département. Il en faisait une véritable obsession. Nos échanges avec lui sont devenus pénibles, car il ne parlait que de ça. Puis comme il n'obtenait pas satisfaction, il a fini par aller à Toronto.

Malgré tout, il m'aura fait prendre conscience que je devrais, moi aussi, tenter d'obtenir de telles conditions. C'était ça, le problème du groupe : le cheminement de carrière, de simple adjoint de recherche à professeur, n'était pas clair. On ne savait pas comment cette situation allait être gérée.

Christopher Canning : Ce n'était pas clair pour vous non plus à l'époque?

P[r] Hechtman : En fait, au tout début, je ne pensais pas à ça. Mais, avec les années – et l'insistance de Rennie [le D[r] Gold] –, j'admets que cette question a fini par me préoccuper également. Tout le monde est à la recherche de stabilité et de sécurité dans sa carrière.

Christopher Canning : Vous dites que vous meniez vos travaux chacun de votre côté, mais avez-vous publié des articles en collaboration avec certains de vos collègues au sein du groupe? Dans l'affirmative, avec qui avez-vous coécrit et comment s'est passé l'expérience? Comment fonctionnait la démarche de publication au début?

P[r] Hechtman : Une chose est sûre, nous n'avions pas à obtenir l'aval de nos supérieurs avant de publier un article. Nous pouvions présenter ou publier des données à notre guise dès que nous le jugions opportun. Les publications n'étaient pas centralisées.

J'ai donc publié des articles en collaboration avec des étudiants aux cycles supérieurs ou, parfois, avec des techniciens. Cela dit, vous trouverez peut-être un ou deux articles que j'ai publiés avec le D[r] Scriver. Il faut préciser

que, comme vous le savez déjà, j'ai quitté le groupe en 1987, principalement en raison de la perte de ma subvention. J'avais des projets en cours à ce moment-là, et il me fallait trouver des moyens d'avancer tant bien que mal, en obtenant de petites subventions ici et là, et le salaire de l'un de mes étudiants aux cycles supérieurs était également payé par le Dr Scriver. J'avais donc le sentiment de devoir inclure son nom dans l'article, par simple courtoisie. Et il est vrai que j'ai écrit un ou deux articles sur les enjeux liés au dépistage de la maladie de Tay-Sachs, auxquels il a contribué par ses idées et diverses données.

Certains des articles que j'ai publiés faisaient mention d'une certaine Eva Andermann. Neurologue, plus précisément neurogénéticienne, elle parcourait le Québec pour mener des recherches sur la maladie de Tay-Sachs dans la population canadienne-française. Or, chaque fois qu'elle me fournissait de l'information sur un patient – le plus souvent sous forme de cellules – que j'incorporais à mes travaux de recherche, il me semblait tout naturel d'ajouter son nom à la publication. C'est la façon de faire en médecine. Vous savez, les articles sont remplis de noms de médecins qui effectuent de simples examens chez un patient dont le cas est abordé dans la publication. Mais, bien souvent, j'étais le seul chercheur proprement dit. Les autres étaient des étudiants ou des techniciens.

Christopher Canning : Et c'est vous qui étiez responsable de la recherche fondamentale? Par exemple, votre nom figure dans une publication de 1970 sur le transport des acides aminés neutres, votre sujet de thèse de doctorat, je crois. Le nom du Dr Scriver y figure également. La recherche fondamentale là-dessus, c'était votre responsabilité?

Pr Hechtman : Oui, mais c'était la façon de faire. Un étudiant aux cycles supérieurs publie avec son mentor, qui est fier de voir le travail accompli par son protégé. Je crois que trois articles ont été publiés sur cette thèse, dont l'un fait également mention d'un certain M. Middleton, celui qui m'a appris comment employer des agents mutagènes. J'ai travaillé à son laboratoire durant six mois. Disons que, dans le milieu de la recherche, la mention des noms dans les publications scientifiques est un sujet si délicat qu'afin d'éviter tout problème, j'ai toujours eu comme politique d'inclure toute personne qui pourrait le moindrement se sentir lésée de voir son nom omis.

Dans un article intitulé *More Than One Mutation Defines Tay-Sachs Disease in French Canada*, je pense, vous verrez une douzaine de noms. Il s'agit tous de médecins qui m'ont fait parvenir des cellules de patients atteints de la maladie de Tay-Sachs. Voilà l'essentiel de leur contribution…

Christopher Canning : Donc, à l'époque, la collaboration entre fondamentalistes, généticiens et médecins n'était pas nécessairement d'ordre scientifique, mais plutôt logistique. Vos collaborateurs vous fournissaient les lignées cellulaires ou tout autre matériel dont vous aviez besoin?

Pr Hechtman : Parfois, ils pouvaient également effectuer des analyses de laboratoire spécialisées. C'était la façon de faire, et ce l'est encore aujourd'hui.

Christopher Canning : Certainement. Dans la première demande que vous avez soumise au groupe, vous indiquiez que votre recherche portait sur la génétique biochimique, la biologie du développement et la différenciation des fonctions cellulaires. Pouvez-vous me décrire ce que cela signifie et le replacer dans le contexte initial du groupe?

Pr Hechtman : Eh bien, il s'agit d'une invention scrivernienne que j'ai…

[rires]

Christopher Canning : Une « invention scrivernienne »? Que voulez-vous dire par là?

Pr Hechtman : Ouais. En fait, vous savez… Avant d'entrer à l'école de médecine, il a obtenu un baccalauréat spécialisé en études anglaises. Il possède donc une excellente maîtrise de la langue. Il sait comment inventer des termes et jouer avec les mots. Je me souviens qu'à l'époque, je me demandais bien de quoi il parlait. Je ne connaissais rien de la biologie du développement. Mais il était question du développement d'une enzyme! La proposition de recherche était fondée sur l'hypothèse selon laquelle on pouvait convertir l'hexosaminidase B, une enzyme, en hexosaminidase A par l'ajout de résidus de sucre. Or, cette association entre les deux enzymes s'est par la suite révélée fausse. Mais c'est ce qu'on croyait à ce moment-là, et c'est pourquoi le Dr Scriver a eu l'idée de « développer » une enzyme. Et j'étais d'accord.

Christopher Canning : Et c'est là, pendant que vous étiez en biochimie, que vous avez entendu parler de biologie du développement pour la première fois?

Pr Hechtman : Eh bien, il en a été question dans plusieurs cours, mais je n'avais jamais prévu d'acquérir de l'expertise dans ce domaine, et vous savez…

Christopher Canning : D'accord, mais comment se fait-il que votre nom figure dans la demande à titre d'expert en biologie du développement?

Pr Hechtman : Hum… si vous éteigniez votre magnétophone, je vous dirais que les scientifiques savent souvent faire preuve d'« imagination ». Si vous voyez ce que je veux dire…

Christopher Canning : C'est ce que nous voulons étudier. Nous étudions…

Pr Hechtman : L'imagination?

Christopher Canning : Ce n'est peut-être pas le bon mot, mais disons le processus de production des faits scientifiques.

Pr Hechtman : De la science-fiction.

Christopher Canning : Bien sûr, dans certains cas, on pourrait voir ça comme de la fiction, mais il existe des processus bien réels et concrets derrière les faits, comme vous le laissez entendre. En tant que sociologues de la science, nous nous intéressons à ces processus.

Pr Hechtman : Je vois.

Christopher Canning : Bien sûr, la science comporte une certaine part de fiction, et il se passe pas mal de choses intéressantes en coulisses, si on peut dire. Ce sont ces jeux de coulisses qui nous intéressent. Alors, le chercheur en moi adore ces histoires-là. C'est génial!

P[r] Hechtman : Vous avez peut-être remarqué que les trois plus jeunes membres du groupe, soit les D[rs] Gold et Rosenblatt et moi-même, étions tous des étudiants du D[r] Scriver. Il va sans dire que cette entreprise était très paternaliste. Le D[r] Fraser, lui, n'était évidemment pas un étudiant du D[r] Scriver, il était même son aîné, mais il était tout simplement impensable de mettre sur pied un groupe de recherche en génétique à McGill, à l'Hôpital pour enfants, sans y inclure Clarke Fraser.

Christopher Canning : Parlons justement du D[r] Fraser, si vous le voulez bien. Son rôle semble avoir été crucial, et souvent même sous-estimé, dans la genèse de la génétique médicale au Canada, et tout particulièrement à Montréal. Alors, comment vos travaux en biochimie ont-ils contribué à ses recherches en cytogénétique, et quelle était la nature de cette relation à l'époque?

P[r] Hechtman : Je dirais que cette relation était inexistante… À mon avis, ce serait une erreur de dire que le D[r] Fraser faisait de la cytogénétique. Il était généticien clinique en chef à l'Hôpital pour enfants, alors il va de soi que la cytogénétique clinique relevait de lui, mais, à ce que je sache, il ne possédait pas de compétences comme cytogénéticien. Il avait l'habitude d'embaucher des personnes relativement expérimentées. Le premier à avoir dirigé ce service, en fait, était Michel Vekemanns, l'un de ses anciens étudiants. Je crois que le D[r] Fraser s'intéressait surtout à la dysmorphologie et à des trucs du même type. C'est ce qui lui tenait à cœur.

Christopher Canning : Je vois. Communiquiez-vous souvent avec lui en tant que membre du groupe à l'époque?

P[r] Hechtman : Pas très souvent. On se rencontrait surtout pour aborder diverses questions d'ordre administratif.

Christopher Canning : Comment était-il à titre de codirecteur ou codirigeant du groupe?

P[r] Hechtman : Il demeurait à distance, comme je le disais. Le D[r] Scriver avait une approche paternaliste, alors que Clarke Fraser nous laissait faire notre travail. Le D[r] Scriver était en mission, tandis que le D[r] Fraser exerçait sa profession.

Christopher Canning : Belle image! À quels domaines de la médecine vous intéressiez-vous à votre arrivée à McGill? Vous travailliez toujours en recherche fondamentale, mais étiez-vous entouré de cliniciens? Je vois que vous vous êtes ultérieurement penché sur la maladie de Tay-Sachs. Comment en êtes-vous venu à mener des travaux sur cette maladie, et sur quels aspects de la recherche fondamentale portaient-ils?

P[r] Hechtman : En fait, ce n'est pas que j'en sois venu à m'intéresser à la maladie de Tay-Sachs : j'ai mené des travaux sur cette maladie dès le départ.

Christopher Canning : Pouvez-vous expliquer brièvement de quoi il s'agit?

Pr Hechtman : Certainement. Elle appartient à un ensemble d'affections appelées « maladies de surcharge lysosomale ». Les lysosomes sont des organites en forme de sac qui contiennent des enzymes servant à la dégradation de substances chimiques complexes. Et s'il y a mutation génétique de n'importe laquelle de ces enzymes, une substance chimique donnée ne se dégrade plus; dans le cas de la maladie de Tay-Sachs, la mutation affecte une enzyme, l'hexosaminidase A.

Christopher Canning : La fameuse « hex A »?

Pr Hechtman : Oui, l'hex A. Et un déficit de production de cette enzyme se traduit par l'accumulation d'un produit de stockage, le ganglioside GM2. Avec le temps, cette accumulation devient si importante dans le cerveau de l'enfant atteint qu'elle provoque la destruction de la quasi-totalité des neurones, ce qui entraîne une paralysie complète ainsi que la perte des facultés mentales, des réflexes et de l'activité cérébrale. La mort survient habituellement autour de l'âge de 3 ou 4 ans.

Si, à l'époque, cette maladie prenait autant d'importance, c'est qu'il y avait un groupe dans lequel elle était cent fois plus fréquente : les Juifs ashkénazes.

Christopher Canning : Oui, je vois que vous avez collaboré avec le Réseau de médecine génétique du Québec, à Montréal.

Pr Hechtman : Oui, et cela nous amène à soulever une autre question.

Christopher Canning : Nous y reviendrons.

Pr Hechtman : D'accord, alors cette maladie a pris de l'importance en raison de l'existence d'une population cible dans laquelle sa fréquence était préoccupante. Nous disposions d'un moyen de dépister l'état de porteur et de poser un diagnostic prénatal chez le fœtus. En d'autres termes, nous avions une solution scientifique à un problème pratique. Cette maladie a donc fait l'objet d'intenses travaux de recherche.

Les chercheurs en médecine disent que leur science permettra de traiter, de guérir ou de prévenir une maladie. Ce n'est pas faux, mais ce n'est pas tout. Ce qui est important aussi, c'est que tout trouble, héréditaire ou non, nous aide à découvrir le fonctionnement normal de l'organisme.

Pour ce qui est du Réseau de médecine génétique du Québec, il s'agit d'une autre invention scrivernienne qui, à mon avis, illustre bien pourquoi le Conseil de recherches médicales du Canada a toujours été fasciné par le Dr Scriver. Il a présenté l'idée d'un lien harmonieux entre la recherche fondamentale et la prestation de services de soins de santé. Vous voyez? Il a donc comblé en bonne partie le fossé administratif qui séparait la médecine de la recherche. Le Réseau de médecine génétique du Québec devait transformer les plus récents fruits de la recherche fondamentale en

moyens de prévenir les maladies génétiques, notamment par le dépistage du statut de porteur de la maladie de Tay-Sachs ou de la thalassémie, ou dans le cas de la phénylcétonurie et de divers autres troubles, par le dépistage néonatal suivi d'une diète. Le Dr Scriver était habile pour établir ces liens et faire valoir ses idées.

Christopher Canning : N'y voyez-vous pas également la possibilité de contribuer au savoir médical?

Pr Hechtman : Oui, absolument! Nul doute que le Réseau de médecine génétique du Québec est devenu un modèle pour d'autres administrations ou établissements au Canada. Des gens des États-Unis lui ont demandé comment il s'y était pris, comment il avait « vendu » son concept et convaincu les décideurs d'agir, comment tout ça fonctionnait et quelles étaient ses sources de financement.

Christopher Canning : Et on était alors au début des maladies mendéliennes monogéniques? La phénylcétonurie, la maladie de Tay-Sachs…

Pr Hechtman : À l'époque, notre connaissance de la génétique médicale se résumait essentiellement à ça.

Enfin, lorsqu'on enseigne aux cycles supérieurs, on est bien conscient qu'il y a plus… comme des anomalies cytogénétiques. Il y a des maladies polygéniques, mais personne ne savait vraiment, à ce moment-là, comment les étudier.

Donc, même si j'ai été engagé comme chercheur, j'aimerais pouvoir dire que j'avais le même portrait global de la situation que le Dr Scriver, mais ma participation au dépistage de la maladie de Tay-Sachs se résumait à visiter, pour le compte du Réseau, les écoles secondaires où on trouvait de nombreux étudiants juifs. Pour le dépistage de la thalassémie, on se rendait dans des écoles à forte concentration d'étudiants grecs et italiens, mais je n'y ai pas pris part. J'accompagnais les techniciens qui allaient prélever des échantillons de sang, mais il y avait également un groupe d'étudiants à qui on devait exposer l'objectif de ce programme, et j'étais la personne désignée pour les renseigner sur la maladie de Tay-Sachs et sur les tests auxquels ils se soumettaient, pour leur expliquer notamment en quoi cette démarche pouvait contribuer à éradiquer la maladie. Et les choses terribles qui pouvaient survenir en l'absence de tests de dépistage.

Voilà en quoi consistait ma participation. Et quelques techniciens procédaient au dépistage sérique au moyen d'un système automatisé. Mais certaines personnes attendaient la grossesse avant de demander un test, et alors, on ne pouvait pas utiliser le sérum, parce que les hormones de grossesse modifient les résultats. Nous devions donc employer une technique de dépistage manuelle à partir de globules blancs. Et c'est moi qui accomplissais ou supervisais cette tâche. Outre la maladie de Tay-Sachs, il existait plusieurs autres troubles lysosomaux, comme la carence en bêta-galactosidase ou en fucosidase et la maladie de Gaucher. La technique de mesure enzymatique était pratiquement la même que dans le cas de la maladie de Tay-Sachs. Et c'est moi qui étais chargé d'effectuer le

test pour les diagnostics prénatals.

Donc, en quelque sorte, mon travail cadrait dans le modèle scrivernien, soit avec l'idée de jumeler la recherche fondamentale et la prestation des soins de santé.

Christopher Canning : Y avait-il une forme de rivalité entre les milieux de la recherche et des soins cliniques? En d'autres termes, était-il toujours entendu que les experts en recherche fondamentale et en soins cliniques devaient travailler en concertation? Je crois comprendre que cette forme de collaboration a toujours été propre à la génétique médicale.

Pr Hechtman : Une rivalité? Un titulaire de doctorat ne pourrait jamais s'improviser clinicien. Ce serait illégal, point à la ligne. Mais l'inverse est possible. Des médecins qui ne possèdent aucune formation de chercheur décident tout bonnement de se lancer en recherche fondamentale. Et l'expérience est souvent très difficile. Il y a toujours, comment dirais-je, une certaine « jalousie interprofessionnelle ».

Les départements de neurologie sont généralement propices à une autre forme de conflit, notamment en raison de la difficulté à établir des diagnostics. D'abord, les cliniciens sont impuissants à aider la majorité de leurs patients, mais s'ils parviennent à établir un diagnostic, ils en font tout un plat. Donc, chaque fois qu'ils ne savaient pas comment obtenir un diagnostic chez un patient, ils me pressaient de demandes… « Pouvez-vous faire ce test? Puis celui-ci? Pouvez-vous faire tous les tests possibles chez ces patients? » En fait, la pression était si forte que j'avais l'impression que ces cliniciens se servaient de mon laboratoire pour procéder au dépistage de pratiquement n'importe quelle maladie, et je suppose qu'ils croyaient que je vivais dans une tour d'ivoire et que je n'étais pas disposé à contribuer au travail clinique. Et je crois que ça a fini par me poser un léger problème.

Christopher Canning : Donc, tous ces médecins des divers départements vous demandaient d'effectuer des recherches pour eux. Ces enzymes [inaudible].

Pr Hechtman : À vrai dire, ce n'était pas de la recherche, mais du dépistage. Et ces demandes ne provenaient pas vraiment de l'ensemble des départements, mais surtout du Département de neurologie.

Christopher Canning : Intéressant.

Pr Hechtman : Quoi qu'il en soit, j'ai composé avec la situation.

Christopher Canning : J'aimerais maintenant aborder un autre sujet, si vous le voulez bien. Selon certains documents obtenus du Dr Rosenblatt, il y aurait eu quelques désaccords internes dans les années 1980 sur l'orientation et la compétitivité du groupe, particulièrement en biologie moléculaire. Vers le début ou le milieu des années 1980, il était entendu que, d'une manière ou d'une autre, la biologie moléculaire était essentielle à l'avancement de la biochimie. Pouvez-vous nous parler de cette période?

Pr Hechtman : Eh bien, ce que vous me rapportez me semble exact. Enfin, je ne sais pas

ce qu'il en pense exactement, mais l'information est juste. Lorsque je me suis joint au groupe, au début des années 1970, la biochimie devait être la prochaine panacée. Mais rapidement, disons vers 1978 ou 1979, on a commencé à publier des articles dans lesquels il apparaissait clairement que la biologie moléculaire était désormais une science de laboratoire utile dans toutes sortes de problèmes d'ordre biologique ou médical, et qui apportait des réponses beaucoup plus rapidement et facilement. Pour vous donner un exemple tout simple…

Christopher Canning : Oui, je vous en prie.

P[r] Hechtman : Plus tard dans ma carrière, j'ai étudié un trouble appelé « déficit en prolidase ». Deux de mes étudiants ont collaboré au projet, l'un au début des années 1970 et l'autre, au milieu des années 1980. Ils avaient tous deux besoin d'enzymes pures pour mener leurs travaux. Le premier a obtenu littéralement de pleins seaux de sang humain périmé et en a fait passer des extraits dans quelque huit colonnes de purification pour finalement en tirer 10 microgrammes d'enzymes pures.

L'autre, une étudiante, a cloné le gène, l'a soumis à de puissants promoteurs, puis l'a inséré dans une bactérie, a ajouté au début de l'enzyme un élément que la colonne d'affinité pouvait reconnaître et, en trois jours, elle a obtenu 50 milligrammes d'enzymes pures. Or, peu importe le degré de connaissance du problème, il est évident qu'on peut mener des recherches beaucoup plus étendues au moyen de 50 milligrammes que de 10 microgrammes. Cet exemple illustre à quel point la biologie moléculaire facilite les choses. Néanmoins, je ne sais pas si les autres membres du groupe me voyaient comme celui qui allait faire d'eux des biologistes moléculaires. Si c'était le cas, ils ont dû être déçus, car je n'adopte pas très facilement de nouvelles technologies.

Au début des années 1980, bien qu'on ait amplement écrit sur le sujet, nous sommes loin d'avoir fait des biologistes moléculaires de nous-mêmes. Par contre, le groupe de l'Hôpital pour enfants de Toronto, lui, y est parvenu. Il a mis sur pied un excellent programme de biologie moléculaire.

Le groupe comptait sur Rod McInnes, aujourd'hui à McGill, Roy Gravel, Don Mahuran et quelques autres dont j'oublie le nom, mais nul doute que, sur le plan des compétences en biologie moléculaire, ce groupe était en mesure d'accomplir beaucoup plus que nous.

Cependant, dix ans plus tard, comme c'est souvent le cas, la biologie moléculaire s'était passablement simplifiée, particulièrement grâce à l'invention de la technique PCR. Donc, à ce moment-là, pratiquement n'importe qui pouvait être biologiste moléculaire. Nous avons pu rattraper une partie de notre retard, mais au début des années 1980, nous n'étions certainement pas à la hauteur dans cet important domaine.

Christopher Canning : C'est exactement le ton de la lettre que le D[r] Scriver a envoyée au reste du groupe en 1985 ou 1986, je crois. On ressentait comme une urgence de se retrousser les manches, comme vous le disiez, pour maîtriser cette nouvelle technologie en biologie moléculaire.

Pr Hechtman : Oui, en effet.

Christopher Canning : Et je crois que c'est pourquoi on a invité Rima Rozen à se joindre au groupe. Le Dr Scriver, notamment, voyait en elle une jeune biologiste moléculaire fort talentueuse.

Pr Hechtman : Oui, elle avait étudié aux cycles supérieurs avec Charles Scriver avant d'aller poursuivre sa formation postdoctorale en biologie moléculaire. Tout comme je suis allé à la Faculté de médecine Albert-Einstein pour apprendre l'enzymologie, une discipline de pointe au début des années 1970, elle, 10 ou 15 années plus tard, est allée étudier la biologie moléculaire, ce qui en faisait une candidate de choix pour le groupe.

Christopher Canning : Si je comprends bien, l'orientation du groupe a même changé par la suite. De toute évidence, la biochimie occupe toujours une place importante, mais avez-vous observé une réorientation du groupe dans les années 1980?

Pr Hechtman : Oui et non. J'ai quitté le groupe au milieu des années 1980, mais, fait plutôt surprenant, j'ai poursuivi mon travail au même laboratoire de l'Hôpital de Montréal pour enfants durant les quinze années qui ont suivi. Malgré mon retrait du groupe, j'ai continué d'en gérer le budget de formation, c'est-à-dire les fonds destinés à la rémunération des étudiants aux cycles supérieurs. Et personne ne trouvait à redire. Je participais même à des séminaires et à d'autres événements. Je n'avais pas le droit de vote sur les dépenses du groupe, mais je crois que les autres membres m'acceptaient un peu… comment disaient-ils… comme un « patriarche »?

Donc, oui, le groupe a changé, et mon travail aussi, à n'en pas douter. La biologie moléculaire y occupait plus de place, avec étude directe des gènes.

Christopher Canning : D'accord. Et comme vous venez de le laisser entendre, le Groupe sur la génétique médicale était-il vraiment un groupe? Vous voyiez-vous toujours comme un groupe à l'époque? Et comment le Conseil de recherches médicales définissait-il les groupes de recherche?

Pr Hechtman : En fait, nous nous penchions sur des troubles de santé différents, mais ils appartenaient tous à la même catégorie, c'est-à-dire qu'ils étaient attribuables à des mutations dans un seul gène. Nous partagions l'objectif commun de les comprendre et de trouver un moyen de les traiter. C'est en quelque sorte ce qui nous unissait, de même que notre adhésion à la démarche du Dr Scriver, soit tisser un réseau harmonieux entre la recherche et les soins cliniques. Je suis assez certain que les autres membres du groupe partagent cette idée.

Christopher Canning : Mais quel était le ciment du groupe?

Pr Hechtman : [rires] Le financement.

Christopher Canning : Selon le modèle de financement du Conseil de recherches médicales?

Pr Hechtman : Oui.

Christopher Canning : Et y avait-il des discussions au sein du groupe sur les moyens de consolider vos liens afin d'optimiser vos probabilités de réussite?

Pr Hechtman : Nous étions surtout animés par le besoin de publier des articles, beaucoup d'articles, qui sont essentiels à l'obtention du financement.

Christopher Canning : À votre avis, pourquoi le groupe a-t-il connu autant de succès pendant toutes ces années? Qu'est-ce qui en a assuré la longévité, ces 37 ans d'activité?

Pr Hechtman : Je crois qu'on a su s'adjoindre de nouvelles personnes qui ont contribué de façon remarquable à la recherche en génétique humaine. Le Dr Pinsky a été le premier, si je me souviens bien, puis Emil Skamene, de l'Institut de recherche de l'Hôpital général de Montréal, a également fait partie du groupe. Bien que son passage ait été bref, il avait auparavant mis sur pied un groupe extrêmement efficace à l'Hôpital général de Montréal, qui étudiait les facteurs génétiques associés aux maladies infectieuses. C'est un apport de première importance.

Vous avez mentionné Rima Rozen et Roy Gravel, et mis à part les personnes qui se sont greffées au groupe et qui ont permis d'élargir notre expertise ainsi que le nombre de professionnels qui œuvraient avec nous, je crois que notre histoire est étroitement liée à l'effervescence du monde scientifique médical à l'époque. En effet, la génétique humaine représentait alors l'avenir de la médecine.

Au moment de mon adhésion au groupe, l'ensemble des quelque 3 000 maladies génétiques répertoriées ne constituait qu'une infime partie des troubles médicaux existants. De plus en plus, on pouvait étudier les composantes génétiques des grandes maladies. C'était notamment le cas de l'hypercholestérolémie, une maladie monogénique très répandue qui accroît la prédisposition à la maladie coronarienne. Les découvertes réalisées durant cette période ont fait passer la génétique d'obscure spécialité confinée aux maladies rares et exotiques à une importante discipline médicale. Et je crois que le Conseil de recherches médicales souhaitait investir dans un domaine scientifique qui gagnait en importance.

Christopher Canning : Et il voulait s'assurer de financer ce type de génétique médicale pour montrer que les chercheurs canadiens étaient présents dans cette sphère importante, bien qu'encore en éclosion.

Pr Hechtman : Tout à fait.

Christopher Canning : Excellent. Lors du symposium de novembre dernier, le Dr Scriver a mentionné que le groupe fonctionnait comme une organisation de base. Qu'en pensez-vous et était-ce le cas lorsque vous en faisiez partie?

Pr Hechtman : Je ne suis pas sûr de comprendre ce qu'il entendait par là.

Christopher Canning : Il voulait dire que la constitution et l'évolution du groupe étaient venues de la base. J'ai trouvé intéressant qu'il emploie cette expression-là pour

désigner le groupe.

Pr Hechtman : J'ai de la difficulté à comprendre ce qu'il veut dire exactement. Je ne vois pas.

Christopher Canning : D'accord, poursuivons alors. Vous avez déjà abordé la question, mais pouvez-vous m'indiquer quelques-unes des avancées les plus importantes principalement attribuables aux travaux du groupe? Quelles sont les grandes percées ou découvertes réalisées grâce aux travaux du groupe dans son ensemble ou bien à ceux de ses membres dans leurs domaines de recherche respectifs?

Pr Hechtman : J'aurais tendance à parler des réalisations sur le plan médical et non scientifique.

Christopher Canning : Intéressant. Pourriez-vous expliquer la distinction entre les deux?

Pr Hechtman : Pour ma part, je crois que mes travaux nous ont aidés à comprendre le fonctionnement des sites actifs d'une enzyme d'importance clinique, telle que l'hexosaminidase A. Au centre de chacun de ces sites actifs se trouvent trois acides aminés. Mon laboratoire en a découvert un. Le deuxième a été découvert par mon labo en collaboration avec un autre. Le troisième, lui, a été découvert par un autre laboratoire. Je crois donc que ces travaux ont une importance sur le plan scientifique; cela dit, ils n'ont nullement contribué à l'éradication quasi complète de la maladie de Tay-Sachs, qui est plutôt attribuable au recours accru aux tests de dépistage génétique. Bien que j'aie également pris part à ces travaux, les résultats obtenus n'ont rien à voir avec la recherche.

À mon avis, l'apport de Rima Rozen est important : elle a montré qu'un polymorphisme relativement fréquent dans un gène qu'elle étudiait était associé à divers complexes ou troubles relativement nombreux. Elle a donc mis au point un très bon modèle qui illustre l'effet que peut avoir un gène dans le contexte de maladies compliquées auxquelles finissent par contribuer de nombreux gènes et possiblement certains facteurs environnementaux.

Christopher Canning : Vous voulez parler du *MTHFR*[3]?

Pr Hechtman : Oui.

Christopher Canning : On vient également de l'associer au cancer du sein, n'est-ce pas?

Pr Hechtman : Ah, vous me l'apprenez, mais je suis sorti du circuit depuis dix ans; mais déjà, à l'époque, ce gène était associé à des affections autres que cardiaques, et je me souviens d'avoir participé aux travaux là-dessus.

Christopher Canning : J'aime bien la distinction que vous faites : la science pour la science est utile au sens où elle contribue à l'enrichissement du savoir, mais, du même coup, la recherche fondamentale peut aussi déboucher sur des bienfaits

[3] Méthylène tétrahydrofolate

médicaux. Alors, je suppose qu'il doit être difficile d'indiquer clairement les bienfaits que procure votre travail de fondamentaliste : votre contribution repose sur votre travail de recherche.

Pr Hechtman : Je vais répondre à cette question en me reportant au travail que j'accomplissais. À l'époque où la fréquence de la maladie de Tay-Sachs s'élevait à un nouveau-né sur 3 600 au sein de la population juive, le Conseil de recherches médicales souhaitait vivement en apprendre davantage sur les propriétés de l'hexosaminidase A, l'enzyme à l'origine de la maladie, vous voyez? Aujourd'hui, les communautés juive et autres ont adhéré au dépistage génétique de la maladie, de sorte que sa fréquence a été réduite de 90 %.

Néanmoins, d'un point de vue scientifique, plusieurs questions importantes demeuraient en suspens au sujet de cette enzyme. Le Conseil de recherches médicales [maintenant les Instituts de recherche en santé du Canada] s'y intéresse-t-il toujours? Je ne sais pas.

Christopher Canning : Intéressant. J'aurais encore quelques questions, si vous le permettez. Connaissiez-vous le directeur du Conseil de recherches médicales de l'époque, Malcolm Brown? Sans le connaître personnellement, vous souvenez-vous de lui comme une figure importante du domaine scientifique à ce moment-là?

Pr Hechtman : Pas vraiment, non. Je l'ai peut-être vu une ou deux fois prononcer une allocution.

Christopher Canning : D'accord. Et que faites-vous actuellement? Êtes-vous à la retraite?

Pr Hechtman : Je suis à la retraite depuis 10 ans.

Christopher Canning : Publiez-vous ou lisez-vous toujours des articles dans le domaine?

Pr Hechtman : Non, j'ai réellement décroché.

Christopher Canning : Et vous êtes heureux?

Pr Hechtman : En général, oui. Je m'adonne à des activités qui me divertissent. Je suis des cours de sciences humaines à McGill. Je vends des livres usagés sur Internet. Je fais du vélo et je joue avec mes petits-enfants. Je fais des choses que j'aime.

Christopher Canning : Formidable. Voilà qui conclut notre entretien. Merci de m'avoir accordé de votre temps.

FIN DE L'ENTRETIEN

Eric Shoubridge, le 8 octobre 2010

Christopher Canning : Ici Christopher Canning en compagnie d'Eric Shoubridge. Nous sommes le 8 octobre 2010. C'est un privilège pour moi de pouvoir m'entretenir avec vous de deux grands sujets. J'aimerais que nous abordions d'abord votre parcours universitaire, qui vous a permis de contribuer grandement à l'avancement de la génétique médicale au Canada. Ensuite, et c'est le principal thème de l'étude, j'aimerais parler de votre participation au sein du groupe de génétique médicale des IRSC[1] – anciennement le CRM[2]. Je vous poserai quelques questions précises, mais il s'agira essentiellement d'une conversation qui me permettra de mieux vous connaître et de découvrir vos réalisations, votre participation dans le groupe et vos recherches en général, ainsi que la façon dont tout cela s'inscrit dans un contexte de génétique médicale.

Pour commencer, parlons un peu de vous, si vous le voulez bien. Pouvez-vous nous parler de votre lieu de naissance et de votre enfance?

Eric Shoubridge : Je suis né à Toronto en 1951, et j'ai grandi à Scarborough, ou « Scarberia », comme l'appellent les natifs de l'endroit. J'ai déménagé à Montréal à l'âge de 17 ans. J'étais en 11e année en Ontario, mais une fois au Québec, on m'a redescendu en 10e année parce que je n'ai pas réussi les examens du Ministère après une session en 11e année.

Ensuite, j'ai fait mon cégep à McGill. La structure de McGill n'avait pas changé, mais on donnait le nom de « cégep » aux premières années d'études. J'ai donc passé cinq ans à McGill, et j'ai obtenu mon baccalauréat.

Comme je m'intéressais à la biologie évolutionniste, j'ai suivi beaucoup de cours de biologie et quelques cours de mathématiques. Je voulais faire des études supérieures, et même si je n'avais pas une idée très précise de la direction que j'allais prendre, j'ai toujours su que je voulais faire de la biologie.

Christopher Canning : Dès le secondaire?

Eric Shoubridge : J'adore la biologie depuis l'enfance. Je ne savais pas exactement où cela allait me mener, mais pendant un moment, j'ai voulu devenir biologiste de la vie marine. Pour moi, ce métier avait quelque chose de prestigieux. Dans un de ses films, Jacques Cousteau se trouve sur son bateau, le Calypso, et dit : « Philippe, apporte une bouteille de vin rouge et nous allons observer le plancton ».

Je me suis même inscrit au programme de biologie marine de McGill, mais je me suis rendu compte que ce n'était pas ce que je voulais faire parce qu'il n'y avait pas d'occasion de faire des expériences. Dans ce domaine, l'approche était plutôt descriptive.

Je me suis donc mis à la recherche d'un superviseur, et c'est à ce moment que Bill Leggett m'a demandé si j'avais envie de faire un doctorat sous sa

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

supervision. Bill était biologiste des pêches, et il est par la suite devenu principal de l'Université Queens.

C'était en 1974. Comme j'avais fait mon baccalauréat à McGill, je voulais aller passer au moins un an ailleurs pour voir la vie sous un autre angle. Bill a donc appelé un de ses amis, Peter Larkin, à UBC[3], et lui a demandé s'il accepterait de me prendre sous son aile pendant un an. Il a accepté. Peter était un homme génial. Il pouvait faire salle comble pour un cours de statistiques. Ça vous donne une idée du genre de professeur qu'il était.

Christopher Canning : En statistiques?

Eric Shoubridge : Oui, en statistiques. J'ai donc fréquenté UBC pendant un an. Le projet avec Bill devait porter sur un poisson qu'il avait étudié : l'alose savoureuse. C'est un gros poisson apprécié des pêcheurs sportifs sur la côte est des États-Unis. Il ressemble à un gros hareng, et il est anadrome comme le saumon. Il remonte donc les cours d'eau pour frayer, et c'est là que les pêcheurs l'attendent.

Bill recevait des fonds d'organisations responsables des pêches pour découvrir pourquoi certains poissons frayent une seule fois et meurent (comme le saumon du Pacifique), alors que d'autres retournent vers l'océan après la fraie et reviennent l'année suivante (comme le saumon de l'Atlantique). À cette époque, des études venaient de révéler qu'il y avait de nombreuses variations génétiques naturelles dans les populations, comme le prouve la diversité isoenzymatique. Auparavant, tout le monde croyait qu'il n'y avait pas beaucoup de variations génétiques naturelles, pour une raison dont je ne me souviens pas. À la lumière de ce que nous savons aujourd'hui, je crois que si des gens se penchaient de nouveau sur la question, ils diraient peut-être « À quoi pensaient-ils? Bien sûr qu'il y a beaucoup de variations génétiques naturelles! ».

J'ai suggéré qu'il pourrait être intéressant d'étudier ces populations de poissons et de voir si on pouvait faire des liens entre les variations génétiques et le cycle biologique des poissons. Voici le cycle biologique :

En Floride, ce poisson se comporte comme le saumon du Pacifique : il remonte le cours d'eau une seule fois, et il meurt. À la hauteur de Terre-Neuve, il se comporte comme le saumon de l'Atlantique : il remonte les rivières pour frayer et retourne dans l'océan. Il fait ce trajet quatre ou cinq fois. Il retourne dans l'océan et revient l'année suivante. Je trouvais ça très intéressant. Ce poisson avait adopté des cycles biologiques différents, mais pourquoi?

Christopher Canning : En effet.

Eric Shoubridge : J'étais naïf; vraiment, vraiment naïf. Et j'ai dit que bien sûr, il y avait toujours des variations naturelles dans les populations. Il y a ce phénotype chez ce poisson; un phénotype vraiment très intéressant. Nous pouvons peut-être l'analyser. Peut-être que les fondements métaboliques deviendront évidents lorsque nous étudierons les variations génétiques dans les différentes populations. De toute évidence, je ne savais pas du tout ce que je faisais.

[3] Université de la Colombie-Britannique

Christopher Canning : Aviez-vous des connaissances en biochimie?

Eric Shoubridge : Pratiquement aucune. J'ai suivi le cours de base. Je pense que presque tous les étudiants en biologie de McGill étaient obligés de suivre un cours du niveau 200 en biologie cellulaire et moléculaire. Mais j'étais loin d'être biochimiste, et je ne connaissais pas grand-chose en génétique. À peine quelques notions en génétique des populations.

Christopher Canning : D'accord.

Eric Shoubridge : Le cours de génétique des populations était donné par Kurt Sittmann, professeur au Département de biologie. C'était un homme très brillant, et j'ai vraiment beaucoup aimé le cours. C'était très intéressant.

Il y avait aussi Peter Grant, qui a fini par se retrouver à Princeton, qui donnait un cours de biologie évolutionniste. Tout s'emboîtait parfaitement. On avait une adaptation évolutive, le poisson; la génétique des populations entrait donc forcément en ligne de compte. On avait ensuite une autre population de ce poisson dans le golfe du Mexique, composée d'espèces légèrement différentes probablement issues d'un croisement avec les espèces de la côte de l'Atlantique lorsque la péninsule de la Floride était submergée. Lorsque la Floride a émergé, je n'arrive pas à me souvenir de quelle période c'était, le Pléistocène tardif je crois, les populations se sont retrouvées isolées et les croisements n'ont plus été possibles.

J'avais donc accès à ça. Nous avons même attrapé des poissons dans un grand nombre de rivières importantes de la côte est de l'Amérique du Nord; j'en ai pêché moi-même parfois seul, parfois avec l'aide de pêcheurs. Ce fut une expérience extraordinaire.

Christopher Canning : C'était le sujet de votre doctorat?

Eric Shoubridge : Ça devait être le sujet de mon doctorat, mais je l'ai finalement utilisé pour ma maîtrise.

Christopher Canning : Je vois.

Eric Shoubridge : Je me suis ensuite rendu sur la côte ouest, et j'ai attrapé des poissons dans toutes les rivières. Ces poissons ne sont pas de la côte ouest à l'origine, mais à la fin du XIX^{e} siècle, le ministère des Pêcheries des États-Unis a décidé, dans sa grande sagesse, de prendre de jeunes poissons et de les disséminer partout sur le continent.

Il y avait beaucoup d'écloseries sur la côte est. Des gens stockaient les larves de poisson dans des fûts de 45 gallons et les transportaient par train un peu partout aux États-Unis. Dès qu'ils voyaient un cours d'eau, comme le Mississippi, ils déversaient une partie des poissons. C'est tout de même incroyable. De nos jours, les gens seraient catastrophés.

Ils sont finalement arrivés au fleuve Columbia, dans l'État de Washington sur la côte ouest, et ils y ont déversé de l'alose savoureuse et un autre poisson, le

bar rayé. Ces espèces n'étaient pas originaires de la côte ouest, mais elles s'y sont établies. Et qu'ont fait ces poissons? Ont-ils adopté le cycle biologique des poissons du Connecticut, du nord-est de la Nouvelle-Angleterre ou encore du Canada, ou ont-ils évolué comme les poissons de la Floride? Je trouvais qu'il s'agissait d'une belle histoire d'évolution.

Christopher Canning : Et vous vouliez savoir quel effet leur nouvel environnement avait eu sur leurs traits phénotypiques?

Eric Shoubridge : Exactement. Et j'espérais réussir à déterminer le fondement génétique des stratégies de cycle biologique. Nous utilisions les différences dans la mobilité électrophorétique des enzymes comme indicateurs de variation génétique parce que personne n'avait encore décodé de génome à cette époque. Évidemment, nous présumions que l'origine de cette variation était génétique.

Dès le début du projet, je me suis rapidement rendu compte que nous étions bien naïfs. Je crois toujours que c'était une idée formidable, mais je n'avais pas les outils pour faire le travail et mon superviseur, Bill Leggett, n'avait pas vraiment les connaissances nécessaires pour me guider. J'ai compris que j'avais besoin d'un complément de formation et que cette étude n'allait pas se transformer en doctorat pour moi.

C'est à ce moment-là que Peter Hochachka, zoologiste et spécialiste de la biochimie comparative qui s'intéressait à l'adaptation biochimique, est venu faire un exposé au Département. Je lui ai dit que je n'étais pas heureux là où j'étais et que je voulais faire autre chose. Il m'a demandé si je voulais travailler avec lui. Et c'est ce que j'ai fait en retournant à UBC pour entreprendre un nouveau doctorat.

Je me suis donné trois ans pour faire mon doctorat. Et j'ai réussi. Je l'ai fait en trois ans et j'ai travaillé sur un projet vraiment intéressant. J'ai étudié les poissons rouges. Ça semble plutôt banal, mais ces poissons sont remarquables d'un point de vue métabolique parce qu'ils peuvent vivre sans oxygène, à basse température, comme dans un étang gelé l'hiver. Et même sans oxygène, ils produisent du dioxyde de carbone. Le dioxyde de carbone est le produit naturel du métabolisme oxydatif chez les humains et tous les vertébrés.

Christopher Canning : Oui, bien sûr.

Eric Shoubridge : Leur capacité à produire du dioxyde de carbone sans oxygène était pour nous un mystère total.

Christopher Canning : Par un autre processus cellulaire?

Eric Shoubridge : En résumé, j'ai découvert que ces poissons produisaient de l'éthanol.

Christopher Canning : Je vois.

Eric Shoubridge : Ils sont en quelque sorte la levure du monde des vertébrés.

Christopher Canning : Intéressant.

Eric Shoubridge : C'était une belle histoire.

Christopher Canning : Effectivement.

Eric Shoubridge : J'ai beaucoup appris sur la biochimie et sur l'étude des voies métaboliques, et j'ai beaucoup travaillé avec des radiotraceurs pour établir la voie anaérobique de la production d'éthanol chez le poisson rouge. Le travail de radiotraçage m'a demandé environ un an. Et au terme de cette année, quelqu'un a publié un article indiquant qu'il était possible d'utiliser la résonance magnétique nucléaire pour étudier les voies métaboliques *in vivo*; il suffisait d'avoir la machine. Je me suis dit qu'il fallait que j'apprenne à faire ça. Avec cette technique, j'aurais pu faire le travail d'une année en une après-midi.

Christopher Canning : Je vois.

Eric Shoubridge : Ce que je ne savais pas à l'époque, parce qu'il n'en était évidemment pas question dans l'article, c'est que la résonance magnétique nucléaire est une technique qui présente une sensibilité très faible et qu'on peut faire cette expérience rapidement uniquement dans des circonstances spéciales, comme en plaçant un milliard de cellules bactériennes dans une éprouvette. J'avais encore cette belle naïveté lorsque je me suis rendu à Oxford pour faire un postdoctorat avec George Radda, qui était alors l'un des gourous de l'utilisation de la résonance magnétique nucléaire sur des organismes vivants. J'ai passé quatre ans là-bas, à faire mon postdoctorat. Et à la fin, je pense que je me suis rendu compte que cette technique avait un avenir très limité. Et un biologiste ne veut pas mettre tous ses œufs dans le même panier en se limitant à une technique. Dès que quelqu'un met au point une autre technique, vous êtes dépassé.

Christopher Canning : C'est logique.

Eric Shoubridge : À cette époque, Bill Feindel, directeur de l'Institut neurologique de Montréal et ancien boursier Rhodes, s'intéressait beaucoup à toutes les techniques qui pouvaient permettre de voir le cerveau; il m'a rendu visite à Oxford et m'a demandé si j'avais envie d'implanter la résonance magnétique nucléaire à l'Institut. Il m'a donc recruté pour que je revienne mettre en place la spectroscopie par résonance magnétique nucléaire à l'Institut neurologique de Montréal avec un neurologue dénommé Doug Arnold, qui faisait un stage de perfectionnement avec George Radda. C'est ce que j'ai fait.

Je suis revenu en 1985, et nous avons travaillé sur la résonance magnétique nucléaire pendant quelques années. Je possédais une machine à haut champ et j'avais développé des façons d'observer les cellules. Mais la sensibilité était trop faible, et j'en suis venu à la conclusion que je n'allais pas pouvoir observer des choses vraiment intéressantes d'un point de vue biologique, ni faire de découvertes fondamentales.

Christopher Canning : Est-ce que vous travailliez toujours avec des poissons ou d'autres organismes?

Eric Shoubridge : Non, pas du tout. À ce stade-là, nous travaillions avec des patients atteints d'une maladie neurologique, principalement des tumeurs cérébrales.

Christopher Canning : À quel moment dans votre parcours avez-vous décidé de commencer à travailler avec des humains?

Eric Shoubridge : Pendant que nous faisions de l'imagerie pour des patients, j'ai mis au point des systèmes cellulaires et j'ai cultivé des cellules humaines pour étudier les voies métaboliques en essayant d'utiliser la technique d'analyse de la régulation métabolique, comme pour les poissons. Mais j'ai dû reconnaître que j'étais dans un cul-de-sac. En fait, je m'en étais rendu compte avant mon retour au Canada.

Christopher Canning : Vous semblez avoir eu plus d'une fois cette impression de ne pas trop savoir où tout ça allait vous mener.

Eric Shoubridge : C'est vrai. Je devais revenir à un niveau plus fondamental. C'était en 1988, environ trois ans après mon retour. À cette époque, on travaillait à une technique appelée « réaction en chaîne de la polymérase », qui promettait de révolutionner la génétique.

Christopher Canning : De la biologie moléculaire?

Eric Shoubridge : De la génétique moléculaire. Désormais, on pouvait amplifier l'ADN.

Christopher Canning : Je vois.

Eric Shoubridge : Auparavant, il fallait savoir comment cloner l'ADN et je n'avais aucune formation dans ce domaine.

Christopher Canning : Je comprends.

Eric Shoubridge : Deux autres événements m'ont convaincu de changer de cap. Un de mes collègues, George Karpati, malheureusement décédé l'année dernière, avait plusieurs patients atteints de maladies métaboliques intéressantes qu'il croyait attribuables à un dysfonctionnement mitochondrial. La même année, quelqu'un en Angleterre a publié dans la revue *Nature* un article dans lequel il faisait état de mutations dans le génome mitochondrial de ces patients. Les mutations étaient associées à une maladie métabolique qui empêchait les patients d'utiliser l'énergie adéquatement, ce qui créait un phénotype neurologique très intéressant appelé « syndrome de Kearns-Sayre ». Chez ces patients, les muscles extraoculaires étaient paralysés et les paupières affaissées. Les patients avaient une intolérance à l'effort, et certains présentaient des troubles de la conduction cardiaque. George m'a dit que ces patients pourraient être intéressants pour mes travaux, et il m'a convaincu.

C'est à ce moment que j'ai réellement fait la transition vers la génétique humaine.

Christopher Canning : Ça semble avoir été une tendance générale dans le groupe. À partir de 1972, la plupart des membres du groupe ont travaillé en biochimie et sur les maladies métaboliques. Au milieu des années 1980, au cours de la révolution de la biologie moléculaire, les formations évoluaient rapidement…

Eric Shoubridge : Je n'ai pas vraiment suivi de formation en bonne et due forme. J'ai simplement suivi mon instinct. Ça avait l'air d'un problème biologique très intéressant, alors nous nous sommes formés sur le terrain. Nous avons appris à faire de la biologie moléculaire sur le tas.

Nous avons beaucoup appris d'un de mes collègues, Ken Hastings, qui travaille toujours dans un bureau près du mien à l'Institut neurologique de Montréal, et de beaucoup d'autres personnes, principalement dans le réseau de McGill.

Christopher Canning : Je comprends.

Eric Shoubridge : Pendant les années 1970, il était impossible d'acheter une enzyme de restriction. Tu devais appeler un gars qui pouvait en cloner une et la purifier dans son laboratoire. Aujourd'hui, les enzymes coûtent quelques dollars. À la fin des années 1980, la réaction en chaîne de la polymérase a changé la donne, et c'est à ce moment que nous avons fait notre entrée en génétique humaine. Ça semble très intéressant parce que c'était lié à ce que j'avais fait jusque-là. On parle de maladies métaboliques, de métabolisme, mais chez l'humain. Et il y a maintenant un fondement génétique.

J'ai commencé par travailler sur des maladies qui mettaient en cause l'ADN mitochondrial parce qu'à ce moment-là, c'était facile de travailler sur ça. Il s'agit d'un petit génome. Il ne compte que 16 500 paires de base, comparativement aux trois milliards de paires dans le génome nucléaire, et nous avions des patients atteints de maladies neurologiques qui présentaient des mutations dans ce génome.

Christopher Canning : Des mutations monogéniques?

Eric Shoubridge : Certaines de ces mutations ne concernaient qu'une seule paire de base.

Christopher Canning : Une seule paire, je comprends.

Eric Shoubridge : Il n'y a que 13 gènes codants pour des protéines dans l'ADN mitochondrial. Il y a 22 gènes de l'ARNt[4] et deux ARN ribosomiques, qui représentent une sorte de squelette pour la traduction de ces 13 protéines, qui se produit dans le compartiment mitochondrial lui-même. Ils font tous partie de la voie de la phosphorylation oxydative, qui nous permet d'utiliser l'oxygène pour produire de l'énergie.

Christopher Canning : D'accord.

Eric Shoubridge : Voilà les maladies que nous avons étudiées depuis ce moment-là. Comme je l'ai déjà dit, c'était facile de travailler sur l'ADN mitochondrial parce qu'il y en a des milliers de copies dans chaque cellule. Nous avons donc commencé par ça.

Christopher Canning : De qui parlez-vous lorsque vous dites « nous »? Vous et le laboratoire ou vous et vos collègues?

[4] Acide ribonucléique de transfert

Eric Shoubridge : De moi, de mon laboratoire. Nous avons commencé par ça, tout simplement. Heureusement, j'ai réussi à recruter quelques personnes très compétentes. J'ai été chanceux parce que personne ne voulait vraiment venir travailler avec moi comme biologiste moléculaire ou comme généticien parce que je n'avais aucune expérience dans le domaine à cette époque. Nous étions curieux, et ce n'était pas tellement compliqué. Ce n'est pas comme si vous décidiez de devenir astrophysicien demain matin. Dès la première page de votre manuel d'astrophysique 101, vous vous rendrez compte que vous devez savoir faire une transformation de Laplace, ou quelque chose du genre, et que vous n'avez pas les connaissances qu'il faut en mathématiques ne serait-ce que pour comprendre de quoi il s'agit.

Mais je crois qu'en biologie, tout le monde joue à armes égales. Si vous êtes un biologiste curieux, vous pouvez apprendre à faire pratiquement n'importe quoi.

Christopher Canning : Quel était le contexte au moment où vous avez commencé à vous intéresser à l'ADN mitochondrial? Quel était le contexte ailleurs dans le monde? Est-ce que ce domaine gagnait en popularité, ou faisiez-vous un peu bande à part sur ce type de travaux?

Eric Shoubridge : Le sujet commençait à être populaire parce que comme je l'ai dit, les premières mutations ont été découvertes en 1988. On savait depuis au moins une vingtaine d'années que certaines familles présentaient des phénotypes neurologiques qui semblaient transmis par la mère. Et on savait depuis 1980 que l'ADN mitochondrial était transmis par la mère chez les mammifères. On trouve dans la littérature médicale un exemple où ce n'est pas le cas, mais habituellement, les mitochondries et l'ADN mitochondrial sont transmis par la mère. Avec le recul, on peut se demander pourquoi personne n'a fait cette observation plus tôt, parce que même à cette époque, il s'agissait d'un génome relativement simple à analyser.

Ironiquement, les premiers cas de mutations de l'ADN mitochondrial signalés étaient sporadiques, mais les patients visés avaient des maladies des muscles squelettiques très particulières. Certaines sections des fibres musculaires renfermaient des tonnes de mitochondries. En raison de cette énorme quantité de mitochondries, les fibres avaient l'air d'avoir été mangées par des mites parce qu'une partie de l'appareil de contraction avait été remplacée par des mitochondries. Manifestement, quelque chose ne tournait pas rond.

Christopher Canning : Est-ce qu'il s'agissait d'une trop grande réplication du…

Eric Shoubridge : Oui, c'est ça. Personne ne comprend parfaitement le phénomène, mais on dirait que la cellule essaie de compenser la mutation du génome mitochondrial qui cause l'anomalie dans le métabolisme oxydatif, ce qui entraîne une intolérance à l'effort ou une fatigabilité accrue.

Et lorsqu'on observe ces mitochondries, on s'aperçoit qu'elles présentent beaucoup de mutations. Il se produit alors une sorte de boucle de rétroaction positive. Normalement, ce sont les signaux qui circulent constamment entre le noyau et les mitochondries qui déterminent la quantité de mitochondries dont le muscle a besoin pour accomplir le travail

demandé.

Si vous voulez courir le marathon, vous devez vous entraîner. Pendant l'entraînement, le nombre de mitochondries augmente parce que ce type d'effort dépend presque entièrement du métabolisme oxydatif. Les cellules de vos muscles doivent donc renfermer plus de mitochondries pour que vous puissiez fournir de tels efforts. Si vous êtes plutôt de type pantouflard, aucun signal n'est envoyé et la quantité de mitochondries diminue.

Christopher Canning : Ces signaux sont produits par l'ADN nucléaire.

Eric Shoubridge : Non. Ils proviennent du métabolisme cellulaire. Nous ne connaissons pas exactement la nature du signal, mais quelque chose dit à vos cellules musculaires qu'elles n'ont pas la capacité de faire ce que vous exigez d'elles, alors elles doivent se reconstruire. Si vous arrêtez de vous entraîner, les cellules musculaires doivent réduire leur capacité.

Nous croyons que les mutations dans l'ADN mitochondrial finissent par envoyer le même signal aux cellules. Les cellules se disent alors « Oups, nous ne suffisons pas à la tâche; nous devons produire des mitochondries ». Toutefois, les modèles (c'est-à-dire l'ADN mitochondrial) présentent des anomalies. Ils produisent donc des mitochondries anormales sans jamais régler le problème de la demande énergétique. Ce qui crée un cercle vicieux. Et on obtient une maladie caractérisée par une accumulation de mitochondries dysfonctionnelles.

Christopher Canning : Dans les muscles squelettiques?

Eric Shoubridge : Oui, dans les muscles squelettiques. Nous ne savons pas si la réaction est la même dans d'autres types de cellules, parce qu'ils ne font pas souvent l'objet de biopsies. C'est facile de biopsier des cellules de muscles squelettiques et de les mettre en culture. On peut donc les étudier en laboratoire. En fait, les cellules que nous mettons en culture sont appelées « cellules satellites ». Tous les muscles contiennent ces cellules quiescentes, qui se trouvent en périphérie des fibres musculaires. Lorsqu'un muscle se déchire – ce qui se produit fréquemment – il doit se réparer. À ce moment-là, une sorte de potion magique dont on ignore la nature exacte est libérée, ce qui réveille les cellules quiescentes. Ces cellules se divisent et agissent comme un pansement. De nouvelles cellules arrivent et réparent la déchirure pour rétablir la fonction du muscle. Les cellules souches retournent d'où elles viennent et restent en quiescence jusqu'à ce que le muscle soit de nouveau lésé.

Christopher Canning : Comment avez-vous développé un intérêt pour les sciences neurologiques? Comment avez-vous abouti dans un institut neurologique?

Eric Shoubridge : Par accident.

Christopher Canning : Vraiment?

Eric Shoubridge : Oui, réellement par accident.

Christopher Canning : Ce n'était donc pas une transition planifiée?

Eric Shoubridge : En fait, j'avais obtenu une subvention pour aller travailler au Département de biologie de l'Université d'Ottawa.

Christopher Canning : Immédiatement après votre postdoctorat?

Eric Shoubridge : Oui. Lorsque je me demandais où aller travailler, j'ai fait une demande de subvention de démarrage au CRSNG[5]. Je ne me rappelle plus le nom du programme, mais à l'époque, le gouvernement avait des programmes qui incitaient les universités à embaucher des jeunes. Le gouvernement voulait surtout attirer les femmes dans les facultés de sciences, mais les programmes s'adressaient à tous. Toutefois, il fallait avoir un superviseur dans un département.

À ce moment-là, j'avais encore l'intention de travailler en résonance magnétique moléculaire, mais j'avais l'impression que le département n'allait pas avoir les ressources nécessaires parce qu'il fallait acheter une machine, qui coûtait quelques centaines de milliers de dollars. Ça représentait beaucoup d'argent pour le Département de biologie, et je ne pensais pas que ça serait possible.

Au même moment, Bill Feindel, qui a également un bureau tout près d'ici, s'était rendu à Oxford parce que Doug Arnold, qui était neurologue à l'Institut de neurologie de Montréal et qui est également ici maintenant, était allé à ce laboratoire pour apprendre à utiliser la résonance magnétique moléculaire. Et il s'est dit que ce serait une bonne idée de nous embaucher tous les deux. Je lui ai dit que j'aimais la biologie et que je ne voulais pas travailler pour un médecin. Je ne voulais pas être un technicien participant aux recherches d'un médecin. Il m'a dit que ça ne se passerait pas comme ça et que je pourrais avoir mon propre laboratoire. Je lui ai répondu que je voulais bien essayer. C'est comme ça que je me suis retrouvé dans un institut neurologique.

Et si je n'étais pas arrivé ici, je n'aurais jamais travaillé sur des maladies. Jamais. C'est ça qui est incroyable ici. Le Dr Penfield, qui a fondé l'Institut neurologique de Montréal, s'est dit que si on regroupait des neurochirurgiens ou des neurologues et des biologistes, qui sont des gens curieux, les biologistes finiraient par travailler sur certains aspects des maladies. Il a donc réussi à créer un endroit où l'on pourrait amener des chercheurs fondamentaux à travailler sur des maladies neurologiques importantes simplement en les mettant en contact avec des cliniciens.

Christopher Canning : J'ai une question à ce sujet. Les relations étaient-elles bonnes entre les gens du laboratoire et les cliniciens? Je passerai bientôt à des questions sur le groupe, mais j'aimerais savoir si, d'après votre expérience à l'Institut neurologique, les relations étaient bonnes entre les scientifiques fondamentaux et les cliniciens.

Eric Shoubridge : Ici, c'est super. C'est simple, jamais je n'aurais travaillé sur des maladies si un clinicien qui traitait des patients de la clinique des maladies neuromusculaires ne m'avait pas donné envie de le faire. J'allais parfois parler aux patients moi-

[5] Conseil de recherches en sciences naturelles et en génie du Canada

même pour leur expliquer ce que nous avions découvert et ce que nous avions l'intention de faire.

En réalité, il n'existe encore aucun traitement pour la plupart de ces patients. Une grande partie de notre travail consistait à établir le bon diagnostic génétique, pour ainsi savoir à quoi nous avions affaire. On peut parfois arriver à atténuer les symptômes, et nous avons fait quelques essais cliniques. J'estime qu'il est très important que les patients sachent exactement ce qu'ils ont et quelle est la mutation génétique en cause, même si on ne peut pas faire grand-chose pour l'instant.

D'un point de vue clinique, nous voulions découvrir le fondement génétique de la maladie pour ensuite nous demander : « Pourquoi cette mutation génétique produit-elle cette maladie en particulier? Que fait le produit génétique? ». C'était une bonne façon de travailler.

Christopher Canning : Pouvez-vous me parler des modalités diagnostiques? J'aimerais savoir comment vous fonctionnez, comment les patients sont dirigés vers vous, quels sont les tests et les résultats de ces tests.

Eric Shoubridge : Tout a commencé parce que George Karpati, l'homme qui m'a donné envie de m'intéresser à ce domaine, voulait que je mette en place des tests diagnostiques. J'ai donc mis au point beaucoup de tests biochimiques; on ne faisait pas beaucoup de génétique à ce moment-là. Nous avons fait ça pendant quelques années, et je me suis rendu compte que bon nombre des tests biochimiques n'étaient pas vraiment utiles, du moins pour la population adulte. Ils l'étaient dans certains cas, surtout pour les troubles mitochondriaux; nous observions souvent une activité enzymatique à la limite inférieure de la normale, ce qui ne nous apprenait rien de plus que ce que nous révélaient la maladie, le phénotype clinique et, plus tard, la génétique. Nous avons donc cessé de faire ces tests.

À ce moment-là, le FRSQ[6] a lancé un programme de transfert de technologie en collaboration avec Hydro-Québec. L'idée consistait à créer des laboratoires d'experts chargés de transférer les résultats des laboratoires de recherche à l'environnement clinique. Par exemple, si demain nous découvrons une mutation dans un nouveau gène qui cause une maladie neurologique, nous pourrons offrir ce test à n'importe quel patient presque immédiatement.

Christopher Canning : Comment sauriez-vous que la mutation cause une certaine maladie si l'information provient du laboratoire?

Eric Shoubridge : Un médecin appellerait en nous disant : « J'ai un patient qui semble avoir une maladie mitochondriale. Pouvez-vous essayer de comprendre son fondement génétique? ». À cette époque, on parlait toujours d'ADN mitochondrial. Nous procédions au séquençage des gènes candidats et nous trouvions souvent la mutation en cause. Les cas non résolus devenaient des sujets de recherche.

Nous devions faire une demande de subvention au FRSQ chaque année pour avoir le privilège d'effectuer des tests diagnostiques. J'obtenais cette bourse

[6] Fonds de la recherche en santé du Québec, devenu le Fonds de recherche du Québec – Santé (FRQS)

chaque fois, et nous offrions le test gratuitement à toutes les personnes qui nous le demandaient. Le programme a duré cinq ans, et nous faisions chaque année des tests pour 200 à 250 patients d'un peu partout. Au bout de cinq ans, le FRSQ a conclu que le programme fonctionnait très bien, mais il a décidé d'y mettre un terme et d'essayer autre chose.

Je suis allé à l'hôpital et j'ai dit : « Voici ce que nous avons fait. Tout d'abord, nous avons fourni un service aux patients qui sont venus ici. Nous nous sommes forgé une réputation d'experts dans le domaine et avons donné de la visibilité à l'Institut. Et maintenant, le programme se termine et nous n'avons plus de financement. Ne croyez-vous pas qu'il serait judicieux de mettre sur pied un petit laboratoire? »

Nous avions une subvention de 42 200 dollars par année et nous réalisions des tests pour tout le monde gratuitement. Je trouve que c'était plutôt une bonne affaire. L'hôpital nous a répondu qu'il n'était pas intéressé, que ça ne faisait pas partie de sa mission.

Christopher Canning : Et ça s'est terminé comme ça? Wow.

Eric Shoubridge : Oui. Les responsables de l'hôpital ne se préoccupent que des budgets de l'hôpital et ils ne réfléchissent pas à l'établissement dans son ensemble et à ce qu'il représente pour Montréal, le Québec, le Canada et le reste du monde. Ces gens-là ne réfléchissent pas à ça. Ils regardent les livres et le résultat net. Mais il faut savoir que c'est le ministère de la Santé qui les force à faire ça.

Je suis donc allé voir les gens de l'Institut neurologique de Montréal, et ils m'ont dit : « Oui, nous pouvons le faire si nous le faisons selon un principe de recouvrement des coûts. ». C'est ce que nous faisons depuis ce temps-là. Nous perdons encore de l'argent, mais je crois que c'est important d'offrir le service. Et nous ne refusons personne. Certains hôpitaux, comme SickKids à Toronto, nous ont dit qu'ils ne pouvaient pas se le permettre. Je leur ai répondu : « Si vous trouvez quelqu'un disposé à faire les tests gratuitement, dites-le-moi et je vais lui confier tous nos tests demain matin ».

Christopher Canning : Ouais.

Eric Shoubridge : Parce que nos prix étaient extrêmement bas comparativement aux prix imposés par les laboratoires de diagnostic aux États-Unis. De cinq à dix fois moins élevés. Mais là, le gouvernement du Québec a changé les règles une fois de plus. Il a décrété que nous ne pouvions plus faire de la facturation entre hôpitaux. Nous n'avons même plus le droit de réaliser les tests parce que nous ne sommes pas un laboratoire de diagnostic clinique accrédité. Nous travaillons essentiellement dans un laboratoire de recherche et ça nous prend de nouvelles règles.

Je comprends que le gouvernement doit veiller à ce que la qualité soit contrôlée et à ce que les résultats proviennent d'un laboratoire digne de confiance. Je crois qu'il est possible de faire des tests fiables dans un laboratoire de recherche, mais ça ne passera pas au conseil, comme on dit. Donc, si nous voulons continuer, nous devons établir un laboratoire de diagnostic moléculaire.

Christopher Canning : Les tests s'appliquent-ils uniquement aux maladies à apparition tardive?

Eric Shoubridge : Non, ils s'appliquent à une foule de maladies.

Christopher Canning : O. K.

Eric Shoubridge : Il y a vraiment des tests pour toutes sortes de maladies. Après la mise au jour des premières mutations de l'ADN mitochondrial, on a continué de découvrir des mutations à un rythme rapide pendant une dizaine d'années. Ces mutations étaient associées à une énorme variété de phénotypes cliniques qui apparaissaient à divers moments de la vie, que ce soit peu après la naissance ou à un âge avancé. L'autre aspect des maladies mitochondriales, soit celui des gènes nucléaires, n'était toujours pas beaucoup étudié. Dans les mitochondries, il y a probablement de 1 000 à 1 500 protéines qui sont encodées dans le génome nucléaire, alors qu'il y en a 13 qui sont encodées dans l'ADN mitochondrial. Personne ne savait vraiment quel rôle elles jouaient dans les maladies mitochondriales. Je me suis dit qu'il était peut-être temps de s'y intéresser, mais encore fallait-il déterminer comment s'y prendre.

En Amérique du Nord, le pedigree type est le suivant : un père et une mère sains et un enfant décédé très jeune qui avait parfois une sœur ou un frère sain. Habituellement, la naissance se déroule normalement, puis l'enfant meurt au cours des premières semaines, des premiers mois ou des premières années de sa vie, parfois à cause d'une maladie du cerveau, d'une maladie cardiaque ou d'une maladie hépatique. On se demande alors comment faire pour trouver ce qui ne va pas.

Christopher Canning : Je vois.

Eric Shoubridge : À l'époque, on parlait beaucoup de liaison génétique, mais comme nous n'avions pas de grosses familles, nous n'avons pas pu suivre ce filon. J'ai compris qu'il fallait passer par la complémentation fonctionnelle. Les anomalies biochimiques étaient principalement transmises comme des traits récessifs. Nous nous sommes donc dit que si nous pouvions obtenir une copie saine du gène, d'une bibliothèque d'ADNc[7] par exemple, nous pourrions corriger le défaut dans la lignée cellulaire du patient.

Une telle stratégie génétique impartiale semblait nécessaire parce qu'il y avait trop de gènes candidats, dont beaucoup n'étaient pas du tout caractérisés.

Christopher Canning : Vous ne savez pas ce que l'ADN produit? Les protéines qui forment les gènes?

Eric Shoubridge : C'est exact. Nous ne savions pas quels gènes étaient nécessaires et suffisants pour produire une chaîne respiratoire fonctionnelle. Nous en connaissions un grand nombre, mais pas tous. Je me suis demandé quel matériel génétique nous allions utiliser. Nous avons d'abord essayé les bibliothèques d'ADNc, mais les difficultés techniques étaient trop grandes. J'ai ensuite pensé à utiliser un chromosome sain de la lignée cellulaire d'un donneur anonyme pour, au moins, cartographier l'anomalie génétique.

[7] ADN complémentaire

Christopher Canning : Le chromosome en entier?

Eric Shoubridge : Oui, le chromosome en entier. On pouvait déterminer si la copie saine du gène dans ce chromosome pourrait réparer le phénotype. Vous me suivez?

Christopher Canning : Oui.

Eric Shoubridge : Et si on ajoutait tous les chromosomes un à la fois, on pouvait déterminer quel chromosome était porteur du gène défectueux. Il existe une technique appelée « transfert de chromosomes à médiation microcellulaire », élaborée par des gens qui s'intéressaient principalement au cancer et à la cartographie des gènes suppresseurs de tumeur. Dans le monde, un ou deux groupes avaient créé une banque de lignées cellulaires de souris stables, porteuses de chromosomes humains individuels.

Nous les avons marquées à l'aide d'un marqueur de sélection, qui leur a conféré une pharmacorésistance. Après le transfert des chromosomes, les cellules du patient devaient conserver le chromosome humain afin de rester pharmacorésistantes. Nous pouvions alors nous demander si l'anomalie avait été réparée dans les cellules qui avaient reçu une copie supplémentaire d'un chromosome humain sain. C'est ça la complémentation fonctionnelle : on ajoute un complément à l'anomalie fonctionnelle dans la lignée cellulaire.

C'est à ce moment que j'ai commencé à travailler avec le groupe. Il faisait alors une nouvelle demande de subvention au CRM.

Christopher Canning : Nous sommes donc en 2000 et 2001.

Eric Shoubridge : C'est bien ça. J'ai soumis mon projet, mais on m'a dit que je ne pouvais pas le faire.

Christopher Canning : Vous avez d'abord fait une demande en 1994.

Eric Shoubridge : C'est exact.

Christopher Canning : Et vous n'avez pas été admis dans le groupe à ce moment-là.

Eric Shoubridge : C'est bien ça.

Christopher Canning : Je vois.

Eric Shoubridge : On m'a dit que mon projet n'était pas réalisable.

Christopher Canning : C'est le CRM qui vous a dit ça?

Eric Shoubridge : Oui.

Christopher Canning : Mais vous aviez pourtant l'appui du groupe.

Eric Shoubridge : Absolument. Le groupe m'appuyait. Les membres me trouvaient peut-être naïf et je ne sais pas si quelqu'un croyait que ça allait fonctionner. Toujours est-il

qu'ils trouvaient que c'était une bonne idée que je me joigne au groupe. Sinon, j'imagine qu'ils ne m'auraient pas invité.

Christopher Canning : Pouvez-vous être plus précis? Comment en êtes-vous venu à travailler avec le groupe? Comment les membres du groupe savaient-ils ce que vous faisiez? Comment les avez-vous connus? Comment les choses se sont-elles déroulées?

Eric Shoubridge : Tout le monde connaît Charles Scriver. Je le croisais de temps en temps et nous parlions de ce que je faisais. Nous nous intéressions tous les deux à la génétique biochimique. C'est ce sujet qui est à la base de la fondation du groupe. Et Peter Hechtman était encore là.

Christopher Canning : Et David Rosenblatt?

Eric Shoubridge : David Rosenblatt. Je connaissais David et ses recherches sur le métabolisme des vitamines, qui sont également de la génétique biochimique. J'étais en quelque sorte le nouveau venu qui travaillait dans un autre hôpital pas très loin et qui a commencé à s'intéresser aux maladies métaboliques chez l'humain à cause d'événements qui se sont produits en 1988 et 1989. C'est donc par un heureux hasard que je me suis retrouvé dans le groupe.

Christopher Canning : Je vois.

Eric Shoubridge : On m'a invité à me joindre au groupe parce que personne ne faisait ce que je faisais, et que mes travaux correspondaient parfaitement au thème général adopté par le groupe. Nous avons commencé par travailler sur des maladies qui touchent les adultes parce que j'étais ici, à l'Institut neurologique de Montréal, un hôpital pour adultes. Nous étions donc en contact avec des patients adultes aux prises, généralement, avec des problèmes liés à l'ADN mitochondrial.

Les problèmes qui touchent un gène nucléaire sont habituellement des maladies très graves chez les nourrissons. Vous ne connaissez probablement pas ça à propos de la génétique de l'ADN mitochondrial, mais je vous en ai touché un mot tout à l'heure.

Christopher Canning : Je ne connais pas grand-chose sur le sujet.

Eric Shoubridge : Il y a un millier de copies du génome dans la plupart des cellules, mais le nombre de mauvaises copies touchées par la mutation peut varier d'une cellule à l'autre.

Christopher Canning : Je vois.

Eric Shoubridge : Ce n'est pas du tout typique des gènes nucléaires. Dans une maladie récessive, vous recevez une mauvaise copie de votre mère et une mauvaise copie de votre père. Chaque cellule a donc deux mauvaises copies.

Christopher Canning : Je comprends.

Eric Shoubridge : Mais avec l'ADN mitochondrial, comme il y a des milliers de copies, certaines

cellules ne possèdent pas de mauvaises copies, certaines en ont quelques-unes et d'autres en ont beaucoup.

Christopher Canning : Pourquoi?

Eric Shoubridge : Nous ne savons pas vraiment pourquoi des génomes de type sauvage et des génomes mutants se séparent différemment dans différents types de cellules. Les règles semblent très complexes parce qu'elles varient en fonction de la mutation. Il y a d'énormes différences entre les mutations. C'est probablement pourquoi les adultes qui présentent des mutations de l'ADN mitochondrial survivent, parce qu'il y a une sélection qui peut se faire en faveur ou au détriment des mauvaises copies dans différents tissus. On voit donc des personnes qui produisent suffisamment d'ATP[8], suffisamment d'énergie pour survivre. Leurs symptômes représentent l'accumulation de génomes mutants dans certains tissus, du moins en partie.

Toutefois, bon nombre d'enfants ne survivent pas parce qu'ils ont deux mauvaises copies d'un gène nucléaire. Ils ont donc une maladie grave dès le départ.

Christopher Canning : Je comprends.

Eric Shoubridge : Habituellement, tout est normal à la naissance. Nous croyons que le métabolisme oxydatif n'est pas très important *in utero*. Il s'agit principalement d'un métabolisme glycolytique, possiblement parce que l'environnement est relativement pauvre en oxygène. Mais les problèmes apparaissent lorsque l'enfant est en contact avec l'oxygène moléculaire après la naissance.

Christopher Canning : C'est intéressant.

Eric Shoubridge : Au départ, j'ai voulu travailler avec le groupe pour étudier ces graves anomalies biochimiques chez l'enfant, mais le CRM a rejeté ma proposition.

Christopher Canning : Savez-vous pourquoi? Connaissez-vous la raison du CRM?

Eric Shoubridge : Oui. Ils ont simplement dit que ça ne fonctionnerait pas. J'ai ensuite envoyé la même proposition à la Marche des dix sous, la fondation qui a financé la recherche contre la polio. Après l'éradication de la polio, j'imagine que la fondation a cherché une autre cause. Et elle s'est dit qu'il existait beaucoup d'autres anomalies congénitales et qu'elle pourrait soutenir la recherche sur les anomalies congénitales en général. Elle a accepté de financer le projet. Nous l'avons réalisé et nous avons publié un article dans *Nature Genetics*, qui n'est rien de moins que la meilleure revue de génétique en ville.

Christopher Canning : Ça se passe donc quelques années après votre demande de 1994?

Eric Shoubridge : Oui. Notre article a été publié en 1998. Nous avons prouvé que ça pouvait se faire.

Christopher Canning : C'est quand même incroyable.

[8] Adénosine triphosphate

Eric Shoubridge : Oui, c'était incroyable. Nous avons donc obtenu notre financement.

Christopher Canning : Vous n'avez pas réussi en 1994, et vous n'avez pas participé à la demande de subvention du groupe en 1998.

Eric Shoubridge : C'est ça.

Christopher Canning : Est-ce que c'est parce que vous étiez encore en train de faire des recherches indépendantes avec la Marche des dix sous?

Eric Shoubridge : C'est exact.

Christopher Canning : Ces recherches étaient liées au syndrome de Leigh?

Eric Shoubridge : Au syndrome de Leigh, exactement.

Christopher Canning : D'accord.

Eric Shoubridge : Exactement.

Christopher Canning : Il s'agit donc de votre grande percée.

Eric Shoubridge : Oui, parce que nous avons montré que nous pouvions décoder une anomalie génétique comme ça. Et nous avons réussi parce que la théorie était correcte. Mais je dois avouer que je me demandais si des parties des chromosomes avaient été réduites au silence après des années passées dans des cellules de souris et si elles risquaient de ne pas s'exprimer une fois replacées dans une cellule humaine. Mais ça n'a pas été le cas.

Christopher Canning : Ce qui aurait indiqué qu'il s'agissait d'une modification épigénétique?

Eric Schoubridge : Exactement, mais ce n'était apparemment pas le cas, même si cela pourrait être possible dans certains troubles. Notre technique a fonctionné et elle nous a permis de circonscrire l'anomalie génétique dans une petite région du chromosome donneur.

Christopher Canning : Que fait cette cellule mutante avec le troisième chromosome?

Eric Shoubridge : Je ne connais pas vraiment la réponse à cette question. Plusieurs choses étranges se produisent. Parfois, des fragments de chromosomes se perdent ou s'accrochent à un autre chromosome. Parfois, le troisième chromosome reste là, apparemment tout entier. Et je ne sais pas comment il rejoint les deux autres chromosomes, puis se sépare. Toutefois, j'ai remarqué que ces comportements se produisaient très tôt dans l'expérience et qu'ensuite une certaine stabilité s'installait. Les cellules réagissent en fonction de ce qui se produit.

Christopher Canning : Fascinant.

Eric Shoubridge : Oui, c'est étonnant. Pour cette expérience, nous nous sommes procuré les deux lignées cellulaires de patients atteints du syndrome de Leigh auprès de

Garry Brown, un de mes collaborateurs à Oxford qui a obtenu toute une collection de Denise Leigh, la neurologue qui a décrit la maladie dans les années 1950, en Angleterre. Les deux patients avaient succombé à la maladie, qui est associée à une déficience en cytochrome oxydase. J'ai dit à Garry que s'il me donnait ces deux lignées cellulaires, mon laboratoire allait pouvoir déterminer le fondement génétique de la maladie parce que nous avions une idée de la marche à suivre.

Christopher Canning : Je vois.

Eric Shoubridge : Il m'a donc donné les lignées cellulaires et nous avons déterminé que l'anomalie touchait le chromosome 9. Nous avons ensuite effectué plusieurs transferts indépendants du chromosome 9, et nous avons découvert un clone sur lequel un tout petit morceau de l'extrémité du bras long du chromosome 9 s'était intégré à une autre partie du génome. Tout le reste du chromosome 9 avait disparu.

Et sur ce fragment de chromosome 9, il y avait un gène qui a un homologue dans la levure; ce gène-là avait été partiellement caractérisé et avait produit un phénotype mitochondrial. Nous avons alors su que l'affaire était dans le sac.

Nous avons donc fait le séquençage du gène (SURF1), et toutes les mutations découvertes étaient des mutations non-sens, qui introduisaient des codons stop ou des mutations du site d'épissage, qui laissaient présager que nous n'allions pas retrouver la protéine chez les patients. Nous avons ensuite mis au point un anticorps anti-protéine. Les transferts n'ont ensuite révélé aucune trace détectable de protéine. Bref, le gène était invalidé chez tous les patients.

Christopher Canning : Le gène ne produisait tout simplement pas de protéines.

Eric Shoubridge : C'est ça. À cause des mutations. Les mutations avaient toutes pour effet soit de stopper prématurément la transcription en protéine, ce qui provoquait une instabilité, soit d'introduire une mutation du site d'épissage, ce qui provoquait une anomalie de l'épissage et donnait lieu à la fin prématurée de la transcription.

C'est ce qui nous a fait revenir dans le groupe.

Christopher Canning : En 2001, est-ce que vous avez décidé de refaire une demande pour vous joindre au groupe, ou bien est-ce que le groupe vous a demandé de revenir parce que vous aviez fait une belle découverte? Vous rappelez-vous la conversation?

Eric Shoubridge : Non. [rires] Je ne m'en souviens pas. Le groupe voulait faire une nouvelle demande de subvention, et j'imagine que David Rosenblatt m'a appelé et m'a demandé si j'avais le goût de revenir dans le groupe. Je pense que Peter Hechtman avait quitté le groupe à cette époque, mais je ne suis pas certain.

Christopher Canning : En 2001, Rima Rozen était la directrice, et les noms de Roy Gravel, d'Andy Karaplis, de Mark Trifiro, de Susie Tenenhouse et de Robert MacKenzie étaient sur la demande de subvention. Je crois que

David Rosenblatt avait quitté le groupe temporairement parce qu'il n'avait pas obtenu de subvention. Il en a obtenu une six mois plus tard et est revenu dans le groupe.

Eric Shoubridge : Je crois que c'est Rima qui m'a demandé de me joindre au groupe. Nous avions l'habitude de nous croiser à des événements de génétique humaine. Le groupe était sur le point de présenter une nouvelle demande et mon retour tombait bien, j'imagine. Mais honnêtement, je ne me rappelle plus les détails.

Christopher Canning : Je vois. Vous souvenez-vous du processus de demande à ce moment-là? Deviez-vous présenter votre propre demande?

Eric Shoubridge : Oui.

Christopher Canning : Et vous faisiez ensuite une demande tous ensemble? Vous rappelez-vous être passé par ce processus?

Eric Shoubridge : Oui. À ce moment-là, la première fois où ma demande n'a pas été acceptée, nous avons fait une demande de groupe. Et je crois que nous avons obtenu une subvention de groupe.

Ensuite, ils sont venus visiter nos installations. La deuxième fois, lorsque notre demande a été acceptée, je ne crois pas qu'il y ait eu une inspection de nos installations. Nous avions tous obtenu des subventions individuelles, puis nous avons eu une subvention de groupe. Nous devions tous réussir individuellement pour faire partie du groupe. Mais le groupe a présenté une demande en parlant des raisons pour lesquelles c'était utile de travailler en groupe.

Christopher Canning : Je vois.

Eric Shoubridge : Mais qu'est-ce qui unissait les membres du groupe? Pourquoi…

Christopher Canning : C'est exactement de ça que j'aimerais parler.

Eric Shoubridge : Quel était le ciment du groupe?

Christopher Canning : En effet. À votre avis, quel était le ciment du groupe?

Eric Shoubridge : Je dirais que l'esprit d'équipe avant la demande de subvention était meilleur qu'après parce qu'il y avait certains membres du groupe que nous ne voyions que rarement, comme ceux qui travaillaient au Lady Davis. David [Rosenblatt] était la personne que je côtoyais le plus. Il travaillait sur les carences en vitamine B_{12}, dont il est un expert de renommée mondiale, et avec des technologies semblables à celles que nous utilisions pour décoder les anomalies génétiques, qui sont également des maladies récessives autosomiques avec un phénotype cellulaire.

Nous avons donc transféré cette technologie à son laboratoire. Le premier étudiant n'a pas obtenu de très bons résultats parce qu'il n'arrivait pas à faire fonctionner la technologie avec les cellules, pour une raison que j'ignore. Le laboratoire a fini par y arriver et a pu décoder une des anomalies génétiques.

Finalement, les concurrents/collaborateurs ont également découvert le gène, grâce à une autre méthode, et tout correspondait.

Nous faisions des réunions régulièrement, et c'était intéressant de savoir sur quoi les autres travaillaient. Mais ce n'était pas vraiment du travail d'équipe parce que nous avions tous nos projets individuels. Nous n'avions pas tous le même objectif. La dynamique du groupe variait donc beaucoup. Les personnes qui travaillaient dans des domaines connexes avaient évidemment tendance à former un sous-groupe. C'était notamment le cas de Bob MacKenzie, qui travaillait sur le métabolisme du folate et le métabolisme monocarboné, qui formait un sous-groupe avec David [Rosenblatt] et Rima [Rozen].

Pour ma part, je travaillais sur des maladies métaboliques à l'aide de technologies que David pouvait utiliser. Nous avions mis au point certains vecteurs utiles pour l'expression des ADNc et des rétrovirus dans les cellules humaines primaires et nous partagions les techniques. Mais du point de vue de la biologie fondamentale, les travaux ne se recoupaient pas beaucoup.

Christopher Canning : Comment pouviez-vous dire qu'il s'agissait d'un groupe alors?

Eric Shoubridge : C'est une excellente question. [rires] Je crois que ce groupe était en partie fonctionnel et en partie dysfonctionnel.

Christopher Canning : Vous piquez ma curiosité. Pouvez-vous me parler de ces deux aspects?

Eric Shoubridge : D'accord. Je crois que le lien entre David et moi était évident parce que nous nous intéressions tous les deux à des maladies métaboliques et que nous partagions des réactifs. C'était complètement différent pour ceux qui faisaient de la biochimie, même si certains de nos étudiants avaient des choses en commun. Il y avait des liens, mais très minces. Pour Rima, David et Robert MacKenzie, qui s'intéressaient tous au métabolisme du folate, le lien était évident. Mais pour les deux autres personnes…

Christopher Canning : Mark Trifiro et Susie Tennenhouse.

Eric Shoubridge : Susie était sur le point de partir. Elle faisait partie du groupe, mais la retraite était proche.

Christopher Canning : Je vois.

Eric Shoubridge : Comme elle travaillait sur le métabolisme du phosphate…

Christopher Canning : D'accord.

Eric Shoubridge : Elle avait plus de choses en commun avec Andy Karaplis, qui s'intéressait aux os, qu'avec Mark [Trifiro]. Ils faisaient un peu bande à part. De ce point de vue, nous n'étions pas vraiment un groupe. Nous travaillions tous sur différents aspects de problèmes métaboliques. C'était intéressant de savoir ce que faisaient les autres, mais très honnêtement, je ne crois pas que nous ayons déjà fait des choses qui ont fait avancer nos recherches en tant que groupe.

Christopher Canning : C'est intéressant.

Eric Shoubridge : Non, vraiment, je ne crois pas que ce soit arrivé.

Christopher Canning : Quel rôle le Dr Scriver jouait-il à cette époque? Il était à la retraite, mais…

Eric Shoubridge : Aucun.

Christopher Canning : On sait que les Drs Scriver et Fraser, les fondateurs du groupe, ont eu une énorme influence. Est-ce que le Dr Scriver avait encore son mot à dire sur les actions du groupe?

Eric Shoubridge : Non, pas que je sache.

Christopher Canning : Le flambeau a donc été directement transmis à Rima Rozen?

Eric Shoubridge : Oui.

Christopher Canning : Qui a fait son postdoctorat avec le Dr Scriver, de toute façon.

Eric Shoubridge : C'est exact.

Christopher Canning : Bien.

Eric Shoubridge : Tout comme David, si je ne me trompe pas.

Christopher Canning : Je crois que oui.

Eric Shoubridge : David Rosenblatt, il a travaillé avec…

Christopher Canning : Il est revenu travailler avec lui après son postdoctorat.

Eric Shoubridge : Il n'a peut-être pas présenté de projet, mais il a travaillé avec le groupe.

Christopher Canning : Je vois.

Eric Shoubridge : Je ne me rappelle plus le statut qu'il avait. Il avait peut-être une bourse de recherche.

Christopher Canning : Une bourse de recherche juste avant son postdoctorat, mais il est allé aux États-Unis et il a été recruté de nouveau en 1975.

Eric Shoubridge : D'accord. C'était avant mon arrivée.

Christopher Canning : Exact.

Eric Shoubridge : Je suis arrivé en 1985, et j'ai commencé à travailler avec les membres du groupe sur le tard.

Christopher Canning : Connaissez-vous bien le Dr Scriver?

Eric Shoubridge : Oui, je le connais bien.

Christopher Canning : O. K.

Eric Shoubridge : Nous nous croisions souvent. Et il a maintenant des livres de publiés.

Christopher Canning : Oui, je les ai vus en ligne.

Eric Shoubridge : Je travaille avec Grant Mitchell, généticien à Sainte-Justine, à la rédaction d'une section sur les maladies mitochondriales pour le livre de Charles. Il m'a souvent demandé de rédiger un chapitre, et… disons simplement que je ne l'ai jamais fait. [rires] Quelqu'un d'autre s'en est chargé. Il voulait que j'écrive un chapitre différent, mais il voulait aussi conserver celui de l'autre personne. Je trouvais que ça n'avait pas vraiment de sens. Il m'a dit que j'avais un point de vue complètement différent sur le sujet, ce qui est vrai, mais je lui ai répondu que je n'aimais pas la structure du livre et que je ne croyais pas que ça fonctionnerait.

Puis, l'année dernière, j'ai reçu un appel de Grant qui me disait que le livre allait être remanié, et que la nouvelle version serait publiée en format numérique et non papier. Je trouvais que c'était une très bonne idée. Ça prendrait trop de temps de publier une version papier. Tout bouge si vite dans le domaine des sciences. Ce livre sera un excellent ouvrage de référence parce qu'il renferme beaucoup de données historiques. J'ai déjà eu un excellent ouvrage sur la génétique des cellules somatiques, que j'ai lu il y a bien longtemps. Je crois que c'est ce livre qui m'a donné l'idée de mes travaux sur les chromosomes. Quelqu'un me l'a « emprunté » et ne me l'a jamais rendu.

Mais ce livre parlait des débuts de la discipline et des personnes qui y ont participé. Je trouvais ça fascinant d'apprendre des choses sur les personnes qui ont mis au point les différents milieux de culture que j'utilisais dans le laboratoire, comme le milieu de Dulbecco. Il y a de vraies personnes derrière ces produits. On remonte dans le temps pour découvrir tout ce qu'elles ont dû faire pour surmonter les problèmes pendant la création des produits que nous tenons pour acquis aujourd'hui.

Les livres d'histoire sont vraiment intéressants. Ils font de bons ouvrages de référence. Les articles ne nous donnent pas ce genre de faits historiques. Il suffit d'imprimer le PDF si ça nous intéresse. Mais le généticien qui veut en savoir plus sur le phénotype d'un de ces patients consultera les sources en ligne pour connaître les toutes dernières découvertes sur la maladie. C'est donc beaucoup plus logique, à mon avis.

Et je pense que les gens accepteront plus facilement d'écrire cet ouvrage s'ils savent qu'ils peuvent mettre l'information à jour facilement. Nous avons donc divisé le travail en parties facilement gérables. Par exemple, une personne pourrait rédiger un chapitre sur une anomalie biochimique, puis un autre sur d'autres troubles reliés aux mêmes problèmes, soit des problèmes mitochondriaux. Mais elle n'aura pas à produire une centaine de pages qui renvoient à une tonne de références. Ce n'est donc pas une grosse tâche qui n'a pas d'allure. C'est logique que ce soit les personnes qui ont le plus d'expérience dans un domaine, les experts, qui rédigent leur partie et qui la gardent à jour. C'est comme ça que l'ouvrage évoluera.

Christopher Canning : Revenons au groupe. Avez-vous déjà publié des articles avec d'autres membres? Avez-vous travaillé en collaboration avec…

Eric Shoubridge : David et moi avons publié deux articles ensemble. Roy [Gravel] était encore membre du groupe, mais je n'ai rien publié avec lui. Je crois que je n'ai publié qu'avec David.

Christopher Canning : Je vois. Comment c'était de faire partie du groupe alors que vous n'étiez pas médecin? Est-ce que ça posait problème?

Eric Shoubridge : Pas du tout.

Christopher Canning : Comme la plupart d'entre eux… mais pas tous.

Eric Shoubridge : Non, Roy n'est pas médecin. Rima non plus. Bob, lui, était médecin.

Christopher Canning : Les personnes qui sont arrivées plus tard n'étaient pas médecins, alors qu'au début…

Eric Shoubridge : Au début, ils étaient tous médecins.

Christopher Canning : Exact.

Eric Shoubridge : Ils étaient médecins, et certains possédaient aussi un doctorat.

Christopher Canning : Intéressant.

Eric Shoubridge : En fait, Mark est médecin, bien entendu, et David l'est aussi, mais Bob MacKenzie ne l'est pas, Rima et Susie Tenenhouse non plus, et je ne le suis pas.

Christopher Canning : Vous étiez tous biochimistes ou biologistes moléculaires de formation.

Eric Shoubridge : Oui, nous nous sommes formés nous-mêmes.

Christopher Canning : Vous vous êtes formés vous-mêmes?

Eric Shoubridge : Oui.

Christopher Canning : Ça m'intéresse. Vous avez effleuré le sujet, mais pourriez-vous me dire comment vous avez vécu le fait d'arriver dans le domaine de la santé sans avoir reçu de formation en santé? Vous voyez ce que je veux dire? Dans le contexte du groupe, comment le point de vue scientifique a-t-il contribué à la compréhension des problèmes de santé?

Eric Shoubridge : Pour être franc, je ne pense pas avoir déjà envisagé le sujet de ce point de vue. J'ai toujours pensé qu'il s'agissait d'un problème biologique fascinant, et il se trouvait que je travaillais avec les maladies génétiques.

C'était tout aussi intéressant que de découvrir que sans oxygène, les poissons produisent de l'éthanol. Nous avons découvert un gène que personne ne connaissait et dont personne ne se doutait qu'il pouvait causer des troubles

neurologiques en cas de dérèglement. Je trouve que c'est fascinant. Et le gène que nous avons découvert s'appelle SURF1. Et que fait SURF1?

Christopher Canning : J'ai déjà entendu parler de ça.

Eric Shoubridge : Il fait partie d'un locus, le locus Surfeit, qui a été découvert par un chercheur en Angleterre, au début des années 1980, je crois. Il lui a donné ce nom [qui signifie « excès »] parce qu'il y avait cinq gènes dans un tout petit morceau d'ADN. À cette époque, il s'agissait de l'ensemble de gènes le plus dense jamais découvert. Il s'est dit « il y a un excès de gènes dans ce locus, donnons à ces gènes le nom de "Surf" ».

On retrouvait la même chose chez les oiseaux, et des oiseaux, il y en a partout.

Personne ne savait vraiment quelle était la fonction de ces gènes à ce moment-là. Et à notre connaissance, ils n'avaient rien à voir les uns avec les autres. Mais ils se retrouvaient dans une petite grappe, ce qui est encore un peu mystérieux pour nous. Nous ne savons toujours pas quelle est la fonction exacte du gène SURF1. Il a probablement une fonction accessoire et permet à l'enzyme d'ajouter un groupe hème à son noyau catalytique.

C'est un genre de petit accessoire, quelque chose qui augmente l'efficacité de l'ajout d'un hème et permet au corps de créer une enzyme très efficacement. Si vous n'en avez pas, vous pourrez produire une enzyme malgré tout et fonctionner, jusqu'à ce que votre corps soit soumis à un stress, comme une infection.

Donc, nous avons trouvé le nouveau gène et, maintenant, tout le monde peut le dépister et établir un diagnostic, ce qui est génial. C'est de la génétique médicale. Par conséquent, si vous voulez obtenir un diagnostic préimplantatoire direct ou effectuer une amniocentèse classique pour déterminer si un fœtus est porteur de l'anomalie ou pour implanter uniquement les embryons qui possèdent au moins une copie saine du gène, vous pouvez le faire. Ce dépistage ouvre la porte à une foule d'options pour la procréation. Vous pourriez aussi diagnostiquer l'anomalie chez un enfant et confirmer qu'il est bien porteur de la maladie à cause de la présence d'une mutation en particulier. Je trouve que c'est un véritable atout. Comme un complément. Mais ce qui mène tout ça, c'est ma curiosité naturelle…

Christopher Canning : Votre curiosité de scientifique?

Eric Shoubridge : En tant que scientifique, je veux savoir quel est le fondement génétique d'une mutation, pourquoi elle cause une maladie en particulier et comment tout ça fonctionne au niveau moléculaire.

Christopher Canning : Diriez-vous que vous êtes un généticien médical?

Eric Shoubridge : Non.

Christopher Canning : Mais vous faites de la génétique médicale?

Eric Shoubridge : C'est exact.

Christopher Canning : C'est intéressant.

Eric Shoubridge : Oui, mais je ne dirais pas que ce n'est pas mon… Si quelqu'un me demandait ce que je fais, je dirais que je suis biologiste, que je m'intéresse à la biologie et aux organismes vivants. Et il se trouve que je travaille en génétique, après tous les hauts et les bas que j'ai connus, comme lorsque je me suis rendu compte que mes recherches ne menaient à rien. Ce fut le cas pour la résonance magnétique moléculaire, où j'étais limité par une technique.

Les chimistes font ce genre de choses. Il y a des cristallographes et des gens qui font des choses très pointues en spectroscopie. Les techniques sont parfois très avancées, et ces personnes aiment ça. J'ai souvent entendu « Pourriez-vous faire de la résonance magnétique moléculaire sur ma protéine préférée » parce que les gens veulent comprendre la structure. Mais en tant que biologiste, ça ne me mène nulle part. Je ne dis pas que la structure n'est pas importante, elle est essentielle, mais ce n'est qu'une pièce du puzzle.

J'aime travailler avec des organismes vivants, et je trouve que la génétique est devenue un outil puissant qui nous permet de découvrir les anomalies et de les manipuler, et de créer des mutations. Nous pouvons faire toutes sortes d'expériences pour connaître la nature et le fonctionnement d'un gène et découvrir pourquoi les mutations l'empêchent de fonctionner et quelle partie d'un système biochimique est en cause. Ultimement, nous voulons trouver une façon de le réparer.

Christopher Canning : Je vois.

Eric Shoubridge : Toutefois, certaines maladies sont si graves, surtout chez les enfants, que certains patients décèdent d'une maladie dégénérative du cerveau. Mais même si on arrive à régler ce problème – et ce n'est pas une mince affaire – on sait qu'un an plus tard, les patients pourraient avoir une maladie cardiaque ou une maladie du foie.

On finirait par simplement essayer de les garder en vie. Et il faut se poser la question, en tant qu'être humain : est-ce une vie? Et est-ce à ça qu'il faut consacrer nos ressources, ou est-il préférable de se concentrer sur les patients qui ont une certaine qualité de vie pour tenter d'améliorer leur vie, de faire en sorte que les parents aient des bébés sains et d'essayer d'éviter les situations catastrophiques?

Christopher Canning : Il semble y avoir un léger décalage par rapport au point de vue du groupe de génétique médicale des premières années, dans les années 1960 et 1970, où les cliniciens et les scientifiques voulaient simplement soigner les gens.

Eric Shoubridge : En effet.

Christopher Canning : Comme vous le dites, de nos jours, on voit plutôt les choses du point de vue de l'étude des systèmes vivants. Diriez-vous que c'était la mentalité du groupe au cours des dernières années?

Eric Shoubridge : Je crois, oui.

Christopher Canning : Vous êtes tous des scientifiques reconnus, mais quand on consulte les demandes, on voit qu'on est passé d'une approche du médecin-scientifique à une approche plus individuelle, axée sur la génétique moléculaire, avec l'arrivée de Rima Rozen, de Roy Gravel, etc.

Eric Shoubridge : Je crois que c'est parce que les outils étaient là.

Christopher Canning : Pouvez-vous m'en dire plus à ce sujet?

Eric Shoubridge : À partir du moment où on peut étudier le génome, procéder à son séquençage et le manipuler, on peut faire pratiquement n'importe quoi avec un système vivant parce que le génome est la base de la cellule vivante. Auparavant, on pouvait observer une enzyme, mais que pouvait-on faire? On pouvait faire de la substitution d'enzyme. Essayer de multiplier une enzyme en utilisant de petites molécules.

Mais les outils avaient leurs limites. Avec la révolution moléculaire, on a pu poser une foule de questions qu'on ne pouvait pas poser auparavant. Je pense que le changement de mentalité est attribuable aux outils disponibles plutôt qu'à une personne qui s'est demandé comment il fallait faire les choses ou organiser le groupe.

Christopher Canning : Je vois.

Eric Shoubridge : Dans une certaine mesure, nous, les scientifiques, sommes dépendants des technologies, mais nous ne sommes pas des esclaves. J'aime apprendre qu'une personne a trouvé une nouvelle méthode. J'ai lu un petit article, paru dans *Nature*, sur des molécules qui nous permettent d'étudier la fluorescence dans les cellules ou un signal produit par les cellules. Une personne a mis au point une technique microscopique nommée « génération de seconde harmonique », ou quelque chose du genre. Nous avons des composés inorganiques; j'ai oublié ce qu'ils sont. Il y a du titane dans l'un d'entre eux, ou du bore, ou quelque chose d'autre qui, quand deux photons le frappent en même temps, émet une lumière à une longueur d'onde très différente de celle du signal d'entrée. Mais ce n'est pas de la fluorescence. On peut détecter ce signal à l'aide de microscopes spéciaux.

Il n'y a aucune cellule vivante en arrière-plan. Certains disent que nous pourrions utiliser ces composés comme marqueurs dans les cellules vivantes, mais il faudrait les attacher à des biomolécules et les intégrer aux cellules. Néanmoins, il y a plein de choses fascinantes qui se passent autour de nous et que nous pouvons utiliser pour examiner des problèmes impossibles à étudier auparavant.

Christopher Canning : Mais ça devient plus difficile d'appliquer ces techniques à la médecine parce que ça complexifie tout. Ironiquement, les avancées technologiques ont créé des incertitudes au sujet de ce que nous pouvons faire et de ce que nous savons.

Eric Shoubridge : C'est exact.

Christopher Canning : Ce qui rend l'application à la médecine beaucoup plus difficile.

Eric Shoubridge : Oui. Et quand on pense à ce qui est disponible pour les gens en médecine… on parle souvent de thérapie génétique, de remplacement protéinique et de toutes sortes de traitements compliqués qui ne sont pas encore réalité. Mais si vous demandez, par exemple, si une personne peut faire un test génétique pour la maladie de Parkinson… Nous le faisions pour les causes génétiques de la maladie de Parkinson, mais les règles ont changé.

Une personne peut probablement obtenir ce test si elle réside au Québec et que son médecin fait une demande aux autorités, qu'il remplit tous les formulaires et qu'il s'adresse aux bons fonctionnaires pour savoir si nous pouvons envoyer les échantillons à Houston, au Texas, et, pour mille dollars, recevoir les résultats. La réponse peut être positive ou négative. Les formulaires peuvent se perdre. C'est parfois difficile d'avoir accès à des techniques que nous connaissons déjà; ça dépend de la maladie.

David Rosenblatt dirige un laboratoire de diagnostic. Si vous avez des antécédents familiaux de maladie de Huntington et que vous voulez faire faire un test, vous pouvez simplement vous rendre à son laboratoire. Si vous avez une maladie mitochondriale, c'est moins facile de savoir où le test se fera. Si vous me trouvez, je vais faire le test, même sans être payé. Ça ne me dérange pas. Je ne vais simplement pas…

Christopher Canning : Vraiment?

Eric Shoubridge : Oui, vraiment.

Christopher Canning : C'est aussi simple que ça?

Eric Shoubridge : Oui. Évidemment, il faut payer un technicien. Mais les tests d'ADN ne sont pas si compliqués, et si j'avais le salaire des quelques bureaucrates qui font marcher ce système, je pourrais organiser tout ça. Ce n'est pas sorcier. Les erreurs sont possibles, mais c'est beaucoup plus difficile de faire fausse route avec l'ADN qu'avec les enzymes.

Christopher Canning : Je vois.

Eric Shoubridge : Par exemple, il y a probablement 20 ou 25 laboratoires dans le monde qui font des tests sur les enzymes que nous avions l'habitude de tester, celles de la phosphorylation oxydative; pas des centaines.

Un jour, quelqu'un en Allemagne s'est dit « envoyons des échantillons dans tous les gros laboratoires du monde pour qu'ils effectuent ces tests ». Évidemment, ils ne pouvaient pas faire ça avec des échantillons humains. Ils ont donc utilisé des tissus bovins, et ils ont obtenu des résultats qui variaient selon un facteur de 10. Même après avoir modifié légèrement certaines données, ils ont obtenu une variation par un facteur de 5, ce qui est énorme.

Christopher Canning : En effet.

Eric Shoubridge : Dernièrement, j'ai entendu un neurologue d'ici parler de ça. Certains

laboratoires pourront vous donner un diagnostic positif si vous en voulez vraiment un.

Christopher Canning : Vous pouvez trouver un laboratoire qui le fera?

Eric Shoubridge : Vous pouvez trouver le laboratoire de diagnostic qui vous donnera un diagnostic positif pour quelque chose. Je crois qu'il est donc important de s'occuper du contrôle de la qualité. Mais en biochimie, c'est délicat. Tout peut changer très vite avec les protéines. Par exemple, si vous faites une pause-café avant d'avoir réalisé votre épreuve et que vous laissez tout en plan sur votre paillasse, les protéines seront peut-être mortes à votre retour 20 minutes plus tard. Vous pourriez alors obtenir un résultat différent, alors que l'ADN…

Christopher Canning : L'ADN, c'est l'ADN.

Eric Shoubridge : C'est l'ADN. Et il finira par se dégrader.

Christopher Canning : Je vois.

Eric Shoubridge : Mais il faut vraiment le malmener pour en arriver là. La technologie est relativement simple. Aujourd'hui, il existe de nombreuses technologies accessibles en ligne qui permettent le séquençage d'un exome et même d'un génome entier. Il est possible de faire faire le séquençage d'exomes entiers pour environ 4 000 dollars.

Christopher Canning : Wow!

Eric Shoubridge : Donc, pour chaque gène qui est exprimé dans votre corps, vous pouvez obtenir demain – bon, pas demain, mais dans quelques semaines, un séquençage pour 4 000 dollars. Pour les génomes, il faut compter entre 10 000 et 15 000 dollars environ. Mais les concurrents sont nombreux, et ils veulent tous finir par offrir le séquençage du génome pour 1 000 dollars. Vous avez dû entendre parler de ça.

Christopher Canning : Oui, oui, absolument.

Eric Shoubridge : Et ils finiront par y arriver parce que les nouvelles technologies de séquençage de l'ADN sont extrêmement créatives.

Christopher Canning : Je vois.

Eric Shoubridge : Je parle de gens extrêmement brillants qui utilisent des instruments de séquençage massivement parallèle qui génèrent des téraoctets de données en un claquement de doigts. C'est l'analyse qui demandera du temps. Je ne sais vraiment pas quelles seront les répercussions sur le diagnostic. Une personne pourrait vous dire : « Je crois que j'ai un patient atteint d'une maladie mitochondriale. Avez-vous une analyse qui permettrait d'éliminer cette possibilité? Savez-vous quels gènes rechercher? » Parfois c'est clair, mais la plupart du temps ça ne l'est pas. S'il s'agit d'un phénotype classique que nous connaissons parce que nous l'étudions depuis 20 ans, vous lui répondrez « Bien sûr ». Si le patient est un jeune enfant atteint d'une déficience en cytochrome oxydase ou du syndrome de Leigh, je dirais que nous avons fort

probablement affaire à un SURF1.

Christopher Canning : D'accord.

Eric Shoubridge : Nous pouvons effectuer un test biochimique rapide pour confirmer le diagnostic et ensuite faire un test génétique; nous pouvons aussi faire un test génétique directement.

Mais si on a affaire à un phénotype complexe et que le profil métabolique nous indique que le patient pourrait avoir une maladie mitochondriale et des troubles hépatiques, entre autres, je me demanderais par où commencer. Il existe un millier de protéines, un millier de gènes… j'exagère un peu… mais il peut y avoir 300 ou 400 éléments de la mitochondrie en jeu dans la chaîne respiratoire. Et nous ne saurions pas vraiment par lequel commencer. Nous pourrions avoir recours au séquençage massivement parallèle, mais le contrôle de la qualité peut nous réserver des surprises avec cette technique. On peut l'utiliser pour découvrir des choses, parce qu'on peut revenir en arrière pour obtenir une confirmation, mais si on essaie d'éliminer une maladie ou d'en prouver l'existence, comment peut-on être certain de ne pas avoir manqué quelque chose? Si on trouve quelque chose, ça peut aller, mais si on ne trouve rien…

Christopher Canning : On ne sait pas pourquoi on n'a rien trouvé.

Eric Shoubridge : Exactement. Je ne sais pas quelles répercussions ces nouvelles techniques auront sur la façon de réaliser les tests. Pour l'instant, je pense que c'est logique de faire des tests à petite échelle. Ainsi, on est certain de pouvoir éliminer le truc.

Christopher Canning : Je comprends.

Eric Shoubridge : Mais si les nouvelles techniques deviennent abordables, on pourrait les utiliser pour faire un tri et éliminer certaines choses rapidement. On pourrait ensuite confirmer les résultats positifs en utilisant des moyens plus classiques, comme une technique indépendante ou orthogonale, et dire « nous l'avons trouvé deux fois avec ces deux méthodes différentes, alors nous sommes presque sûrs que c'est bien ça; pas besoin d'aller plus loin ». Je crois que nous pourrions en venir à ça si cette façon de faire devenait rentable.

Christopher Canning : Vous parlez comme un généticien médical.

Eric Shoubridge : Voilà. Je devrais porter deux chapeaux.

[rires]

Christopher Canning : Tout à fait.

Eric Shoubridge : Je suis un généticien médical.

Christopher Canning : Et voilà.

Eric Shoubridge : Nous avons donc cette technique de diagnostic avec laquelle je ne suis pas

très à l'aise parce que je n'ai pas les compétences nécessaires. Je n'ai aucune attestation de généticien médical qui me donnerait le droit de signer des rapports. Je n'ai aucune attestation de biologiste moléculaire du Collège canadien de généticiens médicaux. Mais David et Rima en ont une, comme d'autres personnes dans le réseau. Si on acquiert les connaissances nécessaires, on peut arriver à le faire et à bien le faire, bien sûr. Je ne vais pas commencer à tester tout et n'importe quoi. Je vais faire des tests sur des éléments que nous connaissons et qui nous intéressent, et pour nos patients. Nous ne ferons pas de génétique du cancer; ce n'est pas notre mission. Je pense donc que ce n'est pas quelque chose d'impossible.

Mais nous finirons par avoir besoin d'une personne qui se portera garante de ces techniques et qui confirmera la valeur des mécanismes de contrôle de la qualité. Lorsqu'un laboratoire de diagnostic est mis sur pied et veut recevoir sa certification, on lui envoie des échantillons à l'aveugle pour confirmer sa compétence. Il y a beaucoup de contrôles, et je crois que c'est une bonne chose.

Je crois toutefois que c'est dommage d'exclure la recherche. Je crois que l'idée du transfert de technologie était excellente parce qu'elle procurait une disponibilité instantanée, gratuitement. Quelqu'un payait bien en partie, mais la somme était relativement petite et il n'était pas nécessaire d'envoyer une facture à quelqu'un simplement pour essayer de payer des salaires. Je considère que ce n'est pas une méthode rentable : quelqu'un doit prendre connaissance des résultats, trouver l'adresse, rédiger une facture et l'envoyer, et quelqu'un doit répondre à l'autre bout. C'est une perte de temps et ça n'a aucun sens.

Mettons en place une douzaine de laboratoires dans la province, et demandons à l'un d'eux de travailler sur la dystrophie musculaire et à un autre de faire de la biochimie pédiatrique. Nous leur donnerons un budget et nous nous attendrons à ce qu'ils fassent du bon travail. On en parle depuis des années et des années.

David Rosenblatt m'a dit que ça allait se faire, et je lui ai répondu qu'il me disait la même chose depuis vingt ans, mais que rien n'avait encore été fait. Nous nous battons toujours avec le système pour trouver une façon de fournir les services.

Christopher Canning : De quoi le système a-t-il peur? Craint-il que cela n'aura aucune incidence directe sur la santé parce que les diagnostics ne sont pas toujours fiables? Doute-t-il des bienfaits potentiels?

Eric Shoubridge : Je crois que le système est un organisme complexe peuplé de bureaucrates. Un jour, un gars qui travaille dans le marketing m'a dit qu'il avait fait une analyse des systèmes de santé du Danemark et du Québec, qui desservent des populations similaires. Je ne me rappelle plus les chiffres exacts, mais en gros, au Québec, il y avait au moins deux fois plus de personnes qui géraient le système que de personnes qui fournissaient les services médicaux.

Je crois qu'il y a, dans notre système, une énorme bureaucratie qui alourdit les processus. Avec un peu de logique, je crois qu'il serait possible de réorganiser

tout ça. Je pense que personne ne pourra nier qu'un test génétique est une façon rentable d'obtenir un diagnostic, quand c'est possible d'en faire un, parce que le résultat est noir ou blanc. Habituellement, c'est noir ou blanc. Il arrive qu'il y ait des zones grises, mais la plupart du temps, c'est noir ou blanc.

Christopher Canning : Vous voulez dire que le résultat vous dira si une personne est atteinte d'une maladie ou non?

Eric Shoubridge : Vous avez une maladie ou vous ne l'avez pas. C'est un test relativement simple et peu coûteux. Les technologies sont les mêmes partout, et beaucoup, beaucoup de gens peuvent les utiliser et les superviser correctement. Il est facile de mettre en place des mécanismes de contrôle de la qualité; plus facile qu'en biochimie, par exemple.

Je ne sais pas pourquoi on ne le fait pas. J'imagine que c'est parce que la volonté n'y est pas, qu'il n'y a pas une personne suffisamment haut placée qui prend les choses en main et qui impose un processus optimal. Mais je peux seulement faire des suppositions. Je suis au bas de l'échelle et j'essaie simplement de faire en sorte que les choses avancent.

Pourquoi est-ce je me démène comme ça? Pourquoi est-ce que je dépense autant d'énergie sur ça?

Christopher Canning : Pour garder le laboratoire de diagnostic en service?

Eric Shoubridge : Oui, et nous arrivons à le faire fonctionner. Nous avons commencé à offrir le service parce que nous faisions de la recherche dans le domaine. J'estimais qu'il fallait offrir quelque chose aux personnes touchées par la maladie, d'une manière ou d'une autre. Nous publions des articles qui obtiennent une grande visibilité parce que nous réussissons à corriger une anomalie génétique, par exemple. Mais avant que nous trouvions une solution, des personnes sont décédées. J'estime que nous nous devons de donner quelque chose aux familles touchées, de leur fournir un service. Et, d'un point de vue plus égoïste, nous pourrions aussi découvrir des cas très intéressants qui nous permettraient de corriger d'autres anomalies génétiques. Toutes ces personnes alimenteraient en quelque sorte le programme de recherche et nous aideraient à trouver de nouvelles solutions.

Christopher Canning : Vous faites de la génétique médicale.

Eric Shoubridge : Pour moi, ça fonctionne, peu importe le point de vue : je suis à la fois un généticien médical et un biologiste moléculaire. Vous avez raison.

Christopher Canning : Pouvez-vous me consacrer encore quelques minutes?

Eric Shoubridge : Oui, bien sûr.

Christopher Canning : J'aimerais terminer avec quelques questions sur le groupe.

Comment le groupe était-il dirigé lorsque Rima Rozen était là? Aussi, lors du symposium de novembre dernier, le D^{r} Scriver a mentionné que le groupe fonctionnait comme une organisation de base. Êtes-vous d'accord pour dire

que le groupe a évolué à partir de la base et qu'il n'y avait pas de structure verticale, des dirigeants vers la base?

Eric Shoubridge : Absolument. La direction du groupe était plutôt une formalité administrative. Chaque année, nous avions des journées consacrées à la recherche. Nous organisions des rencontres avec les étudiants chaque mois, et environ quatre fois par année, les chercheurs principaux se réunissaient autour d'une pizza et d'une bière pour discuter des découvertes et des occasions à saisir.

Ça n'a donc jamais été une structure verticale du haut vers le bas. Tout partait de la base. Une personne avait une idée et la présentait au groupe. Rima n'a jamais dit « Voici ce que nous allons faire. Nous allons dépenser l'argent comme ça et comme ça. ». Les décisions étaient prises en groupe… je précise que nous n'avions pas un gros budget. Je pense que nous avions un quart de million de dollars pour huit personnes.

Christopher Canning : En plus de votre subvention du CRM?

Eric Shoubridge : Oui. Il y avait donc environ 30 000 $ en plus, que nous utilisions pour des trucs comme les fournitures de culture cellulaire.

Christopher Canning : Je vois.

Eric Shoubridge : David faisait aussi des choses comme ça. C'était donc comme un petit ajout, qui servait aussi pour certaines activités du groupe. Mais la majeure partie de l'argent était utilisée dans le cadre des activités du groupe liées aux subventions des IRSC. Je peux confirmer que tout partait de la base. Je ne peux pas parler de la période pendant laquelle Charles était à la tête du groupe. Charles est une personne qui ne donne pas sa place, mais je crois qu'il n'a jamais imposé sa façon de faire. Il aimait avoir l'avis des membres du groupe. Et je pense que si quelqu'un avait essayé de faire la loi, certaines personnes auraient quitté le groupe. Les membres du groupe ne souhaitaient pas ça.

Je ne pense pas qu'on pourrait tirer de bons résultats scientifiques d'une telle structure. La recherche stimulée par la curiosité émane principalement de la base, et c'est là qu'on trouve les choses les plus intéressantes. Lorsqu'il y a un nouveau virus à éradiquer, il faut avoir un chef de groupe solide et un type de gestion du haut vers le bas. Mais ce n'était pas notre mission. Nous essayions juste de trouver les causes génétiques des maladies humaines et de trouver une solution.

Christopher Canning : Les subventions s'appuyaient donc sur des programmes indépendants forts?

Eric Shoubridge : Oui.

Christopher Canning : Et vous pouviez travailler les uns avec les autres à certains moments?

Eric Shoubridge : Oui, absolument. C'était le cas pendant la période où j'étais dans le groupe.

Christopher Canning : Il s'agissait donc d'un groupe qui était, d'une certaine manière, subventionné par les IRSC, mais mené par des programmes de recherches individuels…

Eric Shoubridge : C'est ça.

Christopher Canning : Comment pouvait-il y avoir une dynamique de groupe? Nous en avons déjà un peu parlé, de votre point de vue, et je trouve ça vraiment intéressant.

Eric Shoubridge : Comme je l'ai déjà dit, il y avait une certaine dynamique, mais pas de synergie. Sauf peut-être entre certaines personnes au sein du groupe. Et si quelqu'un avait dit : « Voyons la dynamique du groupe et si les membres fonctionnent vraiment comme un groupe. Ont-ils besoin d'être tous dans la même pièce? », la réponse aurait été non. Catégoriquement, non.

Christopher Canning : Les choses se sont passées comme ça dès le début. Même si, en 1972, le CRM a décrété que tous les membres du groupe devaient travailler au même endroit. Ils ont été au même endroit pendant trois ans, puis tout le monde est parti dans des laboratoires différents. Le groupe n'a jamais été une affaire de lieu physique.

Eric Shoubridge : Exactement.

Christopher Canning : Mais il y avait une collaboration sur le plan des idées?

Eric Shoubridge : Les IRSC ont laissé tomber la notion de groupe et ont plutôt formé des équipes. Ce que vous décrivez est plutôt une équipe, n'est-ce pas?

Christopher Canning : Oui.

Eric Shoubridge : Dans une équipe, tout le monde cherche à résoudre le même problème en adoptant différents points de vue. Prenons la fibrose kystique, par exemple. Nous connaissons l'anomalie génétique, mais pour une autre maladie, nous pourrions ne pas connaître l'anomalie ou la connaître depuis très peu de temps. Maintenant, nous voulons savoir comment elle fonctionne, connaître sa physiologie. Nous avons besoin d'un modèle animal. Nous avons besoin d'un modèle cellulaire. Nous avons besoin d'anticorps. Nous voulons couvrir toute la structure tridimensionnelle de cette protéine. Ça, c'est un travail d'équipe.

Christopher Canning : Parfait. Une dernière question. À votre avis, pourquoi le groupe du CRM a-t-il connu autant de succès pendant si longtemps?

Eric Shoubridge : Je pense que c'est grâce à de bons meneurs. Comme je l'ai déjà dit, les personnes qui ont dirigé l'équipe n'imposaient pas leur façon de faire. Et je pense que les personnes qui formaient le groupe ont toujours réussi à attirer d'autres bonnes personnes. Comme je l'ai dit, chaque membre du groupe avait un programme individuel solide avant d'arriver, et je crois que chaque membre s'est joint au groupe parce qu'il voulait partager ses idées et les technologies, découvrir les travaux des autres et faire partie de quelque chose au lieu de travailler seul de son côté. Je crois que l'esprit de groupe avait surtout un aspect scientifique social. Nous n'avions pas vraiment besoin de travailler ensemble pour réussir, mais je crois que nous avons connu un peu plus de succès parce que nous formions un groupe.

Christopher Canning : Super. Je crois que c'est un beau mot de la fin. Merci infiniment pour votre temps.

Eric Shoubridge : Merci.

FIN DE L'ENTRETIEN

Dr Mark Trifiro, le 22 octobre 2010

Christopher Canning : Nous sommes le 22 octobre 2010. Ici Christopher Canning en compagnie du Dr Mark Trifiro. Dr Trifiro, je suis honoré de pouvoir m'entretenir avec vous de deux sujets. J'aimerais d'abord que nous parlions de votre parcours universitaire, qui vous a permis de contribuer à l'avancement de la génétique médicale. Ensuite, et c'est le principal thème de mon étude, j'aimerais en savoir plus sur votre participation au groupe sur la génétique médicale des IRSC[1], anciennement le CRM[2], dont vous avez été membre de 2001 à 2009, soit jusqu'à ce qu'il cesse d'être financé. Est-ce exact?

Dr Trifiro : Oui, jusqu'en 2009.

Christopher Canning : Nous y reviendrons. J'aimerais d'abord en savoir un peu plus sur vous. Pouvez-vous nous parler de votre lieu de naissance, de votre enfance et de vos premières années d'école?

Dr Trifiro : Je suis né à Montréal de parents d'origine italienne. Mes grands-parents ont immigré au Canada avant la Première Guerre mondiale et mes parents sont nés à Montréal.

J'ai grandi à Montréal dans une communauté multiethnique. Le contexte social dans lequel j'ai baigné était donc quelque peu différent des milieux traditionnels. Mes parents ne cessaient de me rappeler l'importance des études et je crois que l'idée a vite fait son chemin. En fait, j'aimais bien l'école. Je réussissais très bien et mes professeurs ont exercé une profonde influence sur moi dès l'école secondaire. Sans eux, je ne serais probablement pas là où je suis aujourd'hui.

Les études collégiales ont été un peu difficiles, mais là encore… mes professeurs à l'université ont exercé une profonde influence sur moi.

Christopher Canning : Quelle université avez-vous fréquentée?

Dr Trifiro : L'Université McGill. Lorsque j'ai fini mes études secondaires, à Montréal, les cégeps[3] n'existaient pas encore. En fait, le gouvernement avait mis sur pied les cégeps, mais les immeubles eux-mêmes n'étaient pas prêts. Les collèges Vanier et Dawson n'existaient pas encore. Les universités devaient accueillir les activités des cégeps. J'ai donc fait mes études collégiales, puis mes études universitaires, à McGill. Nous n'avons pas beaucoup bougé pendant cinq ans.

J'ai obtenu un baccalauréat en biochimie, et je crois que mes trois dernières années à McGill ont été les plus fantastiques de toutes mes études. J'ai beaucoup aimé le programme spécialisé en biochimie et, après mon baccalauréat, j'ai eu beaucoup de mal à décider de la suite des choses. C'était soit la maîtrise ou le doctorat, soit la médecine.

Comme j'hésitais, je me suis inscrit aux deux programmes et j'ai été accepté

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada
[3] Collège d'enseignement général et professionnel

en médecine. Je me disais que j'aimerais peut-être exercer la médecine tout en faisant de la recherche.

Les quatre années à la Faculté de médecine ont été très, très différentes du baccalauréat en biochimie. J'ai trouvé ça très difficile; il y avait une foule de notions à mémoriser et je n'étais pas habitué à ça. Après mes études en médecine, je me suis inscrit à un programme de résidence à Montréal.

Christopher Canning : À quelle faculté de médecine étiez-vous inscrit?

Dr Trifiro : À McGill.

Christopher Canning : À McGill? O. K., vous avez passé beaucoup de temps ici.

Dr Trifiro : Oui, beaucoup. Je me suis donc inscrit à un programme de résidence ici, à Montréal. En grande partie parce que notre famille est très unie, et nous étions, eux comme moi, très mal à l'aise à l'idée que je m'éloigne de mon frère, de ma sœur, de ma mère et de mon père. C'était très inusité pour nous.

Christopher Canning : C'est souvent le cas dans les familles italiennes, non?

Dr Trifiro : Oui, absolument! Je crois que c'est la principale raison pour laquelle je suis resté ici. Durant ma résidence, je me suis rendu compte que je ne voulais pas trop m'éloigner des sciences fondamentales, même si je n'ai pas travaillé en laboratoire ni rien du genre, parce que c'est très difficile de faire ça.

Puis, j'ai finalement décidé de partir. Bon, je me suis marié, et c'est probablement ce qui m'a amené à me dire : « D'accord, il faut que tu partes. » J'ai fait une demande d'admission à un programme de résidence en endocrinologie à Harvard, et j'y suis resté de 1981 à 1986. C'est à Harvard que j'ai renoué avec la recherche fondamentale et, pendant deux ans, je n'ai pas quitté le laboratoire.

Christopher Canning : On vous permettait de faire du travail de laboratoire pendant votre résidence?

Dr Trifiro : Oui. C'est d'ailleurs pourquoi j'avais choisi le programme de l'Université Harvard, fortement axé sur la recherche fondamentale. C'était le seul programme à offrir deux années de recherche fondamentale. Je me suis dit : « Voici l'occasion rêvée de m'y remettre et de voir si ça me plaît ou non ». Ça faisait huit ans que je n'avais pas fait de recherche fondamentale – quatre ans d'études en médecine et quatre ans de résidence – alors les choses avaient vraiment beaucoup changé.

Et lorsque je suis retourné à Harvard pour faire mon stage de perfectionnement en endocrinologie clinique, le programme avait l'avantage de compter deux années de recherche fondamentale. Or, pendant la période où j'avais cessé de faire de la recherche fondamentale, une nouvelle discipline, la biologie moléculaire, avait vu le jour. J'ai manqué tout ça, alors lorsque j'ai repris le chemin du laboratoire, j'ai dû me familiariser avec la technique de l'ADN recombinant.

Christopher Canning : À cette époque à Harvard, faisiez-vous de la recherche en biochimie ou en endocrinologie?

Dr Trifiro : En endocrinologie. Pendant ces deux années, j'ai beaucoup appris sur la biologie moléculaire. Je suis ensuite revenu à Montréal pour des raisons familiales – je ne voulais pas élever mes enfants aux États-Unis. Je savais que je devais consacrer un peu plus de temps à la recherche si je voulais faire carrière dans ce domaine; c'est pourquoi j'ai fait des études postdoctorales.

J'ai donc passé près de deux ans à l'Institut de recherches cliniques (de l'Hôpital général juif), à l'angle de l'avenue des Pins et de la rue Saint-Urbain, avec un spécialiste en endocrinologie moléculaire.

Après ce long parcours, je sentais que le temps était venu de me joindre à un département universitaire où je pourrais faire de la recherche fondamentale et travailler comme clinicien. En 1990-1991, on m'a offert un poste ici, à l'Hôpital général juif, et on m'a présenté au Dr Pinsky, qui dirigeait le laboratoire de génétique moléculaire.

Christopher Canning : J'ai remarqué que vos travaux sur le récepteur des androgènes étaient très semblables aux siens.

Dr Trifiro : Oui, nous avons commencé ensemble. C'était un très bon mariage, parce que Len [Pinsky] était un généticien classique qui m'en a appris beaucoup sur la génétique et moi, j'étais la jeune recrue qui connaissait toutes les nouvelles techniques en biologie moléculaire. Nous avions beaucoup d'affinités.

Christopher Canning : Que voulez-vous dire exactement?

Dr Trifiro : Le Dr Pinsky était un chercheur en génétique très renommé au Canada, aux États-Unis et partout dans le monde. Sa spécialité était le récepteur des androgènes et ses mutations. Il disposait d'une énorme banque de fibroblastes cutanés prélevés chez des patients qui présentaient une anomalie du récepteur des androgènes appelée « syndrome d'insensibilité aux androgènes ». Il en était à un stade où il devait recourir aux techniques de pointe pour progresser; j'ai sauté sur l'occasion.

Je travaillais en milieu clinique à l'hôpital et à l'Institut de recherches médicales Lady Davis, où j'avais le Dr Pinsky comme voisin. Je crois que ces années de formation en compagnie de Len ont été très, très importantes dans mon parcours. Un mentor comme lui, ça facilite vraiment un début de carrière. Il m'a appris les ficelles du métier, notamment la préparation de demandes de subventions et d'appui salarial. Je m'estime très chanceux, car tout s'est très bien passé.

En résumé, je dirais que j'ai toujours cherché à comprendre le fonctionnement des choses, comme presque tous les scientifiques. J'ai toujours été entouré de gens intéressants, j'ai eu beaucoup de bons professeurs, et Len a été pour moi un excellent mentor qui m'a véritablement permis de mettre ma carrière sur les rails. Je pouvais également compter sur le soutien de l'Université, ce qui était très important.

Christopher Canning : Préfériez-vous travailler en milieu clinique ou faire de la recherche, ou avez-vous constaté qu'il était important de travailler dans ces deux domaines à la fois?

Dr Trifiro : Vous savez, lorsque j'affirme que les professeurs ont exercé une influence sur moi, je fais allusion au fait qu'ils m'ont appris qu'il est important d'acquérir des connaissances, mais qu'il faut également redonner à la science. Comment? En contribuant à la science – et la seule façon de contribuer véritablement à la science est de faire de la recherche. C'est ce qui permet à une discipline d'évoluer. Si vous pouviez contribuer à cet essor d'une autre façon, ce serait bien aussi. Mais ce qu'on m'a appris, c'est que la recherche est essentielle pour faire avancer les choses. Je n'avais donc aucun scrupule à affirmer : « Je peux prendre soin des patients, ce n'est pas un problème ». Je dois faire du bon travail, mais si je veux apporter ma pierre à l'édifice, je dois faire de la recherche. Nous avons donc fait progresser considérablement la recherche sur le récepteur des androgènes; le succès a été au rendez-vous, aucun doute là-dessus.

L'autre événement marquant a été le départ à la retraite de Len [Pinsky]. J'ai trouvé cette période un peu difficile, parce que je perdais en quelque sorte une figure paternelle. Sans compter que je me suis retrouvé avec une foule de responsabilités. Je devais diriger le laboratoire.

Christopher Canning : Travailliez-vous tous les deux dans le même laboratoire à cette époque?

Dr Trifiro : Oui. Alors… à vrai dire, je ne sais pas… Je me retrouvais avec le labo le plus ancien de l'histoire des IRSC. Je serais curieux de savoir à quel moment ses activités ont débuté. Dans les années mille neuf cent…

Christopher Canning : Ce ne serait pas à la fin des années 1960?

Dr Trifiro : Oui, à la fin des années 1960.

Christopher Canning : C'est donc avant qu'il ne mette sur pied le Centre de génétique humaine.

Dr Trifiro : Oui, absolument.

Christopher Canning : D'accord. C'était donc son lieu de travail dans les années 1960. Ici même?

Dr Trifiro : Oui, ici même.

Christopher Canning : Super!

Dr Trifiro : J'ai donc dû composer avec la situation. Évidemment, j'avais un peu plus de travail, mais nous avons réussi à obtenir des subventions. C'est donc pour ça… lorsque Len [Pinsky] et quelqu'un d'autre sont partis, les chercheurs du groupe de génétique médicale des IRSC m'ont demandé de me joindre à eux. Je crois que c'était en 2001.

Christopher Canning : J'aimerais que nous y revenions dans quelques minutes.

Dr Trifiro : Bien sûr. Je crois que j'ai bien résumé la situation. Nous sommes aujourd'hui

en 2010. Le seul autre fait marquant de cette période, c'est qu'on m'a offert le poste de chef du Département d'endocrinologie. J'ai accepté ce poste, assorti de responsabilités cliniques, en 2007.

Christopher Canning : À quel moment avez-vous été nommé directeur de l'Institut Lady Davis?

Dr Trifiro : J'ai simplement pris le relais de Len après son départ.

Christopher Canning : Vous êtes donc le directeur depuis le milieu des années 1990?

Dr Trifiro : Depuis 1996, je crois, ou 1997, lorsque Len [Pinsky] a pris sa retraite.

Christopher Canning : Pendant cette période où vos travaux de recherche fondamentale prenaient leur essor et où vous vous intéressiez de plus en plus à la médecine, à quel moment avez-vous fait le lien entre médecine et génétique? Y a-t-il eu un moment où vous vous êtes dit : « L'aspect génétique de la médecine m'intéresse davantage que la génétique en général »?

Dr Trifiro : Je ne suis pas généticien de formation, mais Len [Pinsky] m'a dit quelque chose que je n'oublierai jamais. [Il m'a dit :] « Va où la science te portera ». Alors, lorsque nous étudiions cette maladie, il était clair que la science nous portait vers la génétique. Il nous fallait comprendre les mécanismes génétiques de ce syndrome. J'ai donc décidé de faire de la médecine, mais à partir du moment où j'étudie le récepteur des androgènes dans ces familles-là, c'est de la génétique.

Et, depuis, je fais de la génétique, mais je crois que la science a évolué au point où la frontière qui sépare la génétique de la recherche sur les protéines est de plus en plus floue. À mon avis, la plupart des scientifiques concilient les deux sans problème.

C'est donc ce que nous faisons depuis les cinq ou six dernières années. Nous avons commencé par les patients. Nous nous sommes d'abord intéressés à la génétique pure, et la génétique nous a enseigné comment trouver ces mutations et en quoi elles consistaient. Nous n'avions jamais compris l'effet des mutations sur les protéines. Alors, au cours des cinq ou six dernières années, c'est ce que nous avons étudié. Nous repoussons les frontières de la génétique pour élucider le rôle de cette mutation au niveau protéique.

Christopher Canning : Vous étudiez donc une mutation génétique qui produit ou non une protéine responsable de malformations sexuelles, n'est-ce pas?

Dr Trifiro : Oui, exactement, et nous comprenons maintenant beaucoup mieux l'effet de cette mutation[MBM1].

Christopher Canning : Bien. Et on peut attribuer ça à l'évolution des technologies de biologie moléculaire observée depuis les dix ou 15 dernières années?

Dr Trifiro : Absolument! La biologie moléculaire nous a permis d'exprimer très facilement les protéines. Or, une fois les protéines exprimées, on peut les examiner sous toutes les coutures.

Christopher Canning : Très bien. J'aimerais que vous nous parliez plus particulièrement de vos débuts dans le groupe. Évidemment, vous collaboriez avec le Dr Pinsky pendant les années 1980 et 1990, mais à quel moment vous a-t-on approché pour vous demander si vous souhaiteriez vous joindre au groupe?

Dr Trifiro : Je ne sais pas trop comment tout ça a commencé, mais je pense… vous savez, le groupe de génétique de McGill est plutôt restreint. Len [Pinsky] s'était assuré que j'aurais un poste officiel au sein du Département de génétique humaine si je me joignais au groupe. J'ai donc obtenu un poste au Département de médecine ainsi qu'au Département de médecine expérimentale, parce que je faisais de la recherche fondamentale, mais j'avais également un poste de professeur agrégé ou affilié au Département de génétique humaine.

Christopher Canning : Avant d'être invité à vous joindre au groupe?

Dr Trifiro : Oui. Au cours de ces années de formation, j'ai appris à bien connaître tous les membres du groupe. De leur côté, ils se sont familiarisés avec mon travail et celui que je faisais avec Len, et ils ont tout simplement décidé de m'offrir une place dans le groupe. Selon moi, c'est parce que nos recherches en génétique allaient drôlement bien à ce moment-là.

Christopher Canning : En quoi vos domaines de recherche se recoupaient-ils à l'époque? Le Dr Pinsky et vous travailliez dans le même domaine, mais qu'en était-il de l'ensemble du groupe?

Dr Trifiro : Je crois que les membres du groupe de génétique [du CRM/IRSC] s'intéressaient surtout à la génétique translationnelle. En d'autres mots, les mécanismes génétiques que nous étudiions étaient étroitement liés aux troubles cliniques. Donc tous leurs travaux avaient trait à des maladies ou à des problèmes de santé bien réels chez l'humain. C'était ça, le fil conducteur.

Len [Pinsky] et moi cadrions très bien avec cette philosophie, parce que, bien évidemment, nous étudiions de vrais patients, de vraies maladies et de vrais phénotypes. C'était la même chose pour les autres membres du groupe.

Christopher Canning : Dans l'espoir de découvrir un jour un traitement?

Dr Trifiro : Oui, fondamentalement, des traitements. Ou pour déterminer quelles sont les personnes exposées à certaines maladies, mais pour ça, il faut réaliser des tests génétiques et savoir de quoi il retourne. C'est pourquoi les tests génétiques et la découverte de traitements étaient au cœur de la recherche en médecine fondamentale.

Christopher Canning : Quels traitements vos propres travaux ont-ils permis de mettre au point ou de faire progresser?

Dr Trifiro : Nous avons poussé l'étude de la génétique un cran plus loin. En effet, tout ce dont nous venons de parler et tous les travaux réalisés en collaboration avec Len [Pinsky] relevaient de la génétique classique. Prenons, par exemple, un cas où la mère est porteuse d'un gène muté. Le risque de transmission à ses enfants est de 50 %; c'est ce qu'on appelle les « mutations dans la lignée germinale ». Nous, nous avons décidé d'étudier une tout autre forme de

génétique : la génétique somatique.

Nous nous sommes donc penchés non seulement sur les mutations dans la lignée germinale du récepteur des androgènes, mais également sur ses mutations somatiques. Je crois que c'était une bonne idée, car nous savons maintenant que la mutation somatique du récepteur des androgènes joue un rôle crucial dans de nombreuses maladies, la plus importante – et de loin – étant le cancer de la prostate. Il est donc clair que les mutations qui surviennent au cours de la vie – les mutations somatiques – jouent un rôle de tout premier plan dans certaines maladies.

L'étude des mutations dans la lignée germinale et des mutations somatiques dans un même labo représente le scénario idéal, simplement parce que les mutations dans la lignée germinale constituent en fait une perte de fonction. En d'autres mots, ces gens ont un développement sexuel anormal en raison de la perte d'une propriété. Ils devraient avoir un récepteur des androgènes normal qui permettrait un développement normal des caractères sexuels masculins. Si on enlève ça…

Christopher Canning : Le problème est causé uniquement par la mutation d'un gène?

Dr Trifiro : Oui. La perte de ce gène entraîne une perte de fonction, et l'étude structure-fonction d'une mutation perte de fonction est intéressante, parce qu'elle nous permet de connaître la nature de la mutation. Nous avons étudié à fond ces protéines. Nous connaissons la cause du dysfonctionnement protéique.

La mutation somatique est d'une tout autre nature. En effet, les mutations somatiques constituent plutôt un gain de fonction. Les protéines fonctionnent bien, mais acquièrent une nouvelle fonction ou de nouvelles propriétés structurales.

Christopher Canning : Pouvez-vous me donner d'autres exemples de phénotypes qui résultent de ce phénomène?

Dr Trifiro : Bon, si le récepteur des androgènes présente une mutation perte de fonction, il est défectueux. Et les dysfonctionnements sont multiples.

Christopher Canning : Le récepteur des androgènes se trouve dans le cytoplasme, n'est-ce pas?

Dr Trifiro : Oui, et il se lie à la testostérone, une hormone mâle. Il se déplace ensuite vers le noyau, où il régule l'expression d'une multitude de gènes. Nous avons trouvé des mutations à peu près partout – un grand nombre de mutations –, alors la protéine ne peut se lier au ligand. Elle ne peut donc pas se déplacer.

Christopher Canning : Sait-on pourquoi la protéine ne peut se lier au ligand?

Dr Trifiro : Oui. Le domaine de liaison du récepteur des androgènes est une structure tridimensionnelle très complexe. Si une mutation en altère l'architecture, le ligand ne pourra pas s'y adapter et il n'y aura tout simplement pas de fixation.

Il y a donc toutes ces mutations, et des mutations où le ligand se lie parfaitement, mais ne se rend pas au noyau ou n'arrive pas à se lier à l'ADN; il

ne peut pas se lier au gène. Les gènes sont censés être activés, ou le ligand se lie aux gènes, mais ne peut en déclencher l'expression.

Bon, ça, c'est un type de mutation. Les autres, les mutations somatiques, sont bien différentes. Il y a des mutations faux-sens, mais elles sont d'une tout autre nature. L'étude de ces deux types de mutations est un bon exercice de comparaison, parce qu'on a une protéine qui correspond d'un côté à une perte de fonction avec phénotype biologique bien précis, et de l'autre côté – par un mécanisme complètement différent –, à un gain de fonction avec phénotype protéique bien défini; en comparant les deux, on comprend le fonctionnement des protéines. Donc, quand on s'intéresse au fonctionnement des protéines, l'étude d'une seule et même protéine associée à des mutations soit perte de fonction, soit gain de fonction, nous permet de comprendre très bien le fonctionnement des protéines. Et c'est ce qu'on a pu faire en ayant deux sources de mutations : pas seulement des pertes de fonction, mais aussi des gains de fonction.

Christopher Canning : Au début, vos travaux portaient uniquement sur la perte de fonction ?

Dr Trifiro : Oui.

Christopher Canning : Maintenant, vous avez combiné les deux. Est-ce sous l'influence du Dr Pinsky?

Dr Trifiro : Comme je le disais plus tôt, il faut aller là où la science vous porte, et c'est là qu'elle nous a emmenés. C'est là qu'il fallait aller.

Christopher Canning : Nous? Parlez-vous de votre laboratoire ou d'autre chose?

Dr Trifiro : Je parle du laboratoire.

Christopher Canning : Quel genre de liens entreteniez-vous avec les autres membres du groupe? À cette époque, vous travailliez avec Rima Rozen, Roy Gravel, le Dr MacKenzie[JF2], Susie Tenenhouse[MBM3]…

Dr Trifiro : Nous avions des réunions au moins deux ou trois fois par année. Je les aidais à organiser leurs rencontres à l'intention des postdoctorants, alors j'en suis venu à connaître tous leurs postdoctorants et les étudiants aux cycles supérieurs, puisque nous organisions également une rencontre annuelle où les étudiants de notre groupe se réunissaient et présentaient leurs travaux à leurs pairs. C'était intéressant. Notre groupe fonctionnait assez bien.

Christopher Canning : Avez-vous collaboré avec plusieurs autres membres pour la publication d'articles? À l'époque, en quoi consistait votre collaboration?

Dr Trifiro : Comme nous avions… nous sommes tous assez compétitifs dans nos disciplines respectives, et il était parfois difficile de travailler en collaboration. C'était beaucoup plus facile pour certains, parce je pense qu'à un moment donné, trois d'entre eux travaillaient sur le métabolisme du folate, alors d'emblée, ils collaboraient étroitement.

Christopher Canning : Rima Rozen, par exemple?

Dr Trifiro : Oui, et même le Dr MacKenzie[JF4], c'était naturel chez lui. On faisait appel à nous chaque fois qu'il était question de stéroïdes sexuels.

Christopher Canning : Mais vous étiez les seuls à travailler là-dessus?

Dr Trifiro : Nous étions les seuls à travailler sur le récepteur des androgènes et d'autres trucs du genre.

Christopher Canning : Les relations étaient-elles cordiales entre tous les membres du groupe? Et le lieu de travail posait-il problème, surtout que vous, vous travaillez ici, à l'Institut Lady Davis? Pendant les premières années du groupe, le CRM estimait que tous les membres d'un groupe devaient travailler au même endroit, ce qui, de toute évidence, n'était pas le cas à l'époque. Vous souvenez-vous de discussions à ce sujet?

Dr Trifiro : Non, pas en 1990 ni pendant l'année 1995-1996. Je vous aurais répondu « peut-être » si vous m'aviez parlé des années 1960 et 1970, car, à cette époque, il était important que les chercheurs soient regroupés. Ensuite, les modes de communication ont beaucoup évolué et Internet a tout révolutionné. L'échange de documents se fait maintenant à la vitesse de l'éclair. Je crois qu'au début, le fait que les chercheurs soient dispersés était un problème, mais par la suite, absolument pas. C'était très facile, au point où Roy Gravel, qui vivait à Calgary, participait sans problème aux travaux du groupe.

Christopher Canning : Il a dirigé le groupe pendant quatre ans à partir de Calgary.

Dr Trifiro : Ce qui prouve, je crois, qu'il n'est pas absolument nécessaire de regrouper les chercheurs.

Christopher Canning : Qu'en était-il alors de la direction du groupe? À l'époque, quelqu'un dirigeait le groupe; en 2001, ce devait être Rima Rozen. Oh, excusez-moi, donc Roy Gravel était le directeur en 1998, mais il était à Calgary juste avant votre arrivée dans le groupe. Comment cela se traduisait-il pour la direction du groupe? Aviez-vous l'impression que quelqu'un dirigeait le groupe?

Dr Trifiro : Oui, tout à fait. Il y a la personne qui dirige et la notion de direction, plus générale; mais lorsqu'on parle de cette direction, il faut toujours tenir compte de la personne qui l'incarne. Nous ne parlons pas d'un groupe. Nous parlons d'une seule personne, et, à mon avis, lorsque vous parlez d'une personne en particulier, il ne faut jamais généraliser, car chaque personne est différente. Nous étions donc extrêmement privilégiés de compter Roy [Gravel] parmi nous, même si je ne faisais pas encore partie du groupe. Je connais Roy et sa façon de travailler; c'est un gars formidable.

Il aurait pu se trouver en Amérique du Sud et exercer une énorme influence sur le groupe. Ça fait partie de sa personnalité. Sa façon de travailler, de communiquer. Je crois que certaines personnes ont cette faculté d'assumer le rôle de meneur pour faire avancer les choses, et c'est ce qu'il a fait.

Rima [Rozen] était faite de la même étoffe. Elle avait cette même compétitivité, elle était très intelligente, vraiment brillante, elle a pris la relève sans problème!

Christopher Canning : Qu'entendez-vous par « compétitivité »?

Dr Trifiro : Si vous devez livrer concurrence à d'autres chercheurs pendant des années pour obtenir des subventions des IRSC [Instituts de recherche en santé du Canada], vous devez faire preuve de compétitivité et d'ingéniosité, comme Roy Gravel et Rima Rozen, des champions en la matière. Vous les nommez à un poste, vous leur en demandez toujours plus et ils vous en donnent toujours plus. Ils se montrent toujours à la hauteur. Pas de problème!

Christopher Canning : Dans ce groupe, créé par les Drs Scriver et Fraser – des scientifiques respectés au plus haut point – s'attendait-on à ce que les nouveaux membres soient de la même trempe?

Dr Trifiro : D'après moi, les derniers arrivés n'ont probablement pas ressenti autant de pression. Nous entendons encore parler d'eux, mais je peux vous dire que Len [Pinsky], Roy et Rima Rozen en parlaient.

Christopher Canning : De quoi au juste?

Dr Trifiro : Je crois que les Drs Scriver et Fraser étaient des scientifiques dans l'âme et que leur travail était toute leur vie. Ils n'avaient qu'un but dans la vie – se réaliser comme scientifiques – et je crois qu'ils ont un peu déteint sur les chercheurs de la génération suivante.

Christopher Canning : Eux aussi voulaient devenir de bons scientifiques et faire de la recherche fondamentale?

Dr Trifiro : Oui. Ils voulaient également changer les choses et apporter leur contribution à la société grâce à la science.

Christopher Canning : De toute évidence, il était entendu que ces recherches scientifiques devaient contribuer d'une façon ou d'une autre au travail clinique, n'est-ce pas?

Dr Trifiro : Oui, mais le point de départ de leurs recherches scientifiques, c'était le patient.

Christopher Canning : Ils étaient des médecins généticiens, une rareté de nos jours.

Dr Trifiro : Effectivement, on en compte très peu. Nous en avons encore quelques-uns. Mais ils se font beaucoup plus rares…

Christopher Canning : Il y avait le pédiatre et le généticien.

Dr Trifiro : Oui. Ils ont vu le phénotype et se sont dit : « Je me demande pourquoi cet enfant-là a ce phénotype? »

Christopher Canning : C'est exact. Ils avaient un patient et se sont dit : « Ce phénotype-là, je veux le comprendre ». J'imagine que maintenant, les cliniciens vous envoient des phénotypes?

Dr Trifiro : Oui. La génétique est maintenant reconnue. La génétique médicale, la génétique de l'adulte et la génétique pédiatrique sont des disciplines en soi, et les spécialistes sont formés pour ça.

Christopher Canning : Nous avons effleuré le sujet, mais j'aimerais qu'on revienne sur vos travaux sur le récepteur des androgènes. Comment ont-ils contribué ou contribueront-ils peut-être à l'enrichissement de nos connaissances en santé? Qu'en attendez-vous exactement?

Dr Trifiro : Bon, d'abord, mieux comprendre la perte de fonction, alors en présence d'une perte complète de la fonction du récepteur des androgènes…

Christopher Canning : Dans la lignée germinale?

Dr Trifiro : Dans la lignée germinale : l'individu de sexe masculin, génétiquement masculin, présente un phénotype féminin.

Christopher Canning : Génétiquement masculin, mais avec un phénotype féminin?

Dr Trifiro : Oui, un phénotype complètement féminin. Avant, ces personnes naissaient, menaient une vie normale jusqu'à l'âge de 14 ou de 15 ans et s'apercevaient qu'elles n'avaient pas de règles. Elles ne le savaient pas encore, mais elles n'avaient pas de gonades féminines. Elles avaient des gonades masculines.

Christopher Canning : Des testicules.

Dr Trifiro : Oui, des testicules. Ils ne sont pas visibles, mais ils sont bien là et il n'y a pas d'utérus. Pas d'utérus, pas de règles. Alors, à l'époque, on posait le diagnostic beaucoup plus tard et il n'y avait rien à faire.

Ces personnes menaient une vie pleinement satisfaisante malgré leurs anomalies physiques. Bon, ça, c'est une chose.

Christopher Canning : Des anomalies internes?

Dr Trifiro : Oui.

Christopher Canning : Mais extérieurement?

Dr Trifiro : Tout était normal. Dans bien des cas, elles se mariaient, réussissaient dans la vie, adoptaient parfois des enfants; bref, elles avaient une vie normale, mais elles ne pouvaient pas avoir d'enfants.

Et bien souvent, il y a probablement très, très longtemps, on ne parlait pas de ces anomalies. Il y a également l'autre mutation perte de fonction dans la lignée germinale caractérisée par une perte partielle de la fonction du récepteur. C'est un gros problème, parce qu'à la naissance, l'enfant peut avoir des organes génitaux mixtes et devra peut-être subir de nombreuses interventions chirurgicales. Un soutien psychologique sera peut-être également nécessaire.

Christopher Canning : C'est difficile pour les parents, j'imagine, puisqu'ils doivent décider de l'identité sexuelle de leur enfant?

Dr Trifiro : C'est difficile pour les parents et difficile pour l'enfant. Imaginez… L'identité sexuelle est très importante. Quand tu ne sais pas exactement ce qui se

passe… Tout ça pour dire qu'à l'arrivée de la génétique moléculaire, nous avons pu cerner le problème et séquencer le gène du récepteur des androgènes. Nous avons pu mettre en évidence une mutation dans une famille donnée. Pour la toute première fois, nous pouvions dire : « Vous, vous êtes porteur; vous, vous ne l'êtes pas; vous, vous l'êtes; vous, vous ne l'êtes pas; et vous, vous pouvez devenir enceinte. » Nous pouvions dire si le fœtus était touché ou non.

À partir de ce moment-là, nous avions prise sur le résultat. Comment, me direz-vous? D'accord, nous parlons de la possibilité de recourir à l'avortement, mais cette intervention doit être pratiquée très tôt au cours de la grossesse et soulève de nombreuses questions d'ordre éthique. Nous n'avons jamais abordé les questions éthiques, parce qu'elles doivent faire l'objet de discussions entre la patiente et son médecin traitant. Or, nous ne sommes pas les médecins traitants : notre rôle se limite à fournir à l'équipe soignante les renseignements dont elle a besoin. Je sais que les membres de cette équipe prendront la bonne décision, mais ils ont besoin de cette information.

Nous pouvions maintenant agir pour vrai sur cette maladie dans la population. En fait, je crois qu'en 2010, il est fort probable que tous les porteurs de ce syndrome de résistance complète aux androgènes aient été identifiés, ou du moins la vaste majorité d'entre eux.

Christopher Canning : Et tout ça en une vingtaine d'années seulement. Pas mal!

Dr Trifiro : Oui, nos travaux ont eu une très large portée.

Christopher Canning : C'est le moins qu'on puisse dire.

Dr Trifiro : Malgré les aspects éthiques. Qui fera quoi?

Christopher Canning : Il s'agit donc d'un seul et unique trouble génétique?

Dr Trifiro : S'il y a un porteur, les plus récentes technologies nous permettent maintenant de prélever l'ADN du fœtus à l'âge de huit semaines, le plus tôt possible, et de déterminer si ce dernier est atteint ou non du syndrome.

Christopher Canning : J'imagine qu'il n'y a pas moyen d'administrer un traitement pendant la grossesse?

Dr Trifiro : Nous savons qu'en présence de certaines mutations, le récepteur demeure en partie fonctionnel. Avec un peu de chance, l'administration de fortes doses d'hormones mâles peut se révéler efficace.

Christopher Canning : Vous injectez de la testostérone et, peut-être…

Dr Trifiro : On l'injecte à un très jeune sujet, et l'enfant peut grandir…

Christopher Canning : Mais cela ne permettra jamais de corriger la mutation, n'est-ce pas?

Dr Trifiro : Jamais. La seule façon de corriger une mutation dans la lignée germinale est d'essayer de l'empêcher de parvenir à maturité. C'est vraiment la seule façon.

Voilà pour les mutations perte de fonction.

Christopher Canning : Parfait! Vous avez abordé ce sujet tout à l'heure, mais j'aimerais y revenir. J'ai obtenu un document qui date des années 1980 dans lequel on soulève certaines préoccupations au sujet de la compétitivité du groupe en biologie moléculaire. Je me demande si ces préoccupations étaient là après le mandat de Charles Scriver, lorsque la biochimie et la cytogénétique avaient le vent dans les voiles.

Vous avez observé ça de façon générale, mais était-ce le cas dans le groupe?

Dr Trifiro : Non, certains chercheurs du groupe n'ont pas fait le saut vers la biologie moléculaire. Charles Scriver était encore dans la biochimie. Les chercheurs avaient raison d'être préoccupés, parce que le CRM/IRSC et les organismes subventionnaires privilégiaient toujours les domaines de pointe. C'est donc un peu plus ardu si tu n'es pas dans un domaine de pointe. Je ne dis pas que c'était impossible d'obtenir des subventions, c'était juste un peu plus difficile.

Bien sûr, les chercheurs étaient préoccupés. Il y a eu une véritable révolution sur une période d'environ huit ans.

Pendant mon passage à Harvard – j'y étais en 1981 – un vent de panique soufflait déjà. Les scientifiques venaient de cloner un gène de l'insuline. Le tout premier clonage d'un gène avait eu lieu en 1979; donc, en l'espace de deux ans…

Christopher Canning : Il s'est produit une véritable explosion technologique, parce qu'à partir de ce moment-là, on pouvait coder le gène.

Dr Trifiro : Exactement.

Christopher Canning : Existait-il des divisions dans le groupe entre les scientifiques fondamentaux et cliniques? Y avait-il des membres qui estimaient qu'il aurait fallu faire plus de recherche fondamentale?

Dr Trifiro : Non, je ne pense pas. Je crois que tout le monde était convaincu que nous faisions de la recherche avec toute la rigueur voulue. Seulement, nous travaillions dans un univers concurrentiel. Nous devions encore rédiger des demandes de subventions octroyées par voie de concours. Et pour que ces demandes soient acceptées, il était assez clair selon moi qu'il fallait intégrer de nouvelles technologies dans le groupe.

Christopher Canning : Effectivement! Dans une demande de subvention du début des années 1990, vous mentionniez que le groupe avait atteint un nouveau niveau d'interdisciplinarité en science. Pourriez-vous nous parler davantage de cette interdisciplinarité? D'après ce que plusieurs disent, il s'agissait là de l'un des principaux objectifs du projet, non?

Dr Trifiro : Je ne sais pas ce qu'ils entendent par « interdisciplinarité ». Vous voulez dire dans le groupe lui-même?

Christopher Canning : Oui, dans le groupe lui-même. Il y avait la génétique des cellules somatiques, la génétique biochimique et physiologique, et la biologie moléculaire, notamment.

Dr Trifiro : Ouais, je pense que ça s'explique par… je ne me souviens pas des détails, peut-être qu'il y a un ou deux… je me demande quand Rima s'est jointe au groupe?

Christopher Canning : C'était en 1987, si je ne m'abuse.

Dr Trifiro : D'accord. D'autres chercheurs se sont-ils joints au groupe à cette époque?

Christopher Canning : De nouveaux membres?

Dr Trifiro : Oui, car il manquait seulement un chercheur bien établi pour changer un peu la façon dont les choses se présentaient.

Christopher Canning : Il semble que Rima Rozen ait été recrutée à titre de biologiste moléculaire.

Dr Trifiro : Oui, c'est là où je veux en venir. Je crois que c'est ce à quoi les gens font allusion. Le recrutement de Rima Rozen prouvait que le groupe avait atteint… à tout le moins, il comptait une recrue rompue à de nouvelles techniques qui faisait souffler sur l'équipe un vent d'innovation.

Cela ne veut pas dire que les autres membres de l'équipe se traînaient les pieds. Croyez-moi, Robert MacKenzie est l'une des personnes qui m'ont le plus influencé dans la vie. Souvenez-vous, j'étudiais la biochimie, et il était un de mes professeurs. Son cours de biochimie était formidable. Il y avait trois professeurs d'exception, qui avaient vraiment la vocation. C'est quelque chose que je n'oublierai jamais, et quand je dis que je leur dois une fière chandelle, je suis on ne peut plus sincère, parce que s'ils n'avaient pas été là, je ne me serais probablement pas dit : « Bon, moi, c'est ça que je veux faire ». Leur passion était contagieuse.

Christopher Canning : Fantastique. J'aimerais vous poser encore quelques questions. À votre avis, à quoi tient la longévité du groupe? Aucun groupe de recherche en santé n'a été actif pendant aussi longtemps au Canada… 37 ans.

Dr Trifiro : Vous savez, cette longévité pourrait fort bien venir des deux fondateurs, qui ont su inculquer ce besoin profond de savoir à ceux qui les ont suivis. Des géants comme eux peuvent exercer une influence durable sur deux ou trois générations de chercheurs, et je crois que c'est ce qui est arrivé… tout cela a déteint sur les chercheurs de l'époque, notamment sur Len [Pinsky]. Par la suite, Len a déteint sur moi, et ainsi de suite pendant… combien de temps, déjà?

Christopher Canning : Trente-sept ans.

Dr Trifiro: Trente-sept ans.

Christopher Canning : De 1972 à 2009, et d'après ce que j'ai cru comprendre, la seule raison pour laquelle il n'a pas obtenu de subvention, c'est qu'on a cessé de financer des groupes pour octroyer plutôt des subventions d'équipe.

Dr Trifiro : C'est vrai, ils sont passés aux subventions d'équipe.

Christopher Canning : Oui, la structure est un peu différente. À votre avis, quel était le ciment de ce groupe? Je pose cette question simplement parce que le CRM et les IRSC ont de multiples façons de définir un groupe. Vous faites le même type de recherche interdisciplinaire, vous travaillez ensemble, vous avez des réunions, mais selon votre expérience, quel était le ciment du groupe? En d'autres mots, qu'est-ce qui faisait de cet ensemble de personnes un véritable groupe?

Dr Trifiro : Je crois que c'était avant tout le niveau exceptionnel de la recherche. Tout le monde faisait un travail formidable. Il y avait en outre un très bon équilibre entre jeunes chercheurs et chercheurs chevronnés. La génétique était au cœur des activités, mais il y avait toutes sortes de patients. Il y avait tous ces troubles médicaux à étudier. Comme vous le savez, un généticien peut étudier un gène sans jamais savoir quelle est son incidence clinique, mais je crois que dans le cas qui nous occupe, il était clair que le point de départ était un problème clinique sur lequel se penchaient des généticiens de premier ordre.

Je crois que tous les chercheurs respectaient le travail de leurs collègues. Ces trois ou quatre facteurs ont contribué à faire de cet ensemble de scientifiques un véritable groupe. Et nous avions tous à cœur, véritablement, de découvrir des gènes responsables de phénotypes cliniques.

Christopher Canning : Dans l'ensemble, croyez-vous que le groupe est une réussite sur ce plan?

Dr Trifiro : Absolument! Et ce n'est probablement pas un hasard si c'est arrivé à McGill : McGill, c'est une grande université qui regroupe un tas de gens. S'il y a une université où un groupe dynamique pouvait s'établir et durer, c'est probablement McGill, parce que ses départements sont riches d'expertises et de compétences diverses. Nous ne travaillons pas en vase clos et nous disposons d'un effectif très important. Il est donc logique que ce soit arrivé à McGill, surtout que nous avions ces deux brillants scientifiques, ces véritables pionniers de la génétique au Canada. La conjoncture était bonne.

Christopher Canning : Bien dit. Les astres étaient favorables. Vous avez ensuite recruté tout ce monde pour tirer pleinement parti de ces atouts-là?

Dr Trifiro : Oui, et c'était bien clair pour tout le monde que si vous vous joigniez au groupe, vous deviez faire acte de présence et vous montrer à la hauteur des attentes du groupe. Pas de doute là-dessus.

Christopher Canning : Il est arrivé que des membres du groupe ne soient pas réinvités, parce que, pour diverses raisons, ils n'avaient pas obtenu de subvention du CRM ou ne publiaient pas assez d'articles?

Dr Trifiro : En fait, c'était surtout le CRM. Je pense que le financement… Tous les cinq ans, ils nous répétaient que le financement allait augmenter, mais le fait est qu'il n'a jamais été suffisant. Et même lorsqu'ils ont créé les IRSC, qui était censé… ils nous ont promis mer et monde… ils nous ont promis la fin de la disette. La réduction des subventions, c'est fini, disaient-ils; et au bout de trois ans seulement, ils ont brisé leurs promesses, et les concours de subventions,

les bourses salariales et les trucs du genre ont commencé.

Christopher Canning : Alors ça n'a fait qu'exacerber la compétition, et certains ont tout simplement mordu la poussière?

Dr Trifiro : Et ça continue; d'après moi, cette année, la compétition sera plus féroce que jamais dans les concours des IRSC.

Christopher Canning : C'est difficile parce qu'il y a de nombreuses demandes et moins de réponses?

Dr Trifiro : Moins de réponses et de trois à quatre fois plus de demandes. C'est fou. C'est comme ça dans beaucoup de domaines, apparemment.

Christopher Canning : Ouais, partout.

Dr Trifiro : Ah, l'argent…

Christopher Canning : Il ne me reste que quelques questions. Au symposium de novembre dernier, le Dr Scriver a soulevé un point très intéressant, et j'aimerais savoir ce que vous en pensez. Il a dit que le groupe avait toujours fonctionné comme une organisation de base, dans le sens où l'évolution était toujours venue de la base. Partagez-vous sa vision des choses? Est-ce ainsi que vous voyez l'histoire du groupe et votre rôle dans le groupe?

Dr Trifiro : C'est un peu difficile de parler des débuts du groupe, mais selon ce que Len [Pinsky] et lui en disaient, c'est comme ça qu'il verrait les choses. C'est beaucoup plus le Département de génétique que l'Université qui a mis le groupe sur pied.

Christopher Canning : En fait, ils ont créé leur propre département de génétique!

Dr Trifiro : Oui, ce sont eux qui ont créé le département, et non l'inverse.

Christopher Canning : Exactement.

Dr Trifiro : Le groupe a grandi et a duré grâce à trois ou quatre personnes qui avaient la perspicacité, l'esprit visionnaire et assez de caractère pour affirmer : « Vous savez quoi, nous devrions former un groupe ». Pas l'inverse. Ce n'est pas le Département de génétique qui a dit : « Vous savez quoi? C'est un concours pour les groupes. Soumettons notre candidature ». Non! Ce sont ces trois ou quatre personnes qui ont dit : « Nous allons former un groupe, c'est ce type de groupe là que nous voulons et ça va marcher rondement ». Nous allons travailler ensemble. Même que le groupe a probablement été mis sur pied avant l'avènement des demandes de subventions de groupe.

Christopher Canning : En fait, la première subvention de groupe a été accordée à l'Université de Montréal en 1968, à une équipe de neurosciences. Le groupe de McGill a donc vu le jour au tout début du programme de subventions de groupe.

Dr Trifiro : Donc, dans l'histoire du groupe… Len en parlait très souvent. Et s'il y a une chose que je retiens de tout ce qu'il m'a dit, c'est que ce groupe-là est né sur l'initiative de ses membres fondateurs et non du Département de génétique.

Christopher Canning : Bien! Qu'en est-il de vos recherches? J'aimerais en savoir davantage sur vos travaux sur le cancer de la prostate. Avez-vous fait d'autres avancées récemment?

Dr Trifiro : Pour donner suite à nos travaux sur les mutations perte de fonction, nous avons étudié les mutations gain de fonction qui, comme leur nom l'indique, apportent quelque chose de nouveau à une protéine donnée. La mutation lui fait faire quelque chose qu'elle ne ferait pas normalement. Ce qui ne veut pas nécessairement dire qu'elle la prive de ses fonctions normales : c'est plutôt qu'elle lui en confère de nouvelles. Dans le cas du récepteur des androgènes, nous avons vu des mutations gain de fonction incroyables.

Voici le topo : en plus de recevoir les hormones mâles et de faire tout son travail, le récepteur des androgènes reçoit plusieurs autres classes de stéroïdes. Donc, disons que tu es une cellule du cancer de la prostate, te voilà promise à une croissance et à une prolifération soutenue.

Christopher Canning : Il reçoit plus d'hormones? Et des hormones, il y en a beaucoup.

Dr Trifiro : Des hormones, il y en a à la tonne.

Christopher Canning : Donc, le récepteur favorise la croissance cellulaire.

Dr Trifiro : Il s'en donne à cœur joie, en fait.

Christopher Canning : Oui, il se gorge d'énergie et contribue à la croissance des cellules cancéreuses de la prostate?

Dr Trifiro : Oui. Et le pire dans tout ça, c'est qu'à une époque, on avait l'habitude de prescrire des antiandrogènes, vous vous souvenez? Eh bien, pour ces mutants, ces antiandrogènes étaient non pas des antiandrogènes, mais bien des androgènes puissants.

Donc, tu donnes un médicament à quelqu'un pour bloquer le récepteur, mais ces mutations te jouent un vilain tour. Elles voyaient arriver l'antiandrogène et se disaient : « Ah, un antiandrogène… super! ».

Christopher Canning : Vous a-t-on octroyé des fonds récemment pour ces travaux?

Dr Trifiro : Oh oui, alors nous y consacrons une bonne partie de notre temps.

Christopher Canning : Bien! C'est donc là-dessus que vous travaillerez pendant un certain temps?

Dr Trifiro : Oui, je crois. En ce qui a trait aux mutations perte de fonction, je crois que nous avons fait le tour de la question. Je ne pense pas que nous puissions aller plus loin. Nous avons cerné le problème, nous en connaissons les facteurs génétiques et nous avons terminé l'étude des protéines. Nous savons maintenant pourquoi la protéine ne fonctionne pas au niveau moléculaire. Nous pouvons difficilement faire plus.

Christopher Canning : Quels seront vos prochains axes de recherche?

Dr Trifiro : Quels seront nos prochains axes de recherche? Les mutations gain de fonction… dans ce cas, nous n'avons pas encore fait le tour de la question. Nous ne connaissons pas toutes les mutations. Il en existe probablement une longue liste, et nous ne connaissons pas encore les propriétés des autres gains de fonction. Nous avons encore beaucoup de pain sur la planche.

Christopher Canning : Bien. Alors voilà, je n'ai plus de questions. Aimeriez-vous ajouter quelque chose?

Dr Trifiro : Non, mais j'aimerais remercier Rima, qui a eu cette idée. Ou Roy… je n'arrive pas à me rappeler qui a eu l'idée. En fait…

Christopher Canning : De réaliser une étude sur ce groupe?

Dr Trifiro : L'idée d'étudier le groupe. Je me souviens, c'était une conversation intéressante. Nous nous disions qu'il fallait faire quelque chose, parce que c'était la fin. Quelqu'un – je crois que c'était Roy – a eu l'idée. Quoi qu'il en soit, c'est une excellente idée. J'espère que les gens – l'Université – mesureront la somme de travail que ce groupe – chacun de ses membres – a accompli; un travail colossal et un dévouement sans borne.

J'aimerais remercier personnellement Len Pinsky pour l'aide qu'il m'a apportée. Il a également exercé une grande influence sur le groupe. Cette rétrospective est une excellente initiative. En regardant les tendances actuelles en science, je me dis qu'on pourrait en tirer de précieux enseignements.

La recherche universitaire a toujours reposé sur le principe voulant que le chercheur doive faire ses preuves. Mais la science ne fonctionne plus comme ça. Elle est de plus en plus interdisciplinaire, et les percées ne peuvent plus être le fait d'un seul chercheur qui travaille en vase clos. À mon avis, on ne devrait pas évaluer le travail individuel d'un chercheur, parce que ce n'est pas ça qui fait avancer la science. C'est le travail en équipe qui mène aux progrès scientifiques. C'est tout de même assez ironique qu'ils aient cessé d'octroyer des subventions d'équipe.

Christopher Canning : En effet, ils ont remplacé les subventions de groupe par les subventions d'équipe.

Dr Trifiro : Mais ils devront revenir aux subventions de groupe, parce qu'il y a beaucoup de pression du côté des nanotechnologies. Il faut que les scientifiques se mettent à l'heure de la modernité et ça, ça veut dire des mégagroupes et des mégaéquipes qui font de la mégascience.

Christopher Canning : Plus nous en savons, plus il faut collaborer, on dirait bien.

Dr Trifiro : Absolument!

Christopher Canning : Parfait.

Dr Trifiro : En terminant, permettez-moi de vous remercier.

Christopher Canning : C’est moi qui vous remercie!

FIN DE L’ENTRETIEN

Dr Andrew Karaplis, le 30 novembre 2010

Christopher Canning : Nous sommes le 30 novembre 2010. Ici Christopher Canning en compagnie du Dr Andrew Karaplis. Dr Karaplis, je suis honoré de pouvoir m'entretenir avec vous de deux grands sujets qui touchent la génétique humaine.

J'aimerais d'abord que nous parlions de votre formation, qui a contribué à l'avancement de la médecine génétique au Canada. Ensuite et surtout, je m'intéresse à votre participation au groupe sur la médecine génétique des IRSC[1] – anciennement le CRM[2] –, dont vous avez été membre de 1998 à 2009 si je ne m'abuse, soit jusqu'à son démantèlement.

Mais parlons d'abord de vous, si vous le voulez bien. Pouvez-vous nous parler de votre lieu de naissance et de votre enfance?

Dr Karaplis : J'ai 55 ans et j'en aurai 56 le mois prochain. Je suis né en 1954 à Athènes, en Grèce, et ma famille a immigré au Canada en 1966. Nous avons fait le voyage en bateau. Après une traversée de 14 jours, nous sommes arrivés au Quai 21 de Halifax, aujourd'hui devenu un lieu historique. De là, on nous a fait monter à bord d'un train qui nous a menés à Montréal. Nous avons vécu à peu près six mois entassés à 14 dans un petit appartement du « ghetto » du Bas-Outremont, jusqu'à ce que nous puissions louer notre propre appartement.

Mon père était mécanicien d'automobiles et ma mère, travailleuse d'usine. Ils ont travaillé tous les deux jusqu'à leur retraite. Mon frère et moi avons fait notre primaire à l'école Guy-Drummond et notre secondaire à la Outremont High School. J'ai choisi les sciences, puis la médecine. Mon frère est devenu ingénieur et, à 58 ans, il est maintenant retraité et vit en Grèce. Il a eu un très beau parcours.

J'ai commencé par étudier en physique. Je suis entré à McGill en 1972, à l'époque où McGill avait un cégep, puis j'ai fait un baccalauréat en biochimie, toujours à McGill. Par la suite, j'ai commencé à faire de la recherche fondamentale en endocrinologie à l'Hôpital Royal Victoria; à cette époque, le laboratoire était dirigé par Sam Solomon.

Christopher Canning : Bien. Avant de parler davantage de votre formation, je m'interroge sur les attentes de vos parents, eux qui étaient des immigrants de première génération.

Dr Karaplis : Eh bien, leurs attentes reflétaient les raisons qui poussaient une famille comme la nôtre à venir s'établir au Canada. Mon père avait alors 42 ans et ma mère, 38. À l'époque, la Grèce était ni plus ni moins en ruines après quatre années d'occupation, suivies de quatre années de guerre civile.

La Grèce devait se rebâtir. Tout comme d'autres Grecs, mes parents sont partis pour le bien de leurs enfants. Les quatre principaux pays vers lesquels se dirigeaient les émigrants grecs étaient le Canada, les États-Unis, l'Australie et l'Afrique du Sud.

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

Christopher Canning : D'accord.

Dr Karaplis : L'Australie, c'était trop loin. En Afrique du Sud, ça bougeait pas mal à l'époque. Mes parents ont donc opté pour le Canada. C'est comme ça que nous nous sommes retrouvés ici. Les gens voulaient simplement offrir à leurs enfants une bonne formation, se faire une bonne vie ici, puis un jour, retourner en Grèce. Je pense que la plupart des immigrants venus de Grèce à l'époque avaient l'intention d'y retourner un jour. Mais ils se sont trop habitués à leur nouvelle vie et ont continué leur petit bonhomme de chemin. Plus le temps passe, plus c'est difficile de retourner dans sa patrie.

Christopher Canning : Et est-ce que les choses se sont bien passées à l'école lorsque vous êtes arrivé à Montréal?

Dr Karaplis : Disons qu'il n'y a pas eu de surprise. Je me rappelle avoir commencé en cinquième année. En Grèce, je n'avais pas fini ma sixième année, parce que nous sommes partis en plein milieu de l'année scolaire. Ici, ils m'ont reculé d'une année, parce que je ne parlais pas un mot d'anglais ni de français. D'ailleurs, lorsque nous sommes arrivés à Montréal, nous ne savions pas du tout qu'il y avait une communauté anglophone et une autre francophone.

Nous sommes simplement allés nous inscrire à l'école la plus près, à trois rues de chez nous. C'était une école catholique francophone, et nous avons été accueillis par une sœur. La première chose qu'elle nous a demandée est : « Êtes-vous catholiques? ». Devant notre réponse négative, elle nous a dit : « Eh bien, je suis désolée, mais vous ne pouvez pas venir ici. Vous devez aller à l'autre école un peu plus loin, là où vont », et je cite, « les Juifs, les protestants et les autres immigrants ».

Christopher Canning : Wow!

Dr Karaplis : Eh oui. J'ai donc appris l'anglais au lieu du français.

Christopher Canning : Je vois.

Dr Karaplis : Je me suis retrouvé dans la classe des « nouveaux Canadiens », où Mlle Gilmore nous enseignait l'anglais.

Christopher Canning : Vous vous rappelez cette époque?

Dr Karaplis : Ce sont des choses qu'on n'oublie pas. Peu importe ce qui nous arrive dans la vie, on n'oublie pas des choses comme celles-là. Au bout d'un an et demi, je gagnais presque tous les prix à l'école.

Christopher Canning : Même si vous ne parliez pas anglais?

Dr Karaplis : Même si je parlais à peine anglais, oui. En fait, à la fin du secondaire, j'ai remporté la médaille d'or du gouverneur.

Christopher Canning : Wow!

Dr Karaplis : Puis je suis entré au cégep, mais malheureusement, je ne travaillais pas très fort. J'étais un ado, alors j'avais probablement d'autres intérêts.

Christopher Canning : C'est ce qu'il y a de bien au cégep [inaudible].

Dr Karaplis : Oui, il y a de la souplesse.

Christopher Canning : Les étudiants peuvent choisir leur programme.

Dr Karaplis : C'est vrai. Sauf qu'à l'époque, je ne savais pas du tout vers quoi me diriger. Et vous savez, les immigrants n'avaient personne vers qui se tourner, quelqu'un qui pouvait leur dire où aller et comment procéder. Alors, je me suis retrouvé en physique. Mais je n'aimais pas ça et après une session, j'ai opté pour les sciences biologiques, puis la biochimie et le baccalauréat en biochimie, que j'ai obtenu en 1977. Ensuite, j'ai commencé à faire de la recherche à l'Hôpital Royal Victoria. J'en ai fait pendant une année, mais je détestais ça.

Christopher Canning : Vraiment?

Dr Karaplis : Après un an, absolument. C'est à ce moment que je me suis dit : « Ce n'est pas pour moi. Je vais essayer d'entrer en médecine ».

Christopher Canning : D'accord.

Dr Karaplis : J'ai donc envoyé ma demande et j'ai été accepté. Mais j'ai finalement reporté d'un an mon entrée en médecine, parce que les choses commençaient à débloquer pour moi au labo et j'aimais davantage la recherche. J'ai donc décidé de faire mon doctorat. J'ai fait de la recherche fondamentale pendant deux ans. Ensuite, je suis entré en médecine et j'ai terminé mes travaux de recherche pendant les week-ends et les vacances d'été en faisant ma scolarité de médecine. J'ai rédigé ma thèse pendant ma résidence en médecine interne.

Christopher Canning : Si je comprends bien, vous meniez les deux de front?

Dr Karaplis : C'est ça, j'ai fait mes études de médecine et mon doctorat en même temps. Le programme MDCM-Ph. D. de McGill n'existait pas à l'époque.

Christopher Canning : Sur quoi portait votre doctorat? Étiez-vous encore en biochimie?

Dr Karaplis : Je travaillais avec Bill Powell, dont le laboratoire faisait partie du groupe de Sam Solomon. Il revenait tout juste de Suède, où il avait fait son postdoctorat. J'ai été son premier étudiant aux cycles supérieurs. J'ai passé deux ans à ses côtés, durant l'été et les week-ends, pendant mes études en médecine. Nos travaux portaient sur les prostaglandines, plus précisément sur les récepteurs de la prostaglandine E.

Christopher Canning : Donc, à ce moment-là, vous vouliez être à la fois médecin et chercheur?

Dr Karaplis : Oui.

Christopher Canning : Et comment êtes-vous passé de la résidence à votre premier poste postdoctoral?

Dr Karaplis : Eh bien, je savais que je voulais aller en endocrinologie. La régulation hormonale, ça m'avait toujours intéressé. Alors, j'ai suivi ma voie.

Christopher Canning : Oui, bien sûr.

Dr Karaplis : Je devais faire ma résidence en médecine interne, et je l'ai faite ici, à l'Hôpital général juif, pendant trois ans. Ensuite, j'ai fait mon *fellowship* en endocrinologie à l'Hôpital Royal Victoria. C'est à ce moment-là, je pense, que j'ai choisi l'endroit où j'allais faire mes études postdoctorales. Vous voyez, les deux années de *fellowship* en endocrinologie comprenaient un an et quatre mois de formation clinique, et huit mois de recherche. C'est le Dr David Goltzman qui m'a aiguillé. Un jour, nous faisions de la clinique ensemble; il s'est approché et m'a dit : « On vient de faire une découverte intéressante dans le domaine du calcium : es-tu au courant? ». Il faisait de la recherche dans ce domaine. « Nous avons découvert une protéine : le peptide apparenté à la PTH[3]. »

Christopher Canning : Je vois ça sur votre C. V.

Dr Karaplis : Oui. Cette protéine a été découverte en 1987 ou 1988. C'était intéressant, parce qu'elle provoque l'hypercalcémie liée au cancer. Elle est sécrétée par les cellules cancéreuses et elle élève le taux sanguin de calcium. Le Dr Goltzman m'a donc proposé de passer mes huit mois de recherche avec lui, en recherche fondamentale. J'y ai vu un défi, parce que la biologie moléculaire m'intéressait. À l'époque, c'était relativement nouveau.

Christopher Canning : La biologie moléculaire était alors en plein essor, non?

Dr Karaplis : Je crois au destin, je pense bien. J'étais tout simplement au bon endroit, au bon moment. David Goltzman m'a dit : « Je vais t'envoyer à l'Institut de recherche en biotechnologie du CNRC[4]. J'ai un collaborateur là-bas, Denis Banville; un scientifique hors pair. C'est un grand spécialiste de la biologie moléculaire, et il t'apprendra tout ce que tu dois savoir sur le sujet. »

Christopher Canning : Et nous sommes en quelle année exactement? 1987?

Dr Karaplis : Fin de 1988.

Christopher Canning : Ces travaux s'inscrivaient donc dans votre *fellowship* en endocrinologie?

Dr Karaplis : Exactement. Je suis donc allé au CNRC. J'ai rencontré Denis et au fil des mois, nous avons développé une solide amitié. Malheureusement, il est aujourd'hui décédé. Il m'a tout appris en biologie moléculaire; c'était un scientifique de grand talent. Je me rappelle de ma première journée dans son labo. Il m'a demandé de séparer un échantillon d'ADN sur gel. Je n'arrivais pas à déterminer où placer les électrodes positive et négative pour séparer l'ADN. Il m'a regardé et a lancé : « Bon, encore un étudiant en médecine. On n'est pas sorti de l'auberge. » Je pense qu'à ses yeux, la place d'un médecin n'était pas dans un labo de recherche fondamentale.

[3] Parathormone
[4] Conseil national de recherches du Canada

Christopher Canning : Ça tiraille donc un peu entre les cliniciens et les chercheurs?

Dr Karaplis : Oh oui, ça a toujours été comme ça et c'est encore le cas aujourd'hui. Et vous savez, notre plus grand défi, c'est d'essayer de concilier tout ce beau monde.

Christopher Canning : J'aimerais que nous nous attardions un peu là-dessus, parce que je pense que pendant des années, le groupe s'est employé à mettre fin à ce schisme.

Dr Karaplis : Effectivement, ça a été et c'est encore l'un de nos plus grands défis.

Christopher Canning : J'aimerais que nous y revenions, si vous le voulez bien?

Dr Karaplis : Oui, bien sûr. Malgré mes lacunes en techniques de laboratoire, nous avons réussi à publier deux articles en huit mois, ce qui était un petit exploit, je crois bien. Je pense qu'à ce moment-là, Denis s'est rendu compte que finalement, le médecin n'était pas complètement dépourvu de talent. Et il en était fort aise, je crois.

Quand j'ai finalement demandé au Dr Goltzman quel était le meilleur endroit pour mon postdoctorat, il m'a dit : « Je pense que tu devrais aller à Boston. Il y a un gros groupe qui travaille sur le calcium là-bas, et ces gens-là vont t'apprendre tout ce que tu dois savoir. » J'ai donc fait mes bagages et pris la direction de Boston avec mon fils de deux ans, Chris, et ma femme, pour y parfaire ma formation pendant trois ans.

Christopher Canning : En biologie moléculaire?

Dr Karaplis : Oui, exactement. Ils commençaient eux aussi à travailler dans ce domaine et étaient très intéressés.

Christopher Canning : C'est donc l'histoire du biochimiste qui se transforme en biologiste moléculaire?

Dr Karaplis : Oui, j'imagine. En fait, j'ai reçu là l'essentiel de ma formation en biologie moléculaire.

Christopher Canning : Si je comprends bien, on utilisait ces techniques d'ADN à la fin des années 1970?

Dr Karaplis : Oui, dans ces années-là. Mais leur utilisation en biologie chez les mammifères est venue un peu plus tard. Chose certaine, on n'en était pas encore tout à fait là, parce que pendant ma formation, je n'ai pas du tout été exposé à ça. Bref, ma famille s'est installée à Boston et je me suis retrouvé dans le laboratoire de Hank Kronenberg. Hank Kronenberg est l'une des personnes les plus intelligentes que j'ai rencontrées dans ma vie.

Cet homme est un puits de science. Il est tout simplement brillant. Mais à l'époque, ses travaux n'allaient pas dans la bonne direction. Sa subvention des NIH[5] n'avait pas été renouvelée. Il n'étudiait pas le peptide apparenté à la PTH, mais plutôt le traitement de la PTH. Nous avons donc perdu du temps à

[5] National Institutes of Health

déterminer à quel type de projet j'allais me consacrer. Puis il y a eu un autre coup du sort, je dirais. Nous étions en train de dîner au labo de l'Hôpital général du Massachusetts. Pendant l'heure du dîner, on diffuse à la télé des exposés présentés dans d'autres établissements; on peut donc s'asseoir là pour manger et voir ce qui se fait ailleurs sans devoir se déplacer d'un bout à l'autre du campus.

Toujours est-il que nous regardions ensemble un exposé de Bruce Spiegelman sur l'adipsine, une protéine qui intervient dans la différenciation des adipocytes; il commençait alors à utiliser la technique d'inactivation de gène chez la souris.

Christopher Canning : Pouvez-vous être plus précis?

D[r] Karaplis : On détruit un gène ciblé du génome de la souris pour étudier les effets de ce gène sur le développement de l'animal.

Christopher Canning : C'est-à-dire quelles protéines seront produites ou non après l'inactivation du gène?

D[r] Karaplis : Oui, c'est-à-dire si on inactive telle protéine, qu'arrivera-t-il à l'animal? Il s'agit au fond d'étudier le phénotype, puis les mécanismes moléculaires sous-jacents.

Christopher Canning : Ah, c'est bon, je comprends.

D[r] Karaplis : Alors, j'ai dit : « C'est très intéressant. Ce serait super de pouvoir inactiver le peptide apparenté à la PTH, parce que même si nous savons qu'il est produit par les cellules cancéreuses, nous n'avons aucune idée de sa fonction physiologique. »

Hank Kronenberg m'a répondu : « Je n'ai jamais étudié cette protéine et je ne suis pas sûr de vouloir m'aventurer là-dedans, mais si ça t'intéresse vraiment, je pourrais trouver la personne qui produit ces souris *knockout* ici et te mettre en rapport avec elle. »

C'est ainsi que j'ai atterri au MIT[6], dans le laboratoire de Richard Mulligan. Il y avait là un chercheur postdoctoral, Victor Tybulewicz, qui faisait du ciblage génétique et obtenait de bons résultats. Je pense qu'il travaillait alors à son premier article. Mais il avait du mal à produire une deuxième souris *knockout*.

Lorsque Victor a su que j'avais une formation en médecine, il s'est, comme tous les autres, demandé ce qu'un médecin pouvait bien faire dans son labo. Au début, il hésitait beaucoup à me montrer quoi que ce soit.

Christopher Canning : Mais pourquoi les chercheurs fondamentaux étaient-ils si craintifs? Ou serait-ce plutôt des réserves?

D[r] Karaplis : Selon moi, ils ont l'impression que nous, les cliniciens, n'avons pas la formation qu'il faut pour faire de la recherche fondamentale avec toute la rigueur voulue. Je ne pense pas que ce soit de la crainte. C'est plutôt le principe du « chacun son métier et les vaches seront bien gardées ». Mais je dois dire qu'après

[6] Massachusetts Institute of Technology

m'avoir vu travaillé, il s'est ravisé, et nous sommes devenus de bons amis. C'est souvent comme ça.

Alors, Victor et moi avons commencé à explorer diverses techniques pour mettre au point une méthode d'inactivation de gène qui soit reproductible. Nous défrichions le terrain. Par exemple, nous ne savions pas quelles cellules souches embryonnaires utiliser. Nous ne savions pas quelles cellules nourricières utiliser. Nous ne savions pas quelle était la meilleure façon d'insérer l'ADN à l'intérieur des cellules souches embryonnaires. Tout était à faire. Ce fut, je dois le dire, une période très difficile pour ma famille et moi. Je n'étais pour ainsi dire jamais à la maison : je passais ma vie au labo.

Finalement, nous nous sommes rendu compte que la mutation étudiée ne se transmettait pas dans la lignée germinale à cause des cellules nourricières que nous utilisions. Nous avons donc changé de cellules nourricières, et les choses se sont replacées.

Christopher Canning : J'aimerais que vous m'expliquiez davantage le processus. Si je comprends bien, vous injectez une mutation dans la cellule, cette mutation est transmise à la lignée germinale, puis vous voyez les effets phénotypiques de l'inactivation du gène?

Dr Karaplis : Oui, c'est ça. Les cellules souches embryonnaires porteuses du gène invalidé doivent demeurer indifférenciées jusqu'à leur réinsertion dans l'embryon. Si elles sont différenciées, elles ne s'intégreront jamais à la lignée de cellules germinales. Les cellules devaient donc absolument rester dédifférenciées. C'est pourquoi nous les laissions dans leur matrice de cellules nourricières.

Les cellules nourricières sont tout simplement une couche de cellules qui sécrètent une protéine appelée « LIF », pour *Leukemia Inhibitory Factor*, et qui gardent les cellules dans un état dédifférencié. Au fil du temps, nous avons constaté que ça ne suffisait pas. Alors, nous avons commencé à utiliser, comme cellules nourricières, des fibroblastes qui provenaient d'embryons de souris.

Nous prenions des embryons de souris 14 jours après l'implantation, les disséquions, puis prélevions des fibroblastes et les irradions pour les empêcher de se multiplier. Grâce à ces fibroblastes, les cellules souches embryonnaires restaient dédifférenciées. Alors, voilà le grand changement que nous avons fait.

Christopher Canning : C'est formidable!

Dr Karaplis : Jusqu'alors, tout le monde utilisait des lignées de cellules nourricières qui s'étaient propagées si souvent qu'elles-mêmes avaient fini par se différencier.

Christopher Canning : Donc la solution était de les irradier pour ne pas…

Dr Karaplis : Oui, exactement, pour ne pas qu'elles prolifèrent, mais qu'elles puissent quand même maintenir les cellules souches embryonnaires dans leur état dédifférencié afin qu'elles s'intègrent à la lignée de cellules germinales.

Christopher Canning : Et leur permettre de rejoindre les cellules germinales. Wow, très intéressant.

Dr Karaplis : Je vais vous raconter une anecdote dont je n'ai pas parlé à beaucoup de gens.

Christopher Canning : Les sociologues des sciences adorent les bonnes histoires.

Dr Karaplis : D'accord, alors ça se passe après la création de la souris *knockout* dépourvue du peptide apparenté à la PTH. Nous savions que les souris dépourvues de cette protéine mouraient à la naissance. Mais nous ignorions pourquoi. Nous savions que leur développement était très anormal, mais nous n'arrivions pas à mettre le doigt sur le problème. Ce n'était pas une sinécure.

C'était une période très difficile pour moi, parce que même si j'avais réussi à créer les souris *knockout*, ces animaux avaient un problème, et il fallait le trouver. La perspective de rédiger un article avant de quitter Boston apparaissait de plus en plus improbable. C'était franchement décourageant : malgré tout le travail et toutes les réalisations accomplis, mon objectif restait inaccessible.

Si mes souvenirs sont bons, il était tard en soirée, et j'attendais la fin d'une expérience au labo. Je suis monté m'asseoir dans la bibliothèque. Il faut que je vous dise que la bibliothèque de l'Institut Whitehead est énorme et renferme des tonnes et des tonnes de livres. Je me suis dit que je pourrais lire un peu pour passer le temps. J'ai commencé à explorer les rayons. Après avoir arpenté quelques allées, j'ai choisi un livre au hasard. Je me souviens qu'il portait sur la génétique humaine. En l'ouvrant, je suis tombé sur un chapitre sur les chondrodysplasies chez l'être humain, des maladies caractérisées par un développement anormal du squelette. Les bébés atteints naissent avec des malformations.

En regardant les images, je me suis dit : « Mon Dieu, ça ressemble comme deux gouttes d'eau à nos souris mutantes ». Le phénotype était exactement le même : la cage thoracique beaucoup plus petite et la langue tirée, parce que les os du visage ne se sont pas développés normalement.

De retour au labo le jour suivant, j'ai commencé à scruter le squelette des souris. Voilà donc comment nous avons constaté que l'absence du peptide apparenté à la PTH provoquait un développement anormal du squelette.

Christopher Canning : C'est donc comme ça qu'est né votre intérêt pour l'appareil squelettique?

Dr Karaplis : Oui.

Christopher Canning : C'est vraiment fascinant. Alors, avant cet épisode, vous considériez-vous comme un spécialiste de la génétique humaine, voire de la médecine génétique?

Dr Karaplis : Non, je ne me voyais pas comme un généticien. J'étais endocrinologue. Au fond, c'est un simple concours de circonstances. C'est une maladie qui touche les êtres humains, évidemment, et je me suis rendu compte que cette protéine pouvait provoquer chez eux une forme de chondrodysplasie semblable à celle que j'observais chez la souris. À l'époque, la plupart des chondrodysplasies humaines portaient le nom de la première personne qui les avait décrites. On en savait fort peu sur les mécanismes moléculaires sous-jacents.

Bref, nous avons fini par comprendre que cette protéine jouait un rôle important dans le développement du squelette. C'était le début de notre quête : nous voulions décrire les mécanismes moléculaires par lesquels cette molécule régulait le développement osseux. Mais un autre défi de taille nous attendait : il fallait démontrer que le peptide apparenté à la PTH était également en cause dans des maladies qui touchaient l'être humain.

Christopher Canning : D'accord. Alors, il fallait établir un lien avec la souris?

Dr Karaplis : Oui, entre les manifestations pathologiques chez la souris et l'humain. De retour à Montréal, lorsque j'ai entrepris ma propre carrière de chercheur à l'Institut Lady Davis de recherches médicales, c'était mon grand objectif. Puis un jour où je cherchais dans Internet des articles sur des chondrodysplasies de l'être humain dont les caractéristiques squelettiques rappelaient celles de nos souris, j'ai trouvé. L'article portait sur la chondrodysplasie de Blomstrand.

J'ai téléphoné à l'auteur le lendemain. Il était en Angleterre. Et c'est alors qu'il m'a annoncé : « Malheureusement, le bébé de l'article est mort il y a quatre ou cinq jours. Alors, je ne suis pas certain que nous soyons en mesure de vous fournir quoi que ce soit. » Finalement, il a réussi à dénicher des lames d'anatomopathologie qui provenaient de ce bébé et nous les a envoyées. Nous avons isolé de l'ADN génomique à partir de tissus inclus dans la paraffine, l'avons soumis à une amplification en chaîne par polymérase et avons ainsi pu montrer que la maladie était causée par une mutation inactivante du récepteur du peptide apparenté à la PTH. Nous venions de relier la maladie de la souris à celle de l'être humain. Voilà donc l'origine de cette composante génétique.

Christopher Canning : C'est donc ce jour-là que vous êtes devenu généticien?

Dr Karaplis : Un généticien amateur.

Christopher Canning : Donc vous êtes endocrinologue d'abord et avant tout?

Dr Karaplis : Oui, c'est bien ça.

Christopher Canning : Avez-vous travaillé sur ces modèles? Vous vous êtes rendu compte que ça s'appliquait chez l'être humain?

Dr Karaplis : Oui, ça s'applique chez l'être humain.

Christopher Canning : C'est ici que vous entrez dans le domaine de la génétique.

Dr Karaplis : Exact.

Christopher Canning : Alors, avez-vous été généticien depuis?

Dr Karaplis : Eh bien, dans une certaine mesure, oui, peut-être.

Christopher Canning : Mais vous êtes endocrinologue, c'est bien ça?

Dr Karaplis : C'est cela, mais je ne suis pas véritablement un généticien. Je m'intéresse aux mécanismes génétiques et moléculaires des maladies du squelette chez l'être humain.

Christopher Canning : D'accord. Alors, quels sont les autres phénotypes que vous étudiez? Les anomalies du développement osseux postnatal, j'imagine?

Dr Karaplis : Oui.

Christopher Canning : À quels autres phénotypes vous intéressez-vous?

Dr Karaplis : Depuis six ou sept ans, nous avons étudié de près la régulation hormonale qui assure l'homéostasie du phosphate. C'est un domaine vraiment très intéressant qui a énormément évolué. On a décrit des mutations dans plusieurs gènes – notamment *PHEX*, *FGF23* et *DMPI* – qui, en gros, entraînent une perte rénale de phosphate et provoquent diverses formes héréditaires de rachitisme.

Christopher Canning : Intéressant, quand on pense au travail du Dr Scriver sur le rachitisme et la carence en vitamine D dans les années 1950 et 1960. C'est donc une autre façon d'aborder le problème?

Dr Karaplis : Oui, absolument. En fait, nous nous consacrons actuellement à l'aspect thérapeutique et tentons de réaliser un maillage laboratoire-clinique. En général, on donne aux patients de la vitamine D et du phosphore. Or, en plus d'avoir des effets indésirables, ce traitement ne reconstitue jamais complètement le tissu osseux pour des raisons qui demeurent nébuleuses.

Nos études génétiques chez la souris ont révélé que la 24-hydroxylase était une composante clé de ce mécanisme; cette enzyme rénale joue un rôle de premier plan dans le métabolisme de la vitamine D. La forme active de la vitamine D est sécrétée par le rein, et c'est la 24-hydroxylase qui régule la quantité de vitamine D active qui rejoindra la circulation sanguine. Donc, nous avons montré que si on inactive cette enzyme chez une souris atteinte d'hypophosphatémie liée à l'X, on corrige toutes les anomalies squelettiques du rachitisme.

Nous nous sommes donc associés à une entreprise pharmaceutique qui fabrique des inhibiteurs de la 24-hydroxylase et avec un groupe de France qui suit un grand nombre d'enfants atteints d'hypophosphatémie liée à l'X pour étudier les bienfaits d'un traitement par un inhibiteur de la 24-hydroxylase chez ces patients.

Christopher Canning : Est-ce la première fois que vous participez à la mise au point d'un traitement?

Dr Karaplis : Oui.

Christopher Canning : Après toutes ces années de recherche, ça doit avoir quelque chose d'exaltant, non?

Dr Karaplis : La recherche dans le domaine thérapeutique, oui, absolument. Mais au fond, c'est comme ça que j'envisage mon rôle. Comme nous le disions tout à l'heure, je trouve qu'un énorme fossé sépare le monde de la recherche de celui de la

médecine clinique. C'est souvent un dialogue de sourds. Ces gens ne parlent pas du tout le même langage. Je pense que les cliniciens-chercheurs peuvent jeter des ponts et agir comme agents de liaison pour, finalement, rapprocher les deux camps.

Rares sont les stagiaires disposés à investir le temps et les efforts nécessaires à cette réconciliation. Malheureusement, le système fait en sorte que la plupart de nos résidents et de nos *fellows* n'ont absolument aucune envie d'embrasser ce type de carrière.

Christopher Canning : Il me semble qu'aux premiers jours de la médecine génétique, disons dans les années 1950, les scientifiques examinaient les anomalies chromosomiques, et le médecin et le scientifique étaient alors une seule et même personne.

Dr Karaplis : Effectivement.

Christopher Canning : Avez-vous le sentiment que nous sommes à des lieues de cette époque et qu'aujourd'hui, la biologie moléculaire et la médecine sont deux choses complètement distinctes?

Dr Karaplis : Certainement. Aujourd'hui, nous sommes hyperspécialisés, parce que la médecine a évolué à un point tel qu'on ne peut plus rester à jour sur tous les fronts. Et évidemment, la recherche est, elle aussi, un monde à part. En ce moment par exemple, je passe de plus en plus de temps à faire de la clinique; or, je constate que je ne suis pas parfaitement à jour en recherche fondamentale. C'est l'un de nos plus grands problèmes; c'est impossible de tout faire sans tourner les coins ronds, parce qu'on manque de temps.

Christopher Canning : Je vois. Faites-vous de la supervision d'étudiants aux cycles supérieurs?

Dr Karaplis : Oui. Actuellement, je supervise un étudiant en médecine expérimentale en fin de parcours et j'ai trois associés de recherche. Ils sont venus faire leur postdoctorat dans mon laboratoire et ne sont jamais repartis.

Christopher Canning : Très intéressant. J'aimerais maintenant qu'on parle un peu du groupe. En fait, vous avez un passé fort intéressant. J'aime bien ces heureux hasards, si fréquents en science. Les gens perçoivent la science comme quelque chose de très organisé, mais en réalité, c'est souvent une question de hasard.

Dr Karaplis : Les heureux hasards… j'y crois vraiment.

Christopher Canning : Alors, reportons-nous à la fin des années 1990, lorsqu'on vous a invité à vous joindre au groupe du CRM. Que saviez-vous des activités de ce groupe, et comment vous êtes-vous retrouvé à en faire partie?

Dr Karaplis : Je connaissais l'existence du groupe grâce à Susie Tenenhouse, avec laquelle j'avais travaillé à la création d'une souris *knockout* dépourvue du cotransporteur rénal sodium-phosphate.

Christopher Canning : Ah oui, elle s'intéressait au transport rénal, n'est-ce pas?

Dr Karaplis : Oui, au transport rénal du phosphate. Je disais donc que nous en sommes venus à collaborer pour la mise au point de ces souris, et finalement toute l'équipe a signé un article paru dans les PNAS[7]. C'est notre intérêt commun pour l'homéostasie du phosphore qui nous a réunis. Et je pense qu'à ce moment-là, elle souhaitait qu'il y ait plus de membres aux intérêts de recherche communs dans le groupe de médecine génétique.

Christopher Canning : C'est-à-dire Rosenblatt et les autres?

Dr Karaplis : David [Rosenblatt], Roy [Gravel] et Rima [Rozen], puis elle, dans un champ de recherche complètement différent. Je pense que l'arrivée d'un chercheur qui travaillait plus ou moins dans le même domaine qu'elle était un atout pour le groupe. C'est à ce moment que Roy m'a demandé de faire un exposé lors de leurs tournées, et par la suite, de me joindre au groupe. Voilà!

Christopher Canning : Je vois. Roy Gravel dirigeait le groupe à cette époque, mais le Dr Scriver était encore là, quoique sa présence était discrète, non?

Dr Karaplis : Très discrète, oui. À l'époque, c'était Roy Gravel, effectivement.

Christopher Canning : Ah, d'accord.

Dr Karaplis : C'est comme ça que les choses se sont passées. Et ensuite, il s'agissait essentiellement de garder le cap sur les subventions. Les interactions étaient plutôt limitées, principalement pour des raisons d'emplacement.

Christopher Canning : Ah, vous me devancez. Justement, quel était le port d'attache du groupe à l'époque?

Dr Karaplis : Ce n'était pas simple pour toutes sortes de raisons. J'étais à l'Institut Lady Davis et les autres, à l'Hôpital pour enfants. Par ailleurs, nos intérêts de recherche étaient différents. Nous avions très peu de choses en commun. Personnellement, j'en avais beaucoup avec Susie, mais elle a pris sa retraite.

Christopher Canning : Elle figurait sur la demande de 2001, mais a pris sa retraite par la suite.

Dr Karaplis : C'est bien ça, je crois.

Christopher Canning : Ce qui veut dire qu'elle aurait fait partie du groupe à partir de 1994 environ, soit pendant à peu près six ans?

Dr Karaplis : Par la suite, on a senti le besoin d'aller chercher d'autres membres, comme le Dr Mark Trifiro, Eric Shoubridge et Bob MacKenzie.

Christopher Canning : D'accord. Comme membre du groupe, aviez-vous le sentiment de devoir tisser des liens?

Dr Karaplis : Oui.

Christopher Canning : Ressentiez-vous de la pression? Quel était le climat au sein du groupe?

[7] Proceedings of the National Academy of Sciences of the United States of America

Dr Karaplis : Je pense que la pression, c'est surtout le directeur qui la subissait. Sa tâche était très difficile. Il ou elle devait d'abord trouver des personnes qui non seulement cadraient bien dans le groupe, mais également constituaient un atout. Et à cet égard, je dois dire qu'au fil des ans, les directeurs ont fait un excellent travail. C'est malheureux qu'on ait dû démanteler le groupe.

Christopher Canning : Peut-on revenir brièvement sur l'organisation spatiale? Où étiez-vous et où étaient les autres membres?

Dr Karaplis : J'étais ici, à l'Institut Lady Davis. Pendant un moment, nous projetions de mettre en place un laboratoire transgénique commun, que j'aurais dirigé. L'idée était d'y produire les souris *knockout* dont les membres du groupe avaient besoin pour leurs recherches. Malheureusement, ça ne s'est pas fait, d'une part parce que je manquais de temps, et d'autre part pour des raisons de politique et des motifs personnels. Bref, ça s'est terminé en queue de poisson.

Alors, on a abandonné cette idée. La principale installation partagée était le Service d'histologie de l'Hôpital pour enfants. De temps en temps, j'y envoyais des échantillons de tissus pour des tests. Mais par ailleurs, les interactions étaient plutôt limitées.

Christopher Canning : D'accord. J'y reviendrai dans une seconde. Pouvez-vous me donner quelques précisions sur le rôle de chacun des membres du groupe? Comment se passaient les échanges entre les membres et quelles étaient les fonctions de chaque membre? En d'autres termes, de quelle nature était l'apport de chacun au groupe?

Dr Karaplis : Je pense que chacun tenait un rôle bien précis. Mais les intérêts étaient quelque peu différents, je dois dire. Par exemple, le Dr Rosenblatt était le gardien de la banque de tissus. Quant à Roy et à Rima, ce sont des gens brillants qui étaient exceptionnellement bien organisés et très bons dans l'affectation des ressources. Ils ont donc dirigé le groupe de main de maître. Susie Tenenhouse, elle, connaissait évidemment son domaine à fond et nous a toujours apporté un soutien précieux. Je n'ai pas vraiment eu affaire au Dr Scriver. Il n'était plus là.

Christopher Canning : Avez-vous eu l'impression que – parce que jusqu'à ce moment-là, jusqu'au milieu des années 1990, ce groupe était celui du Dr Scriver depuis des années. Il l'a dirigé et, bien évidemment, c'est lui qui l'avait fondé. Y avait-il une sorte de distanciation par rapport au Dr Scriver?

Dr Karaplis : Ça fait une mèche, mais si je me souviens bien, il y avait un peu d'appréhension, parce qu'on craignait que le groupe fonctionne moins bien sans lui.

Christopher Canning : Vous rappelez-vous des échanges à ce sujet?

Dr Karaplis : Oui.

Christopher Canning : Bien. Vous rappelez-vous de la structure de financement pour les demandes de groupe? Vous souvenez-vous d'avoir rempli ces formulaires? Cette responsabilité incombait-elle au directeur?

Dr Karaplis : Oui, elle incombait principalement au directeur. Notre responsabilité à nous, c'était de décrocher nos propres subventions, qui allaient grossir la cagnotte du groupe. Il y avait également octroi de fonds au groupe lui-même. Ces fonds étaient affectés en partie à l'entretien de la banque de tissus et au salaire du technicien qui s'en occupait. Évidemment, ces décisions appartenaient aux membres de longue date et, en ma qualité de nouveau venu, j'étais bien mal placé pour m'y opposer.

Christopher Canning : Vous voulez dire les décisions sur l'administration?

Dr Karaplis : Oui, sur l'administration ou même sur le montant que nous allions y consacrer.

Christopher Canning : D'accord. Vous avez mentionné que vous deviez réussir à obtenir des subventions individuellement. Et j'ai constaté, par exemple, que la demande de 1994 de Shoubridge, Nadeau et Malo n'avait pas été acceptée. Il semble qu'il y ait eu un changement dans la structure du CRM; auparavant, on invitait un chercheur à se joindre au groupe pour autant qu'il puisse y amener des fonds. Il devait donc réussir individuellement pour faire partie du groupe?

Dr Karaplis : Oui.

Christopher Canning : Fort intéressant. J'aimerais qu'on fasse un petit retour en arrière. Tout à l'heure, vous disiez être à la fois médecin et généticien. Dans les dernières années, ça n'a pas nécessairement été le cas. Quelles étaient les divisions dans le groupe entre les scientifiques fondamentaux et cliniques? Était-ce une chose dont vous parliez, puisque vous disiez tantôt que c'était – et que c'est encore – une source de dissension dans le monde de la recherche?

Dr Karaplis : Au sein du groupe?

Christopher Canning : Oui, entre vous tous. Avez-vous parlé de…?

Dr Karaplis : Non. À mon avis, le groupe fonctionnait très bien sur ce plan. Le Dr Scriver n'était pas là à l'époque. Ce n'est donc pas lui qui s'occupait des demandes de subvention, mais plutôt le Dr Rosenblatt et moi. Il n'y avait absolument aucune friction ni dissension entre les médecins et les scientifiques. Notre rôle à tous était on ne peut plus clair : nous devions nous appliquer pour décrocher les subventions. Il n'y avait donc aucun problème à ce chapitre.

Christopher Canning : Je vois. Selon vous, est-ce que l'approche interdisciplinaire a fonctionné dans le groupe? On a toujours dit qu'il avait atteint un certain degré d'interdisciplinarité. Alors, je me demande, selon votre expérience et votre connaissance du groupe avant et après votre arrivée comme membre, y avait-il de la collaboration entre les diverses disciplines? Et si oui, qu'est-il ressorti de ce travail interdisciplinaire?

Dr Karaplis : Il y avait de la collaboration jusqu'à un certain point, mais il me semble indéniable qu'il y avait aussi des discordances; des champs de recherche

différents, des intérêts différents. Ces différences étaient flagrantes lors de nos réunions annuelles. Alors, de ce point de vue, je pense que la cohésion n'était pas aussi bonne qu'on aurait pu le croire ou le souhaiter.

Christopher Canning : Je vais vous poser une question que j'ai posée à d'autres membres du groupe. Qu'est-ce qui faisait de ce groupe un groupe? En d'autres termes, quel était le ciment de ce groupe? Je ne sous-entends pas par là que le groupe n'en était pas un, parce que c'en était un de bien des façons, ancré dans la réalité de ses membres et dans les politiques du CRM et des IRSC.

Dr Karaplis : Oui, effectivement.

Christopher Canning : Et il a reçu du financement pendant 37 ans.

Dr Karaplis : Oui, mais je pense que le ciment changeait d'année en année, ou du moins selon l'époque. Cela dit, à partir du moment où je suis arrivé, je ne pense pas qu'il y avait de groupe en bonne et due forme. C'était tout simplement un ensemble de scientifiques très talentueux qui s'intéressaient aux troubles génétiques. Je ne sais pas ce que les autres membres vous ont dit, mais j'ai le sentiment que le ciment de ce groupe était un intérêt à l'égard des fondements génétiques de la maladie chez l'être humain, dans un très large spectre, je dirais. Ce qui nous unissait, c'était cet intérêt commun.

Christopher Canning : C'était le dénominateur commun de ce groupe-là.

Dr Karaplis : Oui. Mais au sein du groupe, les interactions étaient limitées.

Christopher Canning : Alors, pourquoi le CRM et les IRSC ont-ils financé le groupe pendant tout ce temps? Et loin de moi l'idée de minimiser l'apport du groupe. Mais sur le plan sociologique, il est intéressant d'explorer les assises politiques et contextuelles des groupes.

Dr Karaplis : [Rires] Non, non, je comprends. Au fond, je pense que c'est comme ça qu'ils l'ont présenté. Et ça a très bien passé. Ils l'ont présenté comme un groupe parfaitement fonctionnel. Et en fait, il n'était pas dysfonctionnel. C'est simplement, je crois, que les intérêts n'étaient pas aussi bien conjugués qu'on aurait pu le souhaiter, parce que si ça avait été le cas, le groupe aurait eu beaucoup plus de succès.

Christopher Canning : Si la collaboration avait été meilleure?

Dr Karaplis : Absolument. J'en suis profondément convaincu.

Christopher Canning : C'est très intéressant. Alors, quelles sont les réalisations du groupe si vous pouviez – et je ne parle pas ici nécessairement de bienfaits thérapeutiques directs, mais si – si vous envisagez ces 37 années, quels sont à vos yeux les avantages d'un groupe sur la médecine génétique?

Dr Karaplis : Eh bien, je pense que le Dr Scriver a accompli un travail de défrichage hors du commun. Il est l'âme et le pilier du groupe. Mon impression, c'est que le groupe s'est éloigné du chevet du patient pour se concentrer davantage sur la recherche fondamentale. Et dès lors, les retombées de notre travail dans le

domaine thérapeutique, même si elles étaient bel et bien là, ont en quelque sorte quitté l'avant-scène.

Christopher Canning : Le Dr Scriver était face à face avec les patients qu'il traitait.

Dr Karaplis : Peut-être. À mon avis, c'est à ce moment que le groupe a changé. Il s'est éloigné du chevet du malade pour se rapprocher du laboratoire.

Christopher Canning : Très intéressant.

Dr Karaplis : C'est mon point de vue sur ce qui s'est produit, mais je ne dis pas que l'un est plus important que l'autre.

Christopher Canning : Non, bien entendu.

Dr Karaplis : C'est simplement une autre façon d'aborder le même problème.

Christopher Canning : Oui.

Dr Karaplis : Et c'est la raison pour laquelle le volet thérapeutique de notre travail est moins présent.

Christopher Canning : J'en sais fort peu sur les travaux scientifiques des membres du groupe, mais si on regarde les 25 dernières années, quelles sont les retombées thérapeutiques de cette recherche fondamentale?

Dr Karaplis : Elles se résument à peu de choses.

Christopher Canning : Et comme nous le disions, la recherche fondamentale est formidable, essentielle même.

Dr Karaplis : Bien sûr. C'est de là que partent les avancées thérapeutiques, mais je m'interroge sur l'apport de notre groupe aux progrès dans la sphère thérapeutique.

Christopher Canning : Si les cliniciens et les fondamentalistes avaient collaboré davantage, pensez-vous, comme vous l'avez dit, que les résultats auraient été différents?

Dr Karaplis : Oui, je pense que les résultats auraient été bien différents.

Christopher Canning : D'accord. Le Dr Scriver a mentionné – j'aimerais vous poser deux ou trois autres questions, ça vous va? Le Dr Scriver a mentionné au dernier symposium… ça rejoint un peu nos propos. Comme je le disais, lors du symposium de l'automne, il a dit que le groupe fonctionnait comme une organisation de base, dans le sens où l'évolution était toujours venue de la base. Partagez-vous sa vision des choses? J'ai trouvé cela intéressant; il relatait la célèbre histoire du groupe, composé de scientifiques respectés qui ont fait un travail formidable. Je me demande si vous aviez aussi cette impression?

Dr Karaplis : Je ne suis pas sûr de comprendre ce que vous entendez exactement par « organisation de base ». Chose certaine, tous les membres ont apporté quelque chose au groupe. Je ne sais pas si cela répond à votre question.

Christopher Canning : Oui. Savez-vous pourquoi le groupe a cessé d'être financé en 2009? Pourquoi les IRSC ont fermé le robinet?

Dr Karaplis : Je pense que les IRSC ont simplement suivi une politique. Personnellement, je pense qu'il y avait pas mal de grogne chez les personnes qui ne faisaient pas partie d'un groupe comme le nôtre; elles estimaient qu'on ne devrait pas allouer des fonds supplémentaires à des membres de groupes déjà subventionnés. Pourquoi recevraient-ils plus d'argent pour entretenir un esprit de corps qui, si ça se trouve, n'était peut-être même pas là au départ? Et je pense que les IRSC en ont eu vent. Peut-être ont-ils constaté qu'il n'y avait pas grand-chose à gagner à tenter d'entretenir cet esprit de corps, et c'est en partie ce qui a mené au démantèlement.

Christopher Canning : Intéressant. Y avait-il une perception d'élitisme ou simplement de financement injustifié?

Dr Karaplis : Je pense qu'en général, on percevait les groupes comme une élite et on estimait qu'il fallait les démanteler.

Christopher Canning : Qu'il fallait…? Et dans d'autres sphères de recherche, on craignait probablement que les groupes mettent la main sur le gros de l'argent.

Dr Karaplis : Le groupe recevait des sommes considérables en plus des subventions personnelles des chercheurs. Il y avait donc peut-être une perception d'injustice. On se disait qu'il vaudrait sans doute mieux donner cet argent à d'autres chercheurs en quête de subventions, et je dois dire que c'est un point de vue qui se défend.

Christopher Canning : Je pense qu'ils sont passés aux subventions d'équipe qui, si j'ai bien compris la politique, sont précisément conçues pour les projets interdisciplinaires. Le groupe du CRM réunissait divers projets scientifiques, mais les nouvelles subventions d'équipe ont plutôt pour but de financer un seul projet qui s'abreuve à diverses disciplines.

Dr Karaplis : Le projet doit donc être clairement défini.

Christopher Canning : Oui.

Dr Karaplis : Et ce n'était pas notre cas. C'est une partie du problème, à mon avis.

Christopher Canning : Intéressant. Bon, tournons-nous vers l'avenir, si vous le voulez bien. Sur quoi travaillez-vous actuellement? Comme vous l'avez dit tout à l'heure, tous les scientifiques ont des idées. Donc, quels sont vos projets pour les cinq à dix prochaines années et sur quoi travaillez-vous?

Dr Karaplis : Sur deux choses principalement. La première est à visée thérapeutique. Comme je l'ai souligné précédemment, j'étudie avec grand intérêt la possibilité de traiter le rachitisme hypophosphatémique lié à l'X au moyen d'inhibiteurs de

la 24-hydroxylase. C'est un projet qui occupera certainement une grande partie de mon temps.

L'autre est l'ostéoporose. Je traite beaucoup de personnes qui en sont atteintes. Je dirige ici deux cliniques externes où on traite l'ostéoporose. Elles comptent plus de 3 000 patients.

Christopher Canning : Sans nul doute la maladie osseuse la plus fréquente parmi…? Les maladies métaboliques des os. Toutes les personnes de plus de 55 ans en sont atteintes.

Dr Karaplis : Oui, plus ou moins. Et il est clair que c'est une maladie génétique. Le grand sujet actuellement dans l'ostéoporose, c'est un des traitements, Forteo, une PTH. C'est le seul agent anabolique osseux dont nous disposons aujourd'hui, c'est-à-dire le seul qui stimule la formation de tissu osseux. Le problème, c'est que ce médicament doit être injecté chaque jour pendant deux ans.

La grande question est la suivante : comment fonctionne cette protéine? Nous l'ignorons. Un patient qui sécrète trop de PTH à cause d'une maladie parathyroïdienne finit par souffrir d'ostéoporose. Mais si vous administrez de la PTH exogène de manière intermittente – je dis bien intermittente, pas continue – à un patient, du tissu osseux va se former.

Il y a donc là un paradoxe à résoudre. Mais il y a du nouveau sur ce front, quelque chose de vraiment fascinant que nous étudions actuellement, soit le rôle des gènes horloges. L'axe hypothalamo-hypophysaire assure le fonctionnement harmonieux de tous nos systèmes biologiques. Ainsi, la lumière du matin déclenche la sécrétion de cortisol. Et nous croyons que ces signaux ont pour effet de synchroniser les cellules des tissus périphériques. Prenons l'exemple des os. Nous savons que la formation du tissu osseux a lieu la nuit et sa résorption, le jour. Il y a donc forcément quelque chose qui déclenche le passage de l'une à l'autre. Nous avançons que cet élément déclencheur est de nature endogène.

Christopher Canning : La sécrétion de PTH qui serait régie par le rythme circadien, par exemple.

Dr Karaplis : Le concept ici est que la sécrétion de la PTH endogène suivant le rythme circadien est responsable de la formation osseuse. Et en demandant aux patients de s'injecter le médicament une fois par jour, nous reproduisons le rythme circadien. Nous cherchons donc à comprendre ce mécanisme et à en tirer parti, parce qu'il nous indiquera pourquoi certaines personnes répondent au médicament et d'autres non. Parce que si les patients se font leur injection le matin, c'est contre nature, puisque la protéine est normalement sécrétée la nuit.

Christopher Canning : Alors, vous devez l'attraper…?

Dr Karaplis : Ou reproduire le schéma endogène en injectant le médicament le soir plutôt que pendant la journée. Nous tentons donc de déterminer comment intensifier les effets anaboliques du médicament chez nos patients et, une fois de plus, nous jetons des ponts entre la recherche fondamentale et la prise en charge clinique.

Christopher Canning : Dans l'espoir de produire des retombées thérapeutiques?

Dr Karaplis :	Oui.
Christopher Canning :	Fantastique.
Dr Karaplis :	Alors actuellement, nous étudions le potentiel des gènes horloges et du rythme circadien.
Christopher Canning :	Oui et vous établissez des liens entre les neurosciences et le métabolisme?
Dr Karaplis :	Absolument.
Christopher Canning :	Très intéressant. Et, bien entendu, vous avez une subvention qui vous permettra de le faire au cours des prochaines années?
Dr Karaplis :	Oui, une subvention de cinq ans des IRSC.
Christopher Canning :	Fantastique.
Dr Karaplis :	Oui.
Christopher Canning :	Bonne chance!
Dr Karaplis :	Merci beaucoup.
Christopher Canning :	Je n'ai plus de questions. Je vous remercie beaucoup pour cet échange fort enrichissant.
Dr Karaplis :	Merci d'avoir pris le temps de m'écouter.

FIN DE L'ENTRETIEN

P^r Robert MacKenzie, le 2 février 2011

Christopher Canning : Nous sommes le 2 février 2011. Ici Christopher Canning en compagnie du P^r Robert MacKenzie. Professeur MacKenzie, je suis très honoré de pouvoir m'entretenir avec vous de deux grands sujets qui touchent la génétique humaine.

J'aimerais d'abord que nous parlions de votre parcours, qui a contribué à l'avancement de la génétique médicale au Canada et ailleurs dans le monde. Ensuite – et surtout, pour les besoins de notre étude – je m'intéresse à votre participation au groupe sur la médecine génétique des IRSC[1] – anciennement le CRM[2] – auquel vous vous êtes joint en 2001, si je ne m'abuse, et dont vous avez été membre jusqu'à sa dissolution, en 2009.

Mais parlons d'abord de vous, si vous le voulez bien. Où êtes-vous né et où avez-vous passé votre enfance?

P^r MacKenzie : Ah bon, vous voulez remonter loin! Je suis né en Nouvelle-Écosse. J'ai obtenu mon baccalauréat à l'Université McGill, au campus Macdonald, puis ma maîtrise et mon doctorat à l'Université Cornell. J'ai fait ma maîtrise en sciences de la nutrition et mon doctorat, en biochimie. Ensuite, je suis allé à Berkeley pour ma formation postdoctorale avec Jesse Rabinowitz. C'est ce qui m'a amené à m'intéresser au folate. Et c'est le folate qui m'a conduit vers le groupe.

Christopher Canning : Je vois. J'aimerais bien qu'on revienne là-dessus dans quelques minutes. J'ai quelques questions sur votre arrivée dans le groupe. Ça fait un bout de temps, je sais, mais j'aimerais en savoir davantage sur vos travaux en biochimie à l'Université Cornell. Et avez-vous fait des études postdoctorales par la suite? Revenons brièvement sur votre formation universitaire, si vous le voulez bien.

P^r MacKenzie : D'accord, mon doctorat en biochimie à Cornell, qui en fait était plus un projet de chimie organique. Je m'intéressais à la grande variation du potentiel d'oxydoréduction d'une flavoprotéine à l'autre. Par exemple, il y a de la riboflavine tant dans la FAD[3] que dans la FMN[4]. Lorsqu'elle est associée à certaines protéines, le potentiel d'oxydoréduction change; ce n'est pas le cas des couples NAD^+/NADH, qui présentent un potentiel d'oxydoréduction fixe. C'est que la flavine est souvent davantage un groupement prosthétique qu'un cofacteur dissociable.

Bref, il apparaissait clairement que l'interaction flavine-protéine modifiait certaines caractéristiques de la flavine, et pas juste un peu. Donc, nous construisions des modèles pour tenter d'associer chimiquement, par liaison covalente, la molécule de flavine à certains acides aminés contenus dans les protéines afin de pouvoir étudier ces systèmes d'oxydoréduction artificiels et de voir s'il y avait un acide aminé qui, étroitement lié à l'anneau de la flavine, pouvait modifier le potentiel d'oxydoréduction.

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[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada
[3] Flavine adénine dinucléotide
[4] Flavine mononucléotide

Et c'était le cas, jusqu'à un certain point; pas autant que dans la protéine elle-même, mais le maintien de ce lien étroit avec certains acides aminés dans la protéine a sans conteste modifié les propriétés de la flavine.

C'est donc essentiellement ce qui m'a amené vers ce que j'appellerais un modèle d'étude des flavoprotéines. En fait, je n'étudiais qu'une seule flavine et un seul acide aminé à la fois, et je me suis dit que je devrais me consacrer davantage à la chimie des protéines; j'ai donc cherché quelqu'un qui disposait de protéines en grande quantité. À l'époque, Jesse Rabinowitz, à Berkeley, travaillait sur les enzymes folate-dépendantes de *Clostridium*, si bien qu'il avait accès à des grammes d'enzymes.

Je suis donc allé rejoindre Jesse, parce que je souhaitais appliquer mon modèle à une protéine véritable : c'est ainsi que j'ai commencé à étudier la chimie des protéines.

Christopher Canning : Fantastique!

P[r] MacKenzie : Alors, pendant mes études postdoctorales, j'ai étudié les enzymes folate-dépendantes avec Jesse Rabinowitz. En lisant sur le sujet, j'ai constaté que les connaissances sur le folate provenaient en bonne partie des bactéries. Moi, je voulais savoir ce qui se passait chez les mammifères. Or, bon nombre des protéines de mammifères n'avaient été que partiellement purifiées, alors j'ai décidé de poursuivre le travail. Et c'est ce que j'ai fait en arrivant à McGill.

Christopher Canning : Sur quels mammifères travailliez-vous à l'époque?

P[r] MacKenzie : Comme j'avais besoin d'une grande quantité de tissus, je travaillais principalement avec de grands animaux. Nous utilisions des foies de porc, vu qu'il était facile d'en obtenir auprès d'abattoirs; nous en utilisions en bonne quantité – on parle de kilogrammes – pour tenter d'isoler des protéines.

Donc, principalement le porc et aussi le rat, parce qu'au début, dans les années 1970, nous voulions trouver les protéines en jeu dans ce processus. D'autres chercheurs avaient détecté certaines formes d'activité, mais ils n'avaient pas encore totalement isolé les protéines. C'est donc principalement ce que j'ai commencé à faire chez des mammifères, et nous avons découvert que plusieurs des protéines étaient multifonctionnelles – c'est-à-dire qu'un produit génique, un polypeptide, exerçait plus d'une activité enzymatique. C'était révolutionnaire à l'époque, et les gens étaient plutôt sceptiques au début, mais le nombre de protéines multifonctionnelles a augmenté, et il se trouve que le folate se prêtait bien à ces travaux, étant donné que plusieurs de nos protéines étaient multifonctionnelles.

Christopher Canning : Est-ce que cette découverte est venue remettre en question l'idée selon laquelle un gène ne pouvait être associé qu'à une seule activité de la protéine?

P[r] MacKenzie : Eh bien, c'est un gène… avant, c'était un gène, une activité. Un gène, une protéine, mais on s'est aperçu avec le temps que certaines de ces protéines étaient liées entre elles, et souvent, les deux – voire les trois – activités, étaient

exprimées simultanément. Nous avions donc plusieurs protéines multifonctionnelles au sens véritable du terme, c'est-à-dire qu'il ne s'agissait pas de complexes enzymatiques, bien que de tels exemples soient aussi très fréquents.

À l'origine, je me suis d'abord demandé quel avantage présentaient les protéines multifonctionnelles, pourquoi la nature avait réuni ces activités dans un seul et même polypeptide. Les premiers temps, nous avons donc étudié les protéines, et nous avions bien du mal à comprendre pourquoi ces activités se produisaient ensemble. Puis, avec les bons substrats de folate, nous avons trouvé quelques exemples d'activités enzymatiques consécutives dans lesquelles le produit intermédiaire jouait un rôle de canalisateur; plus précisément, la première enzyme convertit la substance A en substance B, puis la substance B est aussitôt soumise à la seconde activité, soit la conversion en substance C. Ainsi, la substance B, soit le produit intermédiaire, n'est jamais dissociée dans le milieu.

Or, de toute évidence, la liaison de ces protéines était favorable sur le plan cinétique. Mais nous nous sommes rendu compte que notre constat ne s'appliquait pas à l'ensemble de ces protéines.

Christopher Canning : Je vois.

P^r^ MacKenzie : Donc l'avantage cinétique, c'était une explication, mais nous n'arrivions pas à comprendre pourquoi d'autres étaient multifonctionnelles. Nous avions une protéine trifonctionnelle. Et une autre qui était bifonctionnelle, mais seulement lorsque ses sous-unités interagissaient de manière à… c'était une drôle de protéine. Il s'agissait d'un tétramère de dimères. Les dimères n'avaient qu'une seule activité, mais lorsqu'ils étaient liés les uns aux autres pour former un octamère (un tétramère de dimères), ils produisaient deux activités. Nous avons constaté que ces activités se manifestaient aux deux interfaces de ces sous-unités, bien qu'elles aient été toutes identiques.

C'est comme si en plaçant deux balles de billard l'une contre l'autre de manière à ce que les numéros se touchent, on obtenait une seule activité. Mais que si on prenait cette paire de balles de billard pour l'attacher à une autre dont les numéros ne se touchent pas, il se produisait une autre activité à cette interface. Nous avons donc découvert que plusieurs mécanismes pouvaient expliquer la nature multifonctionnelle des protéines.

Christopher Canning : Je vois.

P^r^ MacKenzie : C'est ainsi que j'ai commencé à m'intéresser à la chimie des protéines, et pendant des années, notre travail consistait à isoler et à caractériser des protéines.

Christopher Canning : Désolé de vous interrompre… Vous étiez toujours à Cornell à l'époque?

P^r^ MacKenzie : Pardon?

Christopher Canning : Vous étiez toujours à l'Université Cornell à l'époque?

Pr MacKenzie : Non, non, non… Tout ça, c'était à McGill.

Christopher Canning : D'accord.

Pr MacKenzie : Lorsque j'ai découvert le domaine du folate en travaillant avec Jesse Rabinowitz, à Berkeley, j'ai étudié des protéines extraites de *Clostridium*. C'est ce qui m'a amené à m'intéresser au folate, mais Jesse préférait se consacrer aux bactéries. Nous avons étudié certaines protéines d'origine bactérienne. Les bactéries du genre *Clostridium* produisaient énormément d'enzymes folate-dépendantes, mais elles ne les utilisaient pas de la même manière que les mammifères. Les activités produites étaient semblables, mais leur importance sur le plan métabolique était différente. Alors, quand j'ai quitté Jesse pour accepter un poste à McGill, j'ai décidé d'élucider la question chez les mammifères.

J'ai donc passé de nombreuses années à tenter de trouver des protéines et d'en découvrir les propriétés. Nous faisions beaucoup de purifications de protéines, de la chimie des protéines pure et dure; rien à voir avec la génétique.

Christopher Canning : Je vois. En quelle année êtes-vous arrivé à McGill exactement?

Pr MacKenzie : En 1971.

Christopher Canning : Et je présume que votre premier poste était au Département de biochimie?

Pr MacKenzie : Exact.

Christopher Canning : Bien, et vous dites que vous n'étiez pas vraiment généticien, mais, de toute évidence, vous vous êtes intéressé à…

Pr MacKenzie : Je n'ai jamais été généticien. [rires]

Christopher Canning : D'accord. C'est plutôt surprenant, dans la mesure où vous faisiez partie d'un groupe d'experts en génétique médicale.

Pr MacKenzie : En effet.

Christopher Canning : C'est très intéressant en soi. Vous étudiiez donc certains mammifères, mais avez-vous déjà eu l'intention de transposer vos travaux chez l'humain ou d'essayer de comprendre comment ces mécanismes s'appliquaient aux maladies humaines?

Pr MacKenzie : Eh bien, en biochimie, on travaille toujours à partir de modèles, parce que, n'est-ce pas, on peut difficilement demander à quelqu'un de nous fournir un kilogramme de son foie… Il y a de la recherche fondamentale qui ne peut pas se faire chez l'humain, point. La solution? Pour la chimie ou la biochimie fondamentale, ça nous prend des modèles.

Et la bactérie, c'est un modèle qui ne me convenait tout simplement pas. Je voulais quelque chose de plus proche de la réalité, même si c'était pas mal plus

compliqué, parce que les protéines de mammifères étaient beaucoup plus difficiles à purifier. Elles devaient être soumises à bien plus de cycles de purification que les bactéries de *Clostridium*. En fait, Jesse parvenait à obtenir une enzyme de folate pure après une purification par un facteur de 100 environ, mais il nous fallait un facteur de 600 pour obtenir une protéine pure à partir d'un foie de porc. Et comme le foie contient beaucoup plus de protéines, le processus est bien plus complexe.

Christopher Canning : Donc, vous avez consacré la majeure partie de votre carrière à la recherche fondamentale en biochimie?

P[r] MacKenzie : Je dirais que oui, et c'est essentiellement parce que je me suis intéressé dès le départ à la chimie des protéines, à leur fonctionnement, à leur mécanisme, mais particulièrement aux avantages des protéines multifonctionnelles. Nous en avons donc purifié deux à partir d'un foie de porc et les avons étudiées à fond.

Puis, à un moment donné, je ne me rappelle plus en quelle année, nous avons tiré parti d'un truc que Gray Scrimgeour avait observé des années plus tôt… il faudrait que je retrouve l'article pour voir la date. Ça devait faire, quoi, 20 ou 25 ans. Quoi qu'il en soit, il avait annoncé avoir observé une activité enzymatique régulièrement présente dans des cellules de tumeurs ascitiques d'Ehrlich (ce sont des cellules libres qui se développent dans la cavité péritonéale des souris), qu'il n'arrivait toutefois pas à observer chez les souris elles-mêmes.

Alors, nous nous sommes dit que c'était un artéfact qui venait probablement du fait que nous travaillions avec de l'extrait brut et qu'on mesurait un changement spectrophotométrique. Au fond, on n'a pas besoin de caractériser le produit pour observer un changement d'absorption. J'ai donc demandé à un étudiant qui passait l'été dans notre labo de se pencher sur la question. Il se trouve que nous nous étions convaincus qu'il y avait une activité quelconque à cet endroit, et nous avons craint pendant un bon moment que cette activité détectée dans les cellules tumorales d'Ehrlich soit plutôt causée par un organisme qui se développait dans la cavité péritonéale, aux côtés des cellules tumorales; le cas échéant, le changement observé n'aurait pas été le fait d'une enzyme de mammifère, mais bien d'un élément qui contaminait le processus.

C'est comme ça que nous en sommes venus à envisager la mise en culture de lignées cellulaires que nous savions exemptes de toute contamination. Et il se trouve que chacune des lignées cellulaires étudiées présentait cette activité enzymatique particulière, soit celle de la méthylènetétrahydrofolate déshydrogénase NAD-dépendante.

Nous avons donc publié un article qui disait grosso modo « c'est simple, elle est exprimée dans chaque cellule transformée que nous examinons ». Et dans toutes les cellules tumorales qui nous tombaient sous la main, cette activité enzymatique était présente. À ce stade, nous étions certains que nous avions affaire à une protéine de mammifère. Nous nous sommes donc mis en frais de la purifier [la protéine], parce que c'était vraiment, vraiment étrange de ne pas observer l'activité dans les cellules d'une souris, mais de l'observer dans la

cellule d'une tumeur qui se développait dans cette même souris.

Christopher Canning : C'est intéressant, en effet.

Pr MacKenzie : Alors, nous avons fait beaucoup de purification. Nous devions fabriquer des cellules de tumeur ascitique d'Erhlich en quantité industrielle, dans beaucoup, beaucoup de souris. Il fallait leur injecter des cellules tumorales dans la cavité péritonéale, les laisser se développer puis les recueillir et, évidemment, sacrifier les animaux. Nous avons fini par purifier la protéine à partir de ces énormes quantités de cellules tumorales, pour constater que c'était une méthylènetétrahydrofolate déshydrogénase NAD-dépendante dont l'activité ressemblait à une activité décelée auparavant dans une protéine trifonctionnelle.

Cette protéine n'était toutefois pas trifonctionnelle, mais seulement bifonctionnelle. Ça a piqué notre curiosité au plus haut point. C'est là que nous avons commencé à faire du clonage. À ce stade-là, le clonage de protéines était possible à partir d'anticorps. En clonant l'ADNc[5] puis le gène, et en examinant la distribution infracellulaire, nous avons découvert que contrairement à ses congénères, cette bien curieuse méthylènetétrahydrofolate déshydrogénase NAD-dépendante n'était présente, la petite coquine, que dans les mitochondries et non dans le cytoplasme de la cellule.

Christopher Canning : Je vois que vous avez signé récemment quelques articles sur l'ADN mitochondrial.

Pr MacKenzie : Oui. Nous sommes entrés dans l'univers des mitochondries, puisque c'est là que logeait la protéine. Et nous nous sommes demandé pendant très longtemps pourquoi on trouvait cette protéine dans les mitochondries et dans les cellules transformées. Après, nous avons voulu savoir… – j'imagine qu'ici, je commence à lorgner du côté de la génétique, mais à mes yeux, ce n'était pas de la génétique – je voulais répondre à une question de nature biologique, soit : quelle est l'importance de cette protéine? Bon, on sait qu'elle est là. On sait qu'elle est présente dans les mitochondries, mais pas chez la souris adulte. Nous avons donc procédé à une inactivation génique et constaté qu'elle était mortelle pour l'embryon. Les embryons mouraient au bout d'une douzaine de jours.

Christopher Canning : Lorsque cette protéine n'était pas là?

Pr MacKenzie : Oui, ils vivaient une douzaine de jours. Et c'était la mort. À ce stade, les embryons étaient incapables de produire des globules rouges. Et cette protéine n'avait rien à voir avec les globules rouges, du moins pas directement. Ils mouraient parce que l'hématopoïèse, soit le processus de formation des globules rouges, ne s'enclenchait pas. Lorsque ce processus se met en branle chez l'embryon, c'est dans le foie que sont produits les premiers globules rouges. Or, on voyait bien que le foie de ces embryons était blanc, alors que normalement, il est rouge clair à ce stade, parce qu'il fabrique des globules rouges.

[5] ADN complémentaire

Nous voilà encore en train de nous prendre la tête : comment expliquer ça? Puis, à un moment donné, nous nous sommes dit que cette protéine-là devait faire quelque chose pour soutenir – bien qu'elle soit dans les mitochondries – qu'elle devait faire quelque chose pour soutenir la croissance rapide, puisque ce n'est que dans ce contexte qu'on l'observait. Elle était présente dans les tissus en croissance rapide, que ce soit dans l'embryon ou dans les cellules tumorales.

La croissance rapide, donc; de quoi a-t-on besoin pour ça? On a besoin de purines et de pyrimidines, et l'acide folique est le cofacteur qui soutient les unités monocarbonées nécessaires à la synthèse des purines. Nous avons donc pour ainsi dire persévéré et au bout du compte, nous avons découvert que dans les mitochondries, cette protéine fabriquait un produit qui, avec le concours d'une autre enzyme, pouvait être converti en une unité monocarbonée capable de migrer vers le cytoplasme. Et c'est cette unité monocarbonée dans le cytoplasme qui est convertie en purine.

Pour que les purines soient synthétisées en assez grande quantité aux fins de production de l'ADN et de l'ARN, on a besoin de ce processus – en fait, c'est la sérine, un acide aminé, qui est métabolisée dans les mitochondries et aboutit à cette unité monocarbonée grâce à cette enzyme. Elle est libérée dans le cytosol, ce qui permet à la cellule de fabriquer des unités monocarbonées en quantité suffisante pour que les purines soient synthétisées à un rythme qui déclenche l'hématopoïèse.

Comme nos souris privées de ce gène ne pouvaient pas fabriquer de purines assez rapidement, elles n'arrivaient pas à atteindre le seuil de déclenchement de l'hématopoïèse. Notre arrivée dans le groupe résulte donc de nos tentatives de compréhension de ce phénomène. Mais il y avait eu un autre regroupement avant celui-là. On l'appelait le « club du folate ». Plusieurs personnes de McGill, notamment David Rosenblatt, Bernie Cooper et moi-même, étudiaient le folate; nous nous réunissions régulièrement. En fait, ces rencontres ont débuté peu après mon arrivée à McGill; nous parlions du folate et de la vitamine B_{12}.

Dans les circonstances, lorsqu'est venu le moment d'accueillir de nouveaux venus dans le groupe pour remplacer ceux qui étaient partis, j'étais intéressé. Je n'ai pas fait de génétique humaine; mon domaine, c'était plutôt l'expression des protéines et le rôle des gènes. C'est donc à ce moment-là que je suis devenu une sorte de pseudo-généticien, j'imagine.

Christopher Canning : J'allais dire que jusqu'à ce moment-là, vous aviez été de toute évidence un biochimiste. Mais si je comprends bien, vous aviez recours à des techniques de biologie moléculaire.

P^{r} MacKenzie : Ah oui, tout à fait! Je suis passé de la chimie organique à la purification et à la caractérisation de protéines, puis de la chimie des protéines à la biologie moléculaire pour en arriver au clonage et à l'expression de sorte que nous puissions examiner la structure par radiocristallographie. Nous avons étudié les mécanismes, les mécanismes chimiques de certaines de ces protéines. Nous avons tenté d'élucider le processus de canalisation, puis de faire de la

mutagenèse dirigée pour examiner les propriétés; et de là, nous en sommes venus à cloner les gènes pour ensuite les inactiver.

Finalement, je me suis rendu compte que j'aimais bien faire ça. Il ressort de tout ça qu'une carrière, ça se réoriente. Au fond, tu adoptes la technologie dont tu as besoin pour répondre aux questions que tu te poses. J'ai donc commencé par relier deux molécules et j'ai fini par inactiver des gènes chez des souris.

Christopher Canning : Effectivement. Bien entendu, la révolution biologique moléculaire des années 1970 n'est pas étrangère à tout ça…

Pr MacKenzie : Cela va de soi. J'ai eu beaucoup de chance que l'équipe du Département de biochimie soit là pour l'inactivation génique; c'était super d'être dans ce département très, très solide, où on pouvait compter sur un tas de gens pour nous donner du soutien technologique. Mais pour tirer pleinement parti de cette étrange enzyme NAD-dépendante, il fallait que je comprenne bien les mitochondries, et Eric Shoubridge était l'expert du groupe sur le sujet.

Christopher Canning : Ah oui, évidemment.

Pr MacKenzie : C'était génial qu'Eric soit là, parce que nous pouvions échanger des idées. Nous pouvions utiliser certains de ses vecteurs d'expression, entre autres choses. David Rosenblatt et Rima Rozen, eux, étaient bien sûr les spécialistes du folate.

Christopher Canning : J'ai justement remarqué qu'au début des années 1980, vous aviez publié quelques articles avec Rima Rozen.

Pr MacKenzie : Oui, un ou deux peut-être, au milieu des années 1980. Mais c'était au tout début du clonage et de l'expression. Je pense que c'était bien avant la fameuse enzyme NAD-dépendante. D'un autre côté, j'avais besoin de données histologiques, parce qu'il fallait comprendre ce qui se produisait lors de l'inactivation génique. Et les souris mouraient *in utero*.

C'est là que le biochimiste, en proie au désespoir, lève les bras et lance : « Bon, je fais quoi maintenant? ». On sait que les souris meurent. C'est une information importante, mais encore, elles meurent quand? Et de quoi? Il faut voir ce qu'on peut trouver du côté de la pathologie, de l'embryologie et de la cytologie. Nous avions absolument besoin de ce genre d'expertise dans le groupe, et pas seulement pour moi.

Christopher Canning : Je vois.

Pr MacKenzie : Elle a été bien utile lorsque nous avons commencé à examiner des tranches de nos embryons pour comprendre ce qui se passait.

Donc, je le répète, je pense que je me suis joint au groupe parce que c'était la chose à faire pour élargir son expertise en matière de folate : nous étions trois dans le domaine plutôt que deux. Je crois que j'ai apporté au groupe une nette orientation moléculaire, du point de vue de la structure et de la fonction des protéines; mon regard était différent du leur, comme d'ailleurs le leur était

différent du mien en génétique.

Bref, c'était un haut lieu d'échange d'idées, un véritable laboratoire d'idées, où nous pouvions nous aider mutuellement dans nos projets. Parfois, c'étaient des idées folles, mais ces idées-là en faisaient germer d'autres, et je pense que nous nous aidions les uns les autres.

Christopher Canning : Jusqu'à votre adhésion au groupe, en 2001, vous n'aviez pas beaucoup travaillé sur l'humain. De votre point de vue, comment êtes-vous passé de la biochimie, des techniques de biologie moléculaire, à l'étude de maladies qui touchent l'être humain? Et selon vous, dans quelles maladies précisément votre travail a-t-il été ou pourrait-il être utile?

Pr MacKenzie : Ouais, effectivement, j'étais un fondamentaliste et je voulais comprendre comment les choses fonctionnaient. Au tout début, je ne me suis pas dit : « Moi, j'aimerais bien étudier telle maladie ». Non, je me suis plutôt dit : « Mais ça fonctionne comment, donc, une cellule? ». Si tu ne comprends pas ça, tu ne pourras jamais comprendre la maladie. Tout ça pour dire que nous travaillions vraiment au niveau moléculaire. Nous savions que le folate était très important pour tous les mammifères. Qu'il était essentiel pour vivre en santé.

Voilà, nous voulions comprendre le fond des choses. D'abord, j'ai voulu savoir « comment ça marche » plutôt que de partir d'une maladie donnée. Parce qu'à ce stade-là, ce n'était pas clairement défini – sauf, j'imagine… – si tu as une carence en folate, tu fais de l'anémie; et il y avait aussi le lien entre le folate, la vitamine B_{12} et certaines anémies. Mais de mon point de vue de biochimiste, la démarche manquait de rigueur si on envisageait les choses comme ça. Il fallait commencer par le commencement.

Certains préfèrent la démarche inverse, mais personnellement, je trouvais ça un peu descriptif. C'est qu'à l'époque, on n'avait pas vraiment les outils qu'il fallait; aujourd'hui, on a beaucoup plus d'outils pour relier un tas de choses à la maladie, parce qu'on a des outils de dépistage. Mais nous n'avions pas ça dans le temps. Alors, nous savons, je pense, que cette enzyme NAD-dépendante – qui, selon moi, est probablement notre apport le plus important sur le plan métabolique, parce que nous avons pu rédiger deux articles – les derniers articles de mon labo – pour faire le point sur...

Christopher Canning : Pardon, par « nous », vous voulez dire votre laboratoire?

Pr MacKenzie : Mon labo – mes étudiants et moi… Pour faire le point sur l'effet et le rôle de cette enzyme. Ainsi, son expression dans les mitochondries des cellules vouées à une croissance rapide nous dit qu'il y aurait peut-être là un moyen de combattre le cancer. Mais ce n'est pas simple : pour stopper l'expression d'une protéine, tu dois tenter d'inhiber l'activité d'une enzyme logée dans les mitochondries. Bien sûr, c'est probablement faisable, mais à ce stade-là de ma carrière, je n'étais pas disposé à passer six à dix autres années à exploiter ce filon.

C'est là que j'étais rendu. Je me suis dit : « Bon, c'est ici que ça termine ». Après 38 ans de financement du Conseil de recherches médicales et des

Instituts de recherche en santé du Canada, en plus de quelques petites subventions ici et là, je me suis dit que c'était assez. J'ai décidé d'arrêter ça là. Mais l'idée a du potentiel, ça, c'est sûr. Le problème, c'est que si tu trouves le moyen de faire ça, tu vas tuer toutes les cellules qui essaient de se multiplier rapidement. Reste à voir s'il est possible d'y arriver.

Chose certaine, au stade de l'embryogenèse, l'utilisation de tout inhibiteur serait mortelle. On y parviendrait peut-être dans une tumeur chez l'adulte, mais ça reste à voir. Et ç'aurait été un véritable changement de cap pour moi.

Ç'aurait probablement été une bien meilleure façon d'aborder le problème. Mais en ce qui me concerne, j'avais décidé de ne pas investir de temps là-dedans. Et à vrai dire, ce n'était même pas le genre de science qui m'intéressait. Ce que j'aime, c'est la recherche par hypothèse et non les trucs axés sur le dépistage. C'est quelque chose de très valable, mais ça ne m'apporte pas autant de satisfaction.

Christopher Canning : J'aimerais qu'on revienne un peu sur votre participation aux activités du groupe. Vous venez d'aborder le sujet. Vous rappelez-vous avoir été invité et vous souvenez-vous des personnes avec lesquelles vous avez parlé de ça? Comment ont-elles communiqué avec vous pour vous dire qu'elles souhaitaient ajouter un autre biochimiste au groupe?

Pr MacKenzie : J'ai oublié certains détails, mais j'imagine que ça s'est fait par l'intermédiaire de Rima [Rozen], puisqu'à ce moment-là, c'est elle qui dirigeait le groupe. Je suis certain qu'elle en a parlé avec David [Rosenblatt] et j'ignore si elle en a discuté avec d'autres, parce qu'ils perdaient des joueurs à l'époque, notamment Susie Tenenhouse. Elle prenait sa retraite, et il fallait que le groupe recrute pour conserver son statut.

Si tu perds des joueurs et que le groupe rapetisse trop, tu vas perdre ton statut de groupe, et c'était particulièrement vrai de ce groupe-là. Alors, je pense que je cadrais dans le groupe; nous avons fait valoir que nous étions trois à étudier le folate, David comme médecin, Rima comme généticienne moléculaire et moi comme biochimiste, et si je me souviens bien, nous nous sommes dit que nous nous complétions bien et que cette complémentarité servait bien l'étude du métabolisme du folate, un vaste domaine aux très, très nombreuses ramifications.

Christopher Canning : Super. Vous souvenez-vous de la structure de financement à l'époque? Si je comprends bien, vous deviez obtenir chacun votre subvention du CRM, et ensuite seulement vous étiez invités à vous joindre au groupe; vous en rappelez-vous?

Pr MacKenzie : Oh oui, je m'en rappelle très bien. Tu ne pouvais pas faire partie du groupe si tu n'avais pas ta subvention du CRM.

Christopher Canning : D'accord.

Pr MacKenzie : Et si tu perdais ta subvention, tu devais quitter le groupe.

Christopher Canning : Exact.

Pr MacKenzie : Mais dans le groupe, on avait accès à des fonds supplémentaires qui, dans mon cas, m'ont permis d'avoir des techniciens et, en particulier, le soutien dont j'avais besoin en histologie, soit du matériel et un technicien.

Alors, quand j'ai dû trancher mes petits embryons pour faire la lumière sur ce qui se passait, j'étais bien content de pouvoir compter là-dessus. C'est une expertise que je n'avais pas au Département de biochimie et dont j'avais absolument besoin pour avancer dans ma recherche qui, bien sûr, nous amène aujourd'hui… je ne sais trop quel nom lui donner. En fait, c'était un peu comme élargir sans cesse le cadre de la biologie.

Christopher Canning : Je vois. Tout à l'heure, vous vous êtes décrit comme le fondamentaliste du groupe. Vous disiez que le Dr Rosenblatt, lui, était le médecin, mais y avait-il d'autres échanges dans le groupe, lors des réunions et des colloques que vous organisiez, sur la recherche fondamentale et ses applications cliniques? Je vous pose la question uniquement parce qu'en retraçant l'histoire du groupe, j'ai constaté qu'il y avait eu des discussions intéressantes à ce sujet.

Pr MacKenzie : À mon sens, la recherche fondamentale a été, dès le tout début, au cœur des activités du groupe. Mais je ne pense pas qu'il y ait eu beaucoup… ou disons plutôt qu'en biochimie moléculaire, j'étais probablement le fondamentaliste pur et dur de ce groupe-là. À mes yeux, Charles Scriver était un généticien et un spécialiste en biochimie génétique qui en savait un bout sur la biochimie, pas de doute là-dessus, mais il n'avait pas de formation en biochimie, et il lui manquait donc certaines connaissances dans ce domaine, comme les mécanismes moléculaires et ce genre de choses.

L'appellation « biochimiste » ratisse pas mal large. Mettez deux biochimistes côte à côte, et vous pouvez vous retrouver avec deux bibittes complètement différentes. Chaque biochimiste est différent. Certains d'entre nous étaient davantage des praticiens, je dirais, et d'autres, des fondamentalistes purs et durs. Mais ces deux facettes de la biochimie étaient toujours présentes; d'ailleurs, j'invitais Charles Scriver – j'ai donné le cours en médecine, c'est-à-dire le cours de biochimie pour les étudiants de médecine, pendant des années.

J'invitais Charles Scriver à venir parler des erreurs génétiques du métabolisme. Il parlait de la phénylcétonurie et de ce genre de trucs importants. Nous faisions un exposé de biochimie, puis il présentait le cas d'un patient et on étudiait le profil biochimique de cette personne-là; c'était génial. Les étudiants adoraient ça. Tout ça pour dire que j'ai eu affaire aux membres du groupe pendant des années, bien avant d'y adhérer moi-même.

Christopher Canning : Et donc vous étiez parfaitement au fait de ce que faisaient ces gens-là. Charles Scriver faisait de la biochimie; vous aviez entendu parler des travaux de Susie Tenenhouse, comme vous l'avez souligné…

Pr MacKenzie : Oui. Je connaissais Susie; elle, elle était dans le phosphate et les os, et ce n'était pas du tout dans mes cordes. Il y avait plusieurs champs d'intérêt dans le groupe. Et ils ont évolué au fil du temps. Mais lorsqu'est venu le temps de

me joindre au groupe… vous savez, dans ma tête, on ne peut pas simplement réunir des gens qui s'intéressent à la biochimie génétique, mais travaillent à des projets qui n'ont rien à voir les uns avec les autres et justifier ça en se disant que le fil conducteur, c'est la génétique; ça ne tient pas vraiment la route.

Mais là, nous étions trois pour constituer un groupe autour du folate, puis il y avait mes mitochondries et celles d'Eric Shoubridge; bon, lui, il n'était pas dans le folate, mais il étudiait les anomalies des mitochondries. Et le génome mitochondrial – Eric Shoubridge, quel scientifique remarquable – et tout ça se tenait. Sa connaissance des mitochondries et la technique de laboratoire qu'il a mise au point pour étudier les mitochondries dans les lignées cellulaires m'ont été d'une aide inestimable, vraiment.

Christopher Canning : Vous me devancez, parce que j'allais justement vous parler d'interdisciplinarité. Si je comprends bien ce que vous me dites, les membres du groupe sont parvenus à cette interdisciplinarité scientifique en collaborant sous le grand thème de la médecine génétique. Est-ce bien cela?

P[r] MacKenzie : Oui, je pense que c'est une bonne façon de présenter les choses. Et je crois qu'au tout début, la biochimie génétique pouvait aller un peu dans tous les sens, et ça fonctionnait; ça ratissait pas mal large. Mais les modalités de financement se sont resserrées, et le concept de groupe a évolué. À un moment donné, il fallait démontrer que nous faisions véritablement cause commune. Il fallait qu'il y ait un lien, il fallait pouvoir démontrer que le tout était plus que la somme des parties.

Christopher Canning : Voilà, exactement.

P[r] MacKenzie : N'est-ce pas? Et je pense que ce concept a pris de plus en plus d'importance à partir… disons de la fin des années 1990. Il fallait justifier notre statut de groupe, démontrer la valeur ajoutée du groupe. D'après moi, on commençait à se dire que les gens invoquaient le statut de groupe pour aller chercher plus de financement.

Christopher Canning : Ah, intéressant, parce qu'une de mes dernières questions est la suivante : Quel était le ciment du groupe? Mais j'aimerais qu'on y revienne plus tard. Vous rappelez-vous d'échanges entre les membres du groupe sur la constitution de groupes avant la fin des années 1990?

P[r] MacKenzie : Non. En fait, je vous fais part d'une opinion bien personnelle. Parce que je n'avais jamais vraiment pensé à ce groupe avant qu'on m'invite à en faire partie. J'en connaissais l'existence. J'avais eu des échanges avec Charles [Scriver]. Même que comme biochimiste, je lui avais fabriqué des composés qu'il mettait à l'essai chez des enfants atteints de phénylcétonurie : lui et son équipe voulaient savoir si l'enfant avait une forme atypique de la maladie, et je fabriquais de la tétrahydrobioptérine pour lui.

Nous travaillions ensemble depuis belle lurette : ça, c'était probablement dans les années 1980. Je savais donc que le groupe existait, et comme je l'ai déjà mentionné, il y avait le club des amateurs de bières et de folate – en gros, le folate et la vitamine B_{12} – que Bernie Cooper avait fondé avant de quitter

McGill.

Bernie Cooper, David Rosenblatt, moi et… qui d'autre? Ah oui, Michael Whitehead. Michael Whitehead était dans le groupe à titre de spécialiste de la vitamine B_{12}. Il y avait donc le groupe B_{12}-folate : pour David, c'était plus la B_{12}, pour Bernie Cooper, la B_{12} et le folate, et lorsque Bernie a su que j'avais quitté le labo de Jesse Rabinowitz pour venir à McGill, il a dit : « Pourquoi on ne fonderait pas un club d'amateurs de bière? ». Alors, nous nous assoyions autour d'une table et discutions entre nous, mais bien franchement, la plupart d'entre nous ne comprenaient rien à ce que l'autre racontait. Mais nous nous intéressions tous au folate, et c'est là que j'ai rencontré David Rosenblatt.

Christopher Canning : Dans son entrevue, il a parlé de ce club-là, de ces discussions de fin de soirée sur le folate autour d'une bière et d'une baguette.

P[r] MacKenzie : Oui, c'était exactement ça.

Christopher Canning : Je vois.

P[r] MacKenzie : Absolument. Et ce qui est intéressant, c'est que souvent, nous ne comprenions rien à ce que l'autre racontait. En fait, ils ne connaissaient pas grand-chose sur la biochimie de base des protéines et moi, je ne connaissais pas grand-chose sur les trucs cliniques dont ils parlaient, mais nous avons un peu déteint les uns sur les autres. Et nous étions fidèles au rendez-vous. Nous n'aurions raté ces rencontres pour rien au monde.

Alors, David [Rosenblatt], Rima [Rozen] et moi-même, nous avons tous participé à ça. Puis au fil du temps et de l'évolution de mon projet, on en est venu à produire les souris *knockout* et à se dire : « Si c'était arrivé à un être humain – on travaillait sur des souris – mais si ça arrivait à un être humain, les effets seraient les mêmes, non? »

Donc, à un moment donné, c'était logique que je fasse partie du groupe.

Christopher Canning : Oui, super.

P[r] MacKenzie : Je pense qu'avant ça, quand j'étudiais uniquement les protéines et les mécanismes, je n'aurais pas vraiment été à ma place.

Christopher Canning : Effectivement. Super. À vrai dire, à vous entendre, j'ai l'impression que vous avez collaboré plus étroitement avec le groupe que certains des autres membres. Par exemple, j'ai parlé à Mark Trifiro et à Andy Karaplis, et souvent, ils ne collaboraient pas beaucoup avec les autres membres à l'époque. Votre présence dans ce groupe du folate semble avoir fait de vous un plus proche collaborateur.

P[r] MacKenzie : Vous n'avez pas tort.

Christopher Canning : À votre avis, qu'est-ce qui a fait que ce groupe a eu le vent dans les voiles pendant tant d'années, 37 plus précisément?

Pr MacKenzie : Au fond, c'est toujours le facteur humain qui est déterminant. Toujours. J'ai été vice-doyen à la recherche à la Faculté de médecine pendant près de neuf ans. Et s'il y a une chose que je retiens de ces années-là, c'est l'importance primordiale du facteur humain. Au-delà de la science, il y a les scientifiques.

C'est grâce à eux que la science s'incarne. Il faut croire qu'ils étaient au bon endroit, au bon moment, qu'ils étaient ouverts au changement et que la personne qui dirigeait le groupe à l'époque était disposée à rajuster le tir pour que l'argent continue de rentrer.

Christopher Canning : Qu'entendez-vous au juste par « rajuster le tir »?

Pr MacKenzie : Je pense à la direction dans laquelle la science, et notre façon de travailler, allaient évoluer. Autrefois, le scientifique s'affairait dans son labo et sortait de temps en temps de sa tanière en publiant un article.

C'était en grande partie du travail en solo. Mais dans notre groupe, il fallait trouver un dénominateur commun. Prenons les maladies moléculaires, par exemple; que ce soit les os ou une hormone, un problème qui touche les androgènes, le folate ou la vitamine B_{12}. Dans tous ces cas de figure, la biochimie génétique peut apporter des réponses.

Au début, c'était phénoménal, parce que c'était plutôt inédit comme méthode. On parle donc d'une façon de faire qui était alors unique en son genre et qui, je pense, a très, très bien fonctionné. Mais à vrai dire, nous partions des observations chez l'être humain, puis remontions la filière.

Christopher Canning : Je vois.

Pr MacKenzie : Bon, et grâce à la révolution de la biologie moléculaire, on peut aller chercher plus d'information; c'est ce qui m'est arrivé, au fond. À un moment donné, tu as à ta disposition un tas de nouvelles technologies pour répondre à une question qui serait restée sans réponse auparavant. Mais parallèlement à cela, le concept de groupe a évolué. Est arrivé un moment où réunir une bande de scientifiques qui ont le goût de parler de certaines anomalies génétiques en ratissant large, ça n'allait plus tenir pas la route. C'était possible, mais il fallait s'en tenir à un nombre de domaines restreint. Tu ne pouvais pas avoir cinq ou six personnes qui travaillaient dans cinq ou six domaines. On aurait considéré ça comme cinq ou six chercheurs individuels. D'après moi, vers l'an 2000, les organismes subventionnaires commençaient à se faire tirer l'oreille un brin, parce qu'ils ne voyaient pas où était la valeur ajoutée.

Christopher Canning : Si je comprends bien, vous avez senti un changement de cap du côté des organismes subventionnaires? C'est à peu près à l'époque où…

Pr MacKenzie : Ah absolument, absolument.

Christopher Canning : C'est à l'époque de la transition CRM-IRSC?

Pr MacKenzie : Oui, c'est exact, et j'ai participé de très près aux travaux des premiers comités

qui ont mis sur pied les IRSC.

Christopher Canning : Ah, super. Pouvez-vous m'en dire un peu plus à ce sujet?

Pr MacKenzie : On a mis en place les IRSC dans le but de réunir diverses expertises autour d'une question. Ce que ça veut dire en clair, c'est que pour étudier le diabète, par exemple, on va réunir toutes sortes de gens, depuis le biochimiste qui s'intéresse au métabolisme… je ne sais trop, disons des cellules des îlots de Langerhans, jusqu'au médecin qui traite le patient et s'intéresse aux répercussions sociologiques plus vastes du diabète. Alors, au lieu du clivage fondamental-clinique, on a une tentative d'intégration verticale de la recherche en santé.

Et tout ça était possible grâce à l'évolution du savoir : nous avions assez de connaissances, assez de données moléculaires et médicales, et nous pouvions compter sur une énorme poussée technologique. Mais 20 ans plus tard, ça n'aurait pas très bien fonctionné.

Christopher Canning : Et on parlait de ça dans les organismes subventionnaires?

Pr MacKenzie : Ah oui, on en parlait beaucoup, même. L'idée de faire suivre la filière fondamental-clinique-social à un problème était à la base des IRSC.

Christopher Canning : Voilà qui n'est pas dénué d'intérêt, puisque même au tout début, dans les années 1970, c'était la raison d'être du groupe : rapprocher la science fondamentale du patient en la transformant en traitements.

Pr MacKenzie : Bien entendu, mais vous savez, la science fondamentale de l'époque n'avait rien à voir avec celle des années 2000.

Oui et en fait, c'était vrai et le concept fonctionnait; d'ailleurs, si je ne m'abuse, c'est lui qui a donné naissance aux IRSC. Mais en réalité, ça dépendait de ce qui était faisable à ce moment-là. Ce n'était pas grand-chose comparativement à ce que nous pouvons faire aujourd'hui grâce à la technologie qui nous permet de faire de la génétique moléculaire et de la génomique.

Christopher Canning : Est-ce en partie pour cette raison que les IRSC ont cessé de financer les groupes en 2009 pour octroyer plutôt des subventions d'équipe? Ce changement de cap y est-il pour quelque chose?

Pr MacKenzie : Probablement, oui… mais je n'en suis pas sûr à 100 %, parce que je ne suis pas intervenu dans ce dossier. Mais je pense qu'en général, les subventions d'équipe étaient encore plus ciblées.

Christopher Canning : D'accord.

Pr MacKenzie : Donc je pense qu'on aurait pu, par exemple, prendre le groupe du folate… mais même là, je ne suis pas certain que nous aurions été admissibles à une subvention de groupe en faisant valoir notre centre d'intérêt, soit le folate et la vitamine B_{12}; peut-être aurait-il fallu proposer une équipe sur le folate et quelque chose comme la maladie coronarienne.

À mon avis, on voulait une équipe multifactorielle et multidisciplinaire, mais encore plus ciblée que le groupe. Parce que quand on regarde ça attentivement, surtout à la fin… regardez la diversité d'intérêts au sein du groupe à la fin. Et je pense qu'elle était encore plus grande au début.

Christopher Canning : On dirait que vers la fin, même s'il y avait de la collaboration, les projets de recherche étaient un peu plus fragmentés. Ça n'enlève rien au groupe, mais chacun travaillait davantage de son côté; est-ce votre impression également?

Pr MacKenzie : Eh bien, il est apparu clairement, je pense, qu'il fallait être un chercheur subventionné individuellement pour faire partie du groupe. Donc, il fallait que tu aies un projet de recherche solide et un programme de recherche en dehors du groupe.

Christopher Canning : Un projet indépendant, donc.

Pr MacKenzie : C'est cela. Autrement dit, si tu avais absolument besoin de ce groupe pour faire de la recherche, je pense que ça ne fonctionnait pas. Tu n'aurais pas obtenu de financement. C'était donc « montre-moi ton projet de recherche, puis » – du moins c'était comme ça quand je suis arrivé – « montre-moi ton projet de recherche, un projet indépendant, et prouve-moi que tu as assez de financement ». Bon, du financement, on n'en a jamais assez, mais tu devais avoir de l'argent pour mener tes propres recherches. Et si tu te joins au groupe, montre-moi quelle sera la valeur ajoutée et ce que cette interaction va t'apporter.

Pour être franc, dans mon cas à moi, si j'avais collaboré individuellement avec Eric [Shoubridge], Rima [Rozen] et David [Rosenblatt], je serais probablement parvenu au même résultat, sauf que je n'aurais pas eu le financement nécessaire pour le volet histologique. Donc grâce au groupe, j'ai eu accès à des fonds supplémentaires et j'ai pu faire des choses que je ne pouvais pas faire avec ma propre subvention du CRM ou des IRSC.

Christopher Canning : Ce qui était exactement l'objectif de ce type de financement, non?

Pr MacKenzie : Oui, alors en ce qui me concerne, c'était en partie ça, la valeur ajoutée. Et non seulement ça, mais ça te donnait accès à des gens qui possédaient une expertise qui pouvait te servir dans tes travaux.

Ces gens collaborent donc à ta recherche subventionnée ou quelque chose qui ressemble à ça, ou si tu peux travailler en groupe, c'est encore mieux, du moins à mon avis.

Christopher Canning : D'accord. Lorsque vous étiez aux IRSC, avez-vous participé aux discussions qui ont mené à la fin du financement du groupe? Savez-vous pourquoi?

Pr MacKenzie : Non, je n'y étais pas.

Christopher Canning : Non?

Pr MacKenzie : Non.

Christopher Canning : Combien de temps y avez-vous passé?

Pr MacKenzie : Les IRSC n'ont jamais, jamais eu assez d'argent. Il aurait fallu investir beaucoup plus dans ce concept-là pour que ça fonctionne. Nous avons élaboré un concept génial, mais l'État ne l'a jamais pleinement financé.

Ils cherchaient constamment à mieux utiliser leur argent. Et je pense qu'ils avaient toujours l'impression qu'il n'y avait pas assez de valeur ajoutée dans les groupes, et peut-être que les IRSC auraient souhaité des groupes plus ciblés.

Christopher Canning : Je vois.

Pr MacKenzie : Je pense par exemple à une équipe sur le diabète ou l'obésité plutôt qu'à un groupe qui étudie les maladies génétiques dans divers domaines.

Christopher Canning : J'aimerais vous poser quelques questions avant de conclure notre entretien. Nous avons effleuré le sujet, mais j'aimerais savoir précisément : quel était le ciment de ce groupe-là?

Pr MacKenzie : Je crois que pour moi, le ciment du groupe – je ne sais pas trop comment présenter cela, et je ne veux blesser personne – mais pour moi, le ciment du groupe, c'étaient les membres du groupe avec lesquels je collaborais directement.

Il y avait d'autres bons scientifiques dans ce groupe-là, et vous en avez parlé. Mais les gens de l'Hôpital général juif, ils faisaient des choses intéressantes, mais ça n'avait rien à voir avec moi. J'avais bien du plaisir à les écouter raconter ce qu'ils faisaient, mais à mes yeux, ce n'était pas ça, le ciment du groupe, parce que je n'ai jamais vraiment cru qu'il pouvait y avoir de la cohésion dans un groupe formé de gens aux multiples intérêts qui n'avaient que la génétique comme dénominateur commun. Pour moi, un groupe, ce n'est pas ça. Mon groupe à moi, c'était « folate, B_{12} et mitochondries ».

Et ça, ça veut dire Rima, David, Eric et moi. Il y avait donc probablement des groupes dans le groupe.

Christopher Canning : Intéressant. Dites-moi, le facteur spatial y était-il pour quelque chose? Vous étiez selon toute vraisemblance au Département de biochimie de l'Université McGill, et les autres étaient sur le campus ou ailleurs…

Pr MacKenzie : J'étais sur le campus de McGill. David est dans l'un des hôpitaux, Rima est à l'Hôpital pour enfants et Eric est à l'Institut neurologique. Mais à mes yeux, ça ne posait aucun problème, même si nous savons que ça dérangeait peut-être les IRSC. Je pense qu'ils voulaient que les équipes travaillent en collaboration plus étroite non seulement au sens figuré, mais aussi au sens propre, c'est-à-dire tout le monde au même endroit.

Christopher Canning : Oui, et on parlait de ça dès 1972. En fait, c'était un principe écrit noir sur blanc

dans le document du CRM. Tous les membres du groupe devaient travailler au même endroit. Ça ne s'est jamais produit, mais le financement a quand même été maintenu.

Pr MacKenzie : Ouais. Mais, voyez-vous, le concept du « groupe » était un peu plus large à l'époque. Et j'ai l'impression qu'au fil du temps, on est passé du concept de « groupe » au concept d'« équipe », et une équipe, ça travaille sur un problème plus ciblé.

Christopher Canning : Ah, super. Merci pour cette précision. Faites-vous encore de la recherche? En quelle année avez-vous pris votre retraite?

Pr MacKenzie : Oh, j'ai pris ma retraite à la fin du mois de mai dernier.

Christopher Canning : Ah bon, félicitations!

Pr MacKenzie : Et je ne fais pas de recherche.

Christopher Canning : Ah non? D'accord. Quelqu'un – j'ai oublié qui – mais je voulais vous le demander. J'ai entendu dire que vous étiez un professeur fantastique; c'est vrai?

Pr MacKenzie : [rires] J'aimais bien enseigner et je recevais de bons commentaires; ça me plaisait vraiment beaucoup.

Christopher Canning : Quelle matière enseigniez-vous? La biochimie?

Pr MacKenzie : La biochimie. J'ai enseigné la biochimie aux étudiants de médecine pendant des années. Et après, j'ai donné un cours sur le métabolisme de base aux étudiants de deuxième année en sciences biologiques, aux étudiants de biochimie, de physiologie, à certains étudiants de biologie, d'anatomie, de biologie cellulaire et de microbiologie; ils étaient nombreux à suivre ce cours, que nous appelions « régulation du métabolisme ».

Alors, nous leur apprenions non seulement qu'il y avait des voies métaboliques, mais nous tentions aussi de leur en expliquer le fonctionnement. J'adore proposer à mes étudiants des énigmes du genre : « Cette voie fonctionne à merveille dans les muscles. Mais est-ce qu'elle fonctionnerait aussi dans le cœur? »

Et là, tout à coup, tu te rends compte que ça ne peut pas fonctionner comme ça dans le cœur. Tu dois t'efforcer de comprendre le pourquoi du comment, la différence entre les deux; je crois que les étudiants aimaient bien ça. Ça permet de décortiquer le fonctionnement d'un système.

Christopher Canning : Eh bien, voilà, je n'ai plus de questions. Aimeriez-vous ajouter quelque chose? Avez-vous des questions?

Pr MacKenzie : Non, pas vraiment. J'ai bien aimé faire partie du groupe. En réalité, ça ne faisait qu'officialiser des échanges que j'avais déjà avec David et Rima. Je connaissais Eric lorsque j'étais vice-doyen à la recherche. Et je pense que

j'étais vice-doyen lorsque je me suis joint au groupe. Selon moi, le groupe a simplement consolidé des interactions que nous aurions pu avoir autrement. Probablement plus que ça, à vrai dire; je pense que ça m'a permis de pousser certains aspects de ma recherche beaucoup plus loin que j'aurais pu le faire en faisant cavalier seul.

Christopher Canning : Formidable. Merci beaucoup de m'avoir accordé de votre temps.

FIN DE L'ENTRETIEN

Roy Gravel, le 4 février 2011

Christopher Canning : Nous sommes le 4 février 2011. Ici Christopher Canning en compagnie de Roy Gravel. M. Gravel, je suis très honoré de pouvoir m'entretenir avec vous de deux grands sujets qui touchent la génétique humaine.

J'aimerais d'abord que nous parlions de votre parcours universitaire, qui a contribué à l'avancement de la génétique médicale au Canada et ailleurs dans le monde. Ensuite – et surtout, pour les besoins de notre étude – je m'intéresse à votre participation au groupe sur la génétique médicale des IRSC[1] – anciennement le CRM[2] – auquel vous vous êtes joint en 1994 et dont vous avez été membre jusqu'à sa dissolution, en 2009. Vous avez aussi dirigé le groupe de 1994 à 2001.

Mais avant de parler du groupe, parlons un peu de vous. Où êtes-vous né et où avez-vous passé votre enfance?

Roy Gravel : Je suis né à Montréal et j'y ai passé une partie de mon enfance. J'ai fait mes études de premier cycle et ma maîtrise à McGill. Ensuite, j'ai fait une autre maîtrise à Yale, où j'ai aussi obtenu mon doctorat en 1972 et mon postdoctorat en 1974. Cette même année, j'ai décroché mon premier poste à l'Hôpital pour enfants.

En 1989, je suis retourné à Montréal, à McGill et à l'Hôpital de Montréal pour enfants, et je me suis joint à leur Institut de recherche. C'est là que j'ai commencé à m'intéresser à la génétique avec mes collègues de McGill.

Christopher Canning : Fantastique. Mais avant de parler plus en détail de l'Université McGill, dites-moi, quelles attentes avaient vos parents en matière de réussite scolaire, peut-être plus particulièrement en sciences?

Roy Gravel : Que voulez-vous dire?

Christopher Canning : Quelles étaient les attentes…

Roy Gravel : Dans quel contexte?

Christopher Canning : Je me demandais seulement comment vous en étiez venu à vous intéresser aux sciences, disons, quand vous étiez au secondaire.

Roy Gravel : Eh bien, à l'époque où j'étais au secondaire, un chercheur nommé Khorana qui, je crois, était à Vancouver à ce moment-là, commençait à déchiffrer le code génétique. On entendait parler de ça régulièrement à l'école, à mesure que les données étaient publiées. C'est donc dans ce super cours de biologie que mon histoire d'amour avec la génétique a débuté.

Je n'avais pas décidé à ce moment-là de devenir généticien, mais une chose est sûre, le domaine m'intéressait et, comme je l'ai dit, j'ai fait mes études de

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

premier cycle à McGill et c'est durant cette période que mon engouement pour la génétique s'est confirmé.

On peut donc dire que j'ai su assez tôt que je voulais me diriger vers la recherche et la génétique.

Christopher Canning : Et, à ce moment-là, la génétique médicale éveillait-elle chez vous un intérêt particulier ou suiviez-vous tout simplement les cours d'initiation à la génétique du Département de biologie?

Roy Gravel : À vrai dire, comme tout bon étudiant au premier cycle indécis, j'aurais trouvé mon bonheur dans n'importe quel domaine. Et, en fait, je ne me suis pas retrouvé en génétique humaine au tout début. À la maîtrise, j'ai étudié un organisme modèle avec Etta Käfer, à McGill. On n'était pas du tout dans la génétique humaine. C'était fascinant.

Mon doctorat n'avait rien à voir lui non plus avec la génétique humaine. La génétique médicale n'est arrivée qu'à l'étape du postdoctorat.

Christopher Canning : Et sur quoi portaient vos recherches postdoctorales? Je vois que vous étudiiez la vitamine B_{12}?

Roy Gravel : Ouais, en fait, la B_{12} était au cœur de mes travaux, mais pas comme vous l'imaginez. Au doctorat et à la maîtrise, j'ai étudié le métabolisme. Mes recherches portaient sur un champignon appelé « *Aspergillus* » et sur les voies métaboliques. On est donc très proche de ce que j'allais faire dans les maladies humaines, mais disons que traiter le trouble génétique d'un champignon, c'est moins passionnant que traiter un être humain.

Alors voilà, en gros, ma formation. Pour mon postdoctorat, j'ai travaillé dans un labo qui commençait à étudier des cultures de tissus prélevés chez des patients. Ce labo était dirigé par Leon Rosenberg, à l'Université Yale. Il est très certainement l'un des pionniers de la caractérisation des erreurs innées du métabolisme. À l'époque, on étudiait le métabolisme de la vitamine B_{12} et de la biotine.

C'est donc là-dessus que j'ai travaillé pendant mon postdoctorat et, à vrai dire, je n'ai renoué avec la vitamine B_{12} qu'à mon arrivée dans le groupe de McGill, dans les années 1990.

Christopher Canning : Et entre votre postdoctorat et votre adhésion au groupe, qu'avez-vous fait?

Roy Gravel : Au début, j'ai étudié le métabolisme de la biotine, les carboxylases, et tout ça était lié de très près à la vitamine B_{12}; je suis sorti de ce domaine-là, mais il reste que le métabolisme n'était pas bien loin. Puis, après quelques années à l'Hôpital pour enfants de Toronto, je suis passé aux maladies de Tay-Sachs et de Sandhoff, des maladies neurodégénératives qui nous ont tenus bien occupés pendant de nombreuses années. Le groupe dont je faisais partie à Toronto a travaillé sur ces troubles, essentiellement.

Christopher Canning : Vous avez été recruté à Toronto précisément pour ce travail?

Roy Gravel : Eh bien, disons que dans la vie, tu te mets en quête d'un travail et tu espères qu'on va t'embaucher. Dans cette optique, je dirais que Toronto m'a embauché et non que j'ai été recruté à proprement parler, mais j'avais postulé pour un poste à cet endroit, puisqu'ils affichaient des postes à l'époque.

Christopher Canning : Si je ne m'abuse, le Dr Rosenblatt avait travaillé lui aussi avec Leon Rosenberg aux États-Unis, non?

Roy Gravel : Non. Je crois que vous pensez à Rima Rozen.

Christopher Canning : Ah oui, Rima Rozen est allée à Yale pour travailler avec Leon Rosenberg, effectivement.

Roy Gravel : C'est bien ça.

Christopher Canning : Connaissiez-vous son travail à l'époque?

Roy Gravel : Vous dites?

Christopher Canning : Étiez-vous au courant de ce qu'elle faisait à l'époque? Étiez-vous en contact avec elle?

Roy Gravel : Elle est arrivée à Yale après mon départ, si ma mémoire est bonne. Mais apparemment, elle a passé un été ou une partie d'été dans mon laboratoire pendant mon séjour à Toronto, où elle a découvert certaines des technologies que nous utilisions. Malheureusement, je ne me rappelais pas du tout de ça lorsque je l'ai rencontrée à McGill à mon arrivée dans le groupe; c'était assez gênant, merci.

Christopher Canning : Je vois. Et comment cette trajectoire vous a-t-elle mené à votre premier poste à McGill? Vous êtes à l'Hôpital pour enfants de Toronto, puis vous vous retrouvez à McGill en 1989, c'est bien ça?

Roy Gravel : Oui, Charles Scriver avait lancé un appel par lettre à la grandeur du pays. On recherchait un directeur pour l'Institut de recherche de l'Hôpital de Montréal pour enfants. J'ai reçu la lettre – on fonctionnait par lettre à l'époque, pas par courriel – et je l'ai probablement mise de côté, comme on le fait aujourd'hui avec les fameux courriels. Il m'a fait parvenir une deuxième lettre qui disait : « Vous n'avez pas répondu à ma première lettre. Est-ce que ça vous intéresse ou pas? » C'était un peu plus tard, j'imagine. Quoi qu'il en soit, je m'en souviens, parce qu'au fond, il me disait « Tu es censé me répondre », alors que j'avais probablement l'impression que la même lettre avait été envoyée à tout le monde.

Cette lettre m'a fait réfléchir et je me suis dit qu'il serait temps que je fasse autre chose et que je sorte du cadre du laboratoire. J'ai donc manifesté mon intérêt et j'ai ensuite obtenu le poste à McGill.

En fait, on peut dire que c'est Charles Scriver qui m'a recruté à l'Hôpital de Montréal pour enfants, dans ce qui était le centre de ce qu'on appelait à l'époque le « groupe de génétique médicale du CRM ». Charles en était le directeur.

Christopher Canning : Et, à ce moment-là, en quoi consistait votre mandat de directeur de l'Institut de recherche de l'Hôpital de Montréal pour enfants?

Roy Gravel : À l'Institut?

Christopher Canning : Oui.

Roy Gravel : C'est comme le nom l'indique. L'Institut de recherche comptait 40 ou 50 membres et j'assurais un rôle administratif, c'est-à-dire que je distribuais les sous, j'aidais à la conduite des recherches, je dirigeais le programme. Autrement dit, je décidais comment dépenser l'argent. Les fonds que recevait l'Institut servaient à faire fonctionner les programmes de recherche, et la génétique en obtenait une partie comme les autres domaines.

Christopher Canning : Excellent. À vos débuts, vous travailliez sur le métabolisme de la vitamine B_{12} et le métabolisme en général. Comment en êtes-vous venu à orienter vos recherches vers les techniques de biologie moléculaire à la fin des années 1980? Aviez-vous étudié ces nouvelles techniques à Toronto, disons, de la fin des années 1970 jusque dans les années 1980?

Roy Gravel : Eh bien, aux alentours de 1980, le clonage commençait à être bien établi dans le système. Le genre de travail que bon nombre d'entre nous faisaient dans le domaine des maladies génétiques chez les enfants ne se prêtait pas bien au clonage parce que la plupart des gènes exprimaient ce que nous appelions des « protéines de ménage ». Ce sont des protéines présentes en très petites quantités dans les cellules et non pas quelque chose de très présent qu'on aurait pu isoler en grandes quantités.

Donc, dans les débuts du clonage, on s'intéressait beaucoup à l'hémoglobine, par exemple. L'ovalbumine a été un franc succès parce qu'on pouvait trouver beaucoup de cette protéine. Et le concept général de la structure des gènes a été défini. Tout ça s'est passé durant les années 1970.

Alors, quand il a été possible de se pencher sur le type de gènes en cause dans les erreurs innées du métabolisme, le groupe de la génétique à l'Hôpital pour enfants s'est intéressé à ce domaine. On a tout mis de côté pour commencer à apprendre comment faire ces expériences. Et ce qui était vraiment intéressant à l'Hôpital pour enfants à cette époque, c'est que le groupe travaillait beaucoup sur la génétique des cellules somatiques, pour utiliser un terme général. Et de nombreux laboratoires du groupe étaient emballés à l'idée d'en apprendre plus sur ces technologies en même temps. Alors, on s'est beaucoup entraidé et on s'est occupé chacun d'aspects différents de ces technologies pour essayer de les perfectionner. Ensuite, on échangeait nos résultats les uns avec les autres.

Je ne me rappelle plus l'année exacte, mais je me souviens qu'une subvention avait été renouvelée. Donc, j'avais peut-être trois ans devant moi durant lesquels je n'avais pas à me soucier de la subvention. Alors, on a uni nos forces au labo et on s'est dit « Laissons tout tomber, on va apprendre à cloner. » Ça se passait en 1981 ou 1982, je crois. C'est comme ça qu'on s'est retrouvé à cloner des gènes liés aux maladies génétiques au milieu des années 1980.

Christopher Canning : Aviez-vous l'impression que l'Université McGill, le Département de génétique humaine de McGill et les chercheurs là-bas avaient un peu de retard dans la maîtrise de ces techniques moléculaires? Et la seule raison pour laquelle je vous pose cette question c'est qu'au milieu des années 1980, le groupe avait le sentiment que ces technologies leur faisaient défaut et qu'ils n'avançaient pas aussi vite que les gens à Toronto. Avez-vous entendu parler de ça?

Roy Gravel : [Rires] Je suis mal placé pour vous répondre. Eh bien, je ne pourrais pas vous dire officiellement à quel point l'Université McGill était avancée, mais quand je suis arrivé à l'Hôpital de Montréal pour enfants à la fin des années 1980, il y avait une seule machine de PCR à l'Institut et elle était faite maison.

Vers 1987-1988, ces machines sont arrivées sur le marché et nous avons obtenu notre première machine grâce à un don d'une famille à l'Hôpital pour enfants. C'est en grande partie grâce à elle qu'on a pu cloner les gènes en cause dans la maladie de Tay-Sachs. Ça se passait vers la fin des années 1980.

Donc, quand je suis arrivé à Montréal en 1989, le groupe avait deux ou trois machines. Je ne me souviens pas de ce que j'avais, mais j'avais au moins une machine et je sais qu'au moins un ou deux labos en avaient une. Les gens découvraient les avantages considérables de cette réaction pas mal géniale. C'était vraiment les débuts. Autrement dit, on n'avait pas de retard. En fait, quand on a commencé à s'intéresser à la PCR, on ne pouvait pas se procurer de machines au Canada.

Quand on a obtenu ces premières versions, plusieurs endroits avaient des machines faites maison, mais on ne pouvait pas trouver les réactifs et ils n'étaient pas sur le marché au Canada. La compagnie testait les réactifs, et tout le système, à plusieurs endroits aux États-Unis et nous n'y avions pas accès. Et je me souviens que lorsqu'on faisait des recherches sur la maladie de Tay-Sachs et qu'on a cloné l'un des gènes en cause dans cette maladie, on n'avait pas accès à ces réactifs. En fin de compte, ce sont des amis aux États-Unis qui nous ont envoyé le matériel pour réaliser ces expériences. De cette façon, on a pu contourner le problème parce que les compagnies ne collaboraient pas avec nous et ne nous envoyaient pas de matériel.

En fait, j'avais téléphoné à la compagnie pour savoir si elle voulait collaborer avec nous afin qu'on puisse obtenir les réactifs. Mais elle nous a répondu « Envoyez-nous vos échantillons. Nous les analyserons et nous publierons les résultats. Et nous mentionnerons vos noms dans l'article. »

Christopher Canning : [Rires]

Roy Gravel : Et ça ne nous intéressait pas. C'est seulement quelques années après ça que je suis arrivé à Montréal et que j'ai constaté qu'il n'y avait pas de machine de PCR, mais ce n'était pas une très grosse lacune. Mais une fois à Montréal, on a presque immédiatement acheté un grand nombre de ces machines. On en a très rapidement distribué une dizaine à l'Institut, donc on a rattrapé le retard. S'il y a eu un décalage, c'était plutôt au milieu des années 1980, je crois. Mais c'est seulement parce qu'au début, tout le monde n'en était pas au même point.

Dans notre cas, on était emballé par ce projet, mais c'est probablement parce qu'on manquait d'idées avec les méthodes traditionnelles, alors on voulait passer à ces nouvelles technologies. Et, dans mon cas, ça a coïncidé avec la subvention. Je n'aurais pas pris le risque durant l'année, avant que la subvention soit versée, de mettre mon labo sens dessus dessous et de tout recommencer.

Christopher Canning : Je vois. Croyez-vous que votre expérience avec les machines PCR à Toronto est l'une des raisons pour lesquelles le Dr Scriver souhaitait que vous veniez à McGill?

Roy Gravel : Non. Je ne sais pas pourquoi il s'intéressait à moi. Je ne crois pas qu'il était au courant de ce que je vous ai décrit. Enfin, je ne sais pas. On clonait des gènes, donc c'est possible, mais on n'en a jamais discuté. Je crois que j'étais juste là au bon moment, mais je ne pourrais pas vous en dire plus.

Christopher Canning : Eh bien, dans un document que j'ai trouvé dans les dossiers du Dr Rosenblatt, il est mentionné que, au milieu des années 1980, le groupe était à la recherche de personnes qui utilisaient ces techniques au Canada, et votre nom figurait sur une liste de candidats potentiels à qui le groupe voulait demander de venir à McGill. Je ne sais pas si vous étiez au courant.

Roy Gravel : Non. Tout ce que je sais c'est que j'ai reçu cette lettre et que je n'avais pas remarqué qu'elle m'avait été envoyée précisément à moi. Je croyais qu'il l'avait envoyée à plusieurs personnes au pays. Je suis généticien et je m'intéresse au métabolisme. Je le connaissais assurément, alors j'ai dû me retrouver sur la liste par hasard. Je n'ai pas pris cela très au sérieux, ce qui explique peut-être pourquoi, au début, je n'ai pas vraiment répondu. Je ne me voyais pas à ce poste. C'est seulement quand il a présenté les choses un peu différemment dans sa deuxième lettre que j'ai commencé à y songer. Je me suis dit que j'irais leur rendre visite et quand j'y suis allé, j'ai senti… Quand j'étais à Yale et que je me cherchais un emploi un Canada, je voulais revenir à la maison. Bien entendu, j'ai pensé à l'Université McGill, mais il n'y avait pas de poste vacant. Mais je savais que le groupe était là. Je trouvais leur travail très intéressant et, en fait, j'étais déçu de ne pas pouvoir présenter ma candidature à l'époque. Alors, j'étais flatté quand le Dr Scriver m'a contacté.

Christopher Canning : En effet. Avant qu'on parle du groupe comme tel, j'aimerais vous poser deux questions. Quelles maladies humaines – vous avez parlé de la maladie de Tay-Sachs – mais quelles autres maladies humaines avez-vous étudiées en particulier, disons du début de votre carrière jusqu'à aujourd'hui, à Calgary?

Roy Gravel : Pouvez-vous répéter?

Christopher Canning : Quelles maladies étudiez-vous actuellement, et quelles maladies avez-vous étudiées au cours de votre carrière, du début des années 1970 à aujourd'hui?

Roy Gravel : Wow. Eh bien, actuellement, je travaille uniquement sur la vitamine B_{12}. Je suis en fin de carrière, alors dans les dernières années, j'ai commencé à faire de l'élagage pour pouvoir me concentrer davantage sur certains sujets. Quand je suis arrivé à Calgary il y a dix ans, je travaillais sur la maladie de Tay-Sachs, la

biotine, la vitamine B_{12}. Je crois que c'est tout. Du moins, sur le plan du financement, c'étaient les principaux sujets. Au milieu de la décennie, vers 2004 ou 2005, j'ai décidé qu'il était temps de retirer graduellement la maladie de Tay-Sachs pour me concentrer sur le métabolisme des vitamines. Puis, il y a quelques années, j'ai décidé de ne pas renouveler ma subvention de recherche sur la biotine parce que je sentais que la dernière phase de ma carrière approchait. Je me suis dit que je devais en profiter pour me pencher sur les domaines de recherche les plus prometteurs, c'est-à-dire ceux qui avaient les meilleures chances de produire des résultats intéressants, et c'était le cas de la vitamine B_{12}. Alors, depuis deux ans, je travaille exclusivement sur le métabolisme de la vitamine B_{12}.

Christopher Canning : Vous avez un peu bouclé la boucle pour revenir à votre premier sujet de recherche?

Roy Gravel : Oui, ça c'est vrai. Et la raison pour laquelle ça s'est produit pourrait vous intéresser. Je ne suis pas revenu à la vitamine B_{12} parce que je voulais boucler la boucle. David Rosenblatt est venu me voir un jour et m'a dit : « Tu sais, tu es installé à Montréal, tu travailles sur la vitamine B_{12}, on travaille sur la vitamine B_{12}; tu devrais te joindre à l'équipe. » Ça semblait intéressant et l'idée nous a plu. Donc, mon retour à la vitamine B_{12} n'était pas intentionnel; c'est en discutant avec David que je suis arrivé là.

Christopher Canning : D'accord. C'est une excellente entrée en matière pour mes prochaines questions. Tout d'abord, pouvez-vous m'expliquer comment vous en êtes venu à participer au groupe?

Roy Gravel : David a dit… Non, en fait, je ne sais pas. Quelqu'un a dit : « Voudrais-tu être le directeur du groupe à la prochaine demande de subvention? ». Quand je suis arrivé à Montréal, je me souviens que quelqu'un m'avait demandé si je voulais me joindre au groupe. Et à ce moment-là, je ne me souviens plus s'il y avait une subvention qui allait être renouvelée, mais j'ai dit que ça ne serait pas une bonne idée parce que je venais d'arriver. Je n'avais encore jamais dirigé de groupe et les gens s'en sont probablement rendu compte très vite. Mais je me retrouvais maintenant dans cet institut et avec cet énorme travail, assurément durant les premières années. Je devais apprendre comment faire ce genre de chose et, bien sûr, mettre mon labo sur les rails.

Alors, à l'époque, j'ai simplement dit : « Vous savez, ce n'est pas une bonne idée. Je ne pourrais pas beaucoup participer parce que je n'aurais pas vraiment le temps. Je suis ici pour diriger l'Institut, alors c'est ça qui doit être ma priorité. » Puis quelques années plus tard, on m'a demandé si j'aimerais me joindre au groupe et en être le directeur pour la prochaine demande de subvention. Je crois que c'est David qui est venu me voir, mais je n'en suis pas certain; je ne me souviens pas très bien. En ce qui concerne le labo, j'étais proche de Rima Rozen, mais pour ce qui est de ce genre de conversation, c'est fort probablement avec David que ça a eu lieu.

Christopher Canning : D'après les discussions que j'ai eues avec les autres membres, il semble que le groupe voulait garder la direction à l'Hôpital de Montréal pour enfants. Alors, ce n'est pas surprenant qu'on vous ait confié le poste et qu'on l'ait confié ensuite à Rima Rozen parce que vous avez repris les rênes après le D^{r} Scriver en 1994.

Roy Gravel : Oui, mais il est question de la façon dont je me suis joint au groupe, non? Or, je n'en étais pas membre avant ce moment-là. Quand je me suis joint au groupe, l'idée était que j'agirais comme chercheur principal pour la subvention, ce qui est peut-être quand même ce que vous décrivez. En tout cas, il ne fait aucun doute qu'ils voulaient que la direction reste à l'Hôpital de Montréal pour enfants. Je me souviens de ça. Dans le cas de Rima, elle était le choix logique. Quand je suis parti, elle avait atteint les échelons supérieurs et était très reconnue dans son domaine et, comme vous le savez, elle a pris la direction de l'Institut après moi. Elle a repris le flambeau. C'était tout à fait logique qu'elle devienne la nouvelle responsable de la subvention. En partie parce qu'elle était à l'Hôpital de Montréal pour enfants, mais surtout, du moins à mon avis, parce qu'elle était la bonne personne pour ce poste et parce qu'elle s'était taillé une réputation dans son domaine de recherche.

Christopher Canning : Et quel rôle les autres membres du groupe jouaient-ils lorsque vous en faisiez partie? Vous en souvenez-vous? Autrement dit, quels étaient les différents domaines de recherche et en quoi contribuaient-ils au groupe?

Roy Gravel : Eh bien, je n'ai pas fait ce genre de recension, mais on avait réalisé une expérience au début. Je crois que ça concernait la demande de subvention à laquelle je participais pour recruter des gens du côté de la résistance de l'hôte. Emil Skamene était déjà avec nous et on a proposé d'ajouter Danielle Malo, Eric Shoubridge et Joe Nadeau. On voulait amener le groupe dans de nouvelles directions, et c'était en fait un excellent groupe.

Mais, de façon générale, on avait une diversité de sciences, pas seulement de scientifiques. Il y avait des sciences avancées en ce qui concerne les différentes sortes de troubles génétiques étudiés. Si on compare les os et le phosphate au métabolisme de la vitamine B_{12}, on constate qu'ils sont très différents; l'approche est très différente.

Alors, passer à la résistance de l'hôte était intéressant. Emil Skamene était essentiellement le leader du groupe et on a mis tout ça sur pied ensemble. Je crois que le résultat final… Ce dont je ne me souviens pas exactement c'est si on a survécu. Mais le résultat final est qu'on a fini par se séparer parce que le CRM, je crois que c'était encore le CRM, ou les IRSC ne trouvaient pas que c'était une structure cohérente.

Il y avait des écoles de pensée très différentes concernant la nature des travaux de génétique qu'on faisait et c'était, selon nous, très intéressant. Mais ce qu'il est important de retenir c'est que le noyau du groupe était constitué de David [Rosenblatt], de Rima [Rozen] et de nous, et on étudiait la vitamine B_{12} et le folate et on était très intégrés dans la nature de ce travail. Mais à vrai dire, le groupe était constitué de différents domaines et cette diversité se reflétait dans le grand groupe de gens que vous connaissez. Et, nous, on était seulement une petite équipe de personnes qui avaient tendance à travailler étroitement ensemble.

Christopher Canning : Et cette équipe était formée de vous, de Rima Rozen et de David Rosenblatt?

Roy Gravel : Pardon?

Christopher Canning : Cette équipe était formée de vous, de Rima Rozen et de David Rosenblatt?

Roy Gravel : Oui, oui.

Christopher Canning : Et qu'est-ce qu'impliquait la direction du groupe? Je vois que vous avez été le directeur pendant près de huit ans. En quoi consistait votre rôle?

Roy Gravel : Oh là là! Je ne me souviens pas. [Rires] Je crois que la chose la plus importante est que le directeur a la responsabilité d'obtenir le renouvellement de la subvention. Et il faut être tourné vers l'avenir quand on rédige une demande de subvention. Il faut utiliser les progrès qu'on a accomplis pour démontrer qu'on est capable de faire ces choses. Au bout du compte, ce qui vous permet d'obtenir des fonds c'est ce que vous réaliserez par la suite.

On se rencontrait pour discuter de ça, du genre de terrain de jeu qu'on souhaitait établir pour l'avenir et de ce qui serait vendeur auprès des examinateurs de la demande de subvention. Et on était une bonne équipe pour penser à ce genre de choses, à cause de nos enjeux de recherche, bien sûr, mais les formations et les activités qu'on faisait jouaient aussi un rôle là-dedans. On recevait la visite de gens dans le cadre du processus d'examen et on devait se justifier auprès de ces personnes qui nous posaient des questions. Donc, une grande partie du travail de directeur consistait à soutenir le groupe durant ces périodes, quand on demandait une subvention, et Rima a fait la même chose par la suite.

Mais au-delà de ça, entre ces périodes, il était important de parler de recherche, d'y réfléchir et d'interagir, mais de façon informelle. Personne n'avait besoin d'instructions, pour ainsi dire, ni de supervision ou quelque chose du genre. Ce n'est pas comme ça que ça fonctionnait. Alors, on parlait de seulement faire de la recherche, qui serait axée sur nos propres sujets bien sûr. Le petit groupe dont faisaient partie David et Rima était bien plus harmonieux qu'on l'était avec les autres groupes. Mais on s'occupait de programmes aux cycles supérieurs ensemble, on enseignait dans une certaine mesure et on avait ce genre d'interaction à l'Hôpital de Montréal pour enfants et à l'Institut.

Alors, l'importance des interactions dépendait des activités auxquelles on participait.

Christopher Canning : D'accord. Vous rappelez-vous avoir discuté de l'emplacement physique du groupe? Je vous pose cette question parce que, du début des années 1970 jusqu'aux années 1980, le groupe et le CRM estimaient que tout le monde devait travailler au même endroit.

Roy Gravel : Oui.

Christopher Canning : Et, évidemment, ça n'a jamais été le cas puisque vous travailliez à l'Hôpital de Montréal pour enfants et David Rosenblatt, au Département de génétique humaine. Alors, les gens étaient un peu partout.

Roy Gravel : Tout ça est un peu nébuleux dans mon esprit, mais je me souviens de ce problème. L'idée était que les membres d'un groupe devaient travailler

ensemble dans un lieu commun, appelons-le ainsi, c'est-à-dire, à proximité les uns des autres. Cela semblait poser un problème au CRM que quelqu'un se trouve dans une autre partie du campus. On a surmonté cette difficulté, mais je ne me souviens pas des circonstances. Selon moi, ce n'était pas nous. En fait, on n'était pas le groupe test. Il me semble que ça s'est fait de façon indépendante, quoique je ne sais pas vraiment, je ne m'en souviens tout simplement pas. Mais à ce moment-là c'était rendu acceptable et ce n'était plus un problème. Le problème auquel faisait face le groupe de la résistance de l'hôte – qui, évidemment, était éloigné géographiquement; il était ailleurs – c'est qu'aux yeux du CRM, ce qui le différenciait de nous était la nature de son travail scientifique. Les gens du CRM avaient constaté que ce qu'il faisait était bien différent de ce que le reste d'entre nous faisait. Pour notre part, on trouvait que c'était un excellent groupe de scientifiques avec qui on souhaitait interagir parce qu'ils étaient brillants et qu'ils produisaient des résultats de recherche vraiment intéressants.

Alors, parfois les scientifiques veulent travailler ensemble parce qu'ils vont s'enthousiasmer pour leur travail, et non pas précisément parce qu'ils ont besoin d'apprendre une technique ou parce qu'ils font des recherches grâce à la même subvention. Et donc, selon nous, le groupe du CRM était aussi synergique qu'un groupe de personnes qui se penchent ensemble sur leur domaine d'étude.

En tout cas, étrangement, l'élément géographique était un problème. De nos jours, je crois qu'on ne considérerait pas ça comme un problème parce que, bien sûr, ces groupes sont maintenant répartis partout au pays. Quand j'ai quitté l'Université McGill, il a fallu demander la permission pour que je reste dans le groupe des IRSC. À cette époque-là, ce n'était plus un problème. Donc, j'ai eu la permission de travailler à Calgary sans que cela ait une incidence sur le groupe.

Christopher Canning : C'est en fait ma prochaine question. Comment était la collaboration au sein du groupe lorsque vous étiez à Calgary? Évidemment, vous étiez auparavant le directeur, alors qu'est-ce que –

Roy Gravel : Pouvez-vous répéter? Ça a coupé.

Christopher Canning : Je suis en mode mains libres sur mon téléphone cellulaire, alors ça doit être ça le problème. En tout cas, ma question est, et vous y avez un peu fait allusion, comment les choses se sont-elles passées après votre déménagement à Calgary et comment était la collaboration au sein du groupe à ce moment-là, après 1999?

Roy Gravel : Eh bien, tout d'abord, les principaux liens étaient beaucoup plus Rima, David et moi, non? Autrement dit, comme j'étais si loin, mes interactions avec les autres membres du groupe ont diminué considérablement. Et c'était pour les besoins de la recherche. La raison pour laquelle j'avais noué des liens si solides avec David et Rima est que nous collaborions de diverses façons. On se partageait des subventions indépendamment du groupe. Par exemple, dans les années 1990, on avait reçu une subvention des NIH[3]. On avait participé tous

[3] National Institutes of Health

les trois à cette demande. Donc, on avait une motivation extérieure au groupe pour réaliser des recherches sur la vitamine B_{12} et le folate.

Cette collaboration s'est poursuivie après mon départ pour Calgary, et la distance ne changeait pas grand-chose. On pouvait continuer de travailler ensemble. Et je collabore encore aujourd'hui avec David en recherche. Moins avec Rima, quoiqu'on ait eu une subvention ensemble en tant que collaborateurs officiels. Je crois que ça a duré jusqu'aux alentours du moment où le groupe a été dissous, en 2009.

Donc, le lien, la relation que j'ai entretenue avec le groupe après mon déménagement à Calgary, est demeuré bien réel grâce aux collaborations de recherche dans d'autres contextes. En fait, c'était le même contexte que dans le groupe, mais ce que je veux dire c'est qu'on recevait des fonds pour la recherche qui étaient affectés à l'extérieur du groupe et servaient directement à nos travaux sur le folate et la vitamine B_{12}. Vous le savez peut-être, mais au départ, dans les années 1970, le groupe était financé pour mener des activités de recherche, mettre sur pied des installations de base, des programmes de formation et des choses du genre. Mais les IRSC, ou le CRM, ont finalement changé le mandat des groupes afin que ce soit plus des subventions de base et non des subventions de fonctionnement. On attendait des gens qu'ils aient leurs propres subventions indépendantes pour réaliser leurs programmes de recherche.

Donc, après mon arrivée à Calgary, je devais « participer aux fonctions de base du groupe », ce qui n'était pas très commode parce que, par exemple, si le groupe avait une fonction de base liée aux installations pour les animaux, eh bien, mes installations étaient à Calgary et non à Montréal. On a résolu ce problème en m'attribuant des fonds pour la recherche pour remplacer ce dont j'aurais profité si j'avais été à Montréal. Et ça soutenait en particulier mon travail sur les animaux, lié à la vitamine B_{12}.

Donc, la nature du groupe a changé dans la mesure où les interactions pour la recherche n'étaient pas si intégrées parce que le CRM, ou les IRSC plus tard, nous a poussés à ce changement en exigeant que les subventions soient indépendantes.

Christopher Canning : Je parlais avec Robert MacKenzie l'autre jour. Il siégeait aux comités durant le passage du CRM aux IRSC en l'an 2000 et il a dit la même chose. Et c'est super que vous mentionniez cela parce que c'est l'une des choses que nous étudions : le changement de la structure de financement, qui s'est produit à peu près au moment où le CRM est devenu les IRSC vers l'an 2000. Chaque membre devait d'abord décrocher sa subvention avant de demander à faire partie du groupe. C'est de ça que vous parlez?

Roy Gravel : Oui, c'est ce qu'ils faisaient. Et je me souviens pourquoi. Le problème est que, si tu formes un groupe, disons, de dix personnes et que tu fais une demande de renouvellement de subvention, il va y avoir une diversité de talents. Certains de ces talents seront exceptionnels par rapport à ce qu'on voit dans d'autres concours de subventions et d'autres moins. Autrement dit, si toutes ces personnes faisaient une demande individuellement, obtiendraient-elles toutes une subvention?

Christopher Canning : D'accord.

Roy Gravel : Fort probablement que non parce qu'à cette époque, 30 % à 40 % des demandes de subvention présentées aux IRSC étaient acceptées. Beaucoup de gens qui avaient des programmes de recherche tout à fait fantastiques ne recevaient pas de fonds parce qu'il n'y avait tout simplement pas assez d'argent. Mais les groupes étaient à l'abri de tout ça. Si un groupe obtenait des fonds, tout le monde obtenait des fonds. Et je peux vous dire que les gens qui ne faisaient pas partie de groupes ne la trouvaient pas drôle…

Ce genre de problèmes avait semé la pagaille parce que l'argent se faisait de plus en plus rare dans les années 1990. On avait fondé les IRSC pour créer de nouvelles façons de recueillir des fonds et justifier l'existence d'un tel organisme auprès du gouvernement dans le but d'aller chercher des budgets acceptables. Mais le fait est que, du point de vue des chercheurs, le financement n'était pas vraiment mieux. Sur le plan de la structure, les IRSC sont mieux organisés et l'argent a sans contredit augmenté au fil des ans, mais si on tient compte de l'inflation dans les sciences et ailleurs, personne ne dira probablement que les IRSC sont bien financés.

Donc, dans les années 1990, à l'époque où se passaient ces choses-là, les groupes avaient vraiment un statut spécial. D'une certaine façon, ils étaient protégés contre les aspects les plus difficiles des concours de subventions de recherche. Le problème a été réglé comme Bob MacKenzie vous l'a dit, c'est-à-dire qu'il a été décidé que les membres des groupes – et des groupes, il y en avait pas mal – devaient faire leurs propres démarches pour obtenir des fonds, être évalués selon le processus normal et réussir l'évaluation pour être acceptés au sein d'un groupe.

C'était probablement un système plus équitable, mais je crois que ça se faisait au détriment des groupes parce que lorsque les membres d'un groupe travaillent ensemble pour obtenir des fonds, c'est aussi un travail intellectuel. C'est lorsqu'on essaie d'obtenir le renouvellement d'une subvention qu'on est le plus créatif, parce qu'à ce moment-là, on est vraiment tourné vers l'avenir.

Mais quand les gens doivent demander individuellement une subvention, ça n'a plus d'importance. Les membres du groupe vont discuter ensemble de la subvention de base ou de la façon de renouveler cette subvention de base, mais ils ne discuteront pas des moyens d'élaborer des programmes de recherche qui vont intéresser les examinateurs.

Christopher Canning : Comment se fait-il que vous ayez été au courant de ces discussions dans les années 1990? Participiez-vous aux comités du CRM ou des IRSC?

Roy Gravel : Non, non. On avait tous une idée de ce qui se passait! [Rires]

Christopher Canning : [Rires]

Roy Gravel : C'est ce que les gens disaient. Je crois que c'était simplement la rumeur qui circulait. En fait, je ne jouais pas de rôle aux IRSC à cette époque. Je pense donc que c'était l'impression générale. À cette époque, il y avait aussi les

réseaux sur les maladies génétiques, les programmes des Réseaux de centres d'excellence, et le statut soi-disant spécial de ces programmes suscitait également du mécontentement.

À l'époque, il y avait cette opposition entre les chercheurs qui faisaient cavalier seul et les groupes. Les groupes ont pris beaucoup d'importance durant cette période, ou peut-être dans les années 1980 jusqu'aux années 1990. C'est ce qui suscitait ce genre de débats. De nos jours, tout le monde sait que faire de la recherche en solo est très difficile, et de nombreuses structures ont été mises en place pour que les groupes travaillent ensemble, alors maintenant on est rendu ailleurs. Mais c'était la période où il fallait que les gens discutent de la meilleure façon de faire de la recherche et de reconnaître les gens à leur juste valeur.

Christopher Canning : D'accord. C'est excellent. Merci d'avoir mentionné ça parce que c'est l'une des choses qui nous intéressent au plus haut point, ce changement dans la structure de financement. Et, en fait, c'est la description la plus exhaustive qu'on ait entendue. Alors, encore une fois, merci.

J'ai des questions plus précises sur le groupe; avez-vous encore du temps? Si on continuait pendant encore 20 à 30 minutes, ça irait?

Roy Gravel : Oui, c'est bon.

Christopher Canning : Excellent.

À votre connaissance, y avait-il des divisions dans le groupe entre les gens qui faisaient de la recherche fondamentale, ou qui travaillaient en laboratoire, et ceux qui travaillaient comme cliniciens? Durant votre carrière de généticien, mais surtout lorsque vous faisiez partie du groupe, qu'est-ce qui se disait à ce sujet lorsque vous travailliez en génétique médicale?

Roy Gravel : Si je comprends bien votre question, vous voulez savoir où on se situait par rapport à l'opposition entre la recherche fondamentale et la recherche clinique.

Christopher Canning : Oui, et qu'est-ce que les gens en génétique humaine disaient à propos de cette différence entre le travail en laboratoire et le travail clinique?

Roy Gravel : Eh bien, je peux peut-être répondre à cette question du point de vue de ma carrière et de mon expérience personnelle. C'est un problème qui existe encore de nos jours.

Ça vous explique un peu l'origine du problème : j'étudiais le métabolisme dans un champignon et, bien sûr, il n'y avait pas de patients à soigner. Pendant mes études postdoctorales, je suis passé aux cellules humaines, donc je me suis intéressé au métabolisme de la vitamine B_{12} et, dans ce cas-là, il y avait des gens à soigner. Mais tout cela concerne le métabolisme. J'étudiais les gènes – en fait, à cette époque les gènes n'avaient pas encore été vraiment découverts. Alors, l'idée était d'étudier les maladies génétiques, mais sur le plan des problèmes de métabolisme, des protéines, etc.

Les méthodes utilisées sont évidemment différentes si on travaille avec des cellules humaines plutôt qu'avec un champignon, simplement en raison des organismes en cause, mais le processus mental est aussi très très différent. Quand j'étudiais les champignons, j'étais tout à fait heureux de me pencher sur les troubles métaboliques dans les champignons. Dans les faits, ça voulait dire que je provoquais des mutations et qu'ensuite je tentais de comprendre ce que j'avais créé.

Comme vous pouvez l'imaginer, quand on passe aux cellules humaines et qu'on s'intéresse aux patients derrière ces cultures de cellules, c'est le jour et la nuit. Du moins, ce l'était dans mon cas. Et j'ai commencé à intervenir beaucoup plus sur le plan médical. En tant qu'étudiant postdoctoral, j'ai pu faire des visites pour rencontrer les patients qui présentaient ces troubles-là. J'ai joué un rôle très actif dans un programme essentiellement conçu pour amener les étudiants postdoctoraux à comprendre la pertinence de leur travail pour les patients. C'était très efficace et très intéressant, et c'est Leon Rosenberg qui faisait ça.

Tout d'abord, j'ai saisi que mon rôle était de comprendre les gènes, les protéines et les mutations, et tout cela dans le contexte des patients. Je demeurais un chercheur de laboratoire et non un clinicien; je ne suis pas médecin et ce n'est pas à ce titre que j'apportais ma pierre à l'édifice. Mais quand j'étais à Toronto, je participais aux tournées et je me rendais donc auprès des patients atteints de troubles métaboliques. Je poursuivais ainsi le genre de travail que je faisais quand j'étais aux études et je trouvais ça très intéressant.

En ce qui me concerne, ce que je trouvais pertinent était les applications cliniques. Je ne participais pas directement à la mise en œuvre, mon rôle était plutôt d'essayer de les comprendre. Donc, à mes débuts, mon travail impliquait de rencontrer des sujets humains, des patients. Ça a ensuite diminué avec les années. Je me suis concentré davantage sur le travail en laboratoire, mais j'ai toujours étudié les maladies génétiques. Je n'ai jamais fait de recherches dans un domaine scientifique sans que ça concerne les maladies chez les humains. J'ai changé d'organisme quand c'était pertinent d'avoir un modèle pour étudier mes trucs. Donc, j'ai fait des études chez des souris et sur *C. elegans*, un petit ver. C'est ce que je fais actuellement, en passant.

En ce qui concerne Montréal… Même à Toronto, Montréal avait la réputation d'être un endroit où le métabolisme était le centre de l'univers. À Toronto, je ne travaillais pas dans un milieu où les maladies métaboliques étaient le centre d'intérêt principal. Toronto était la Mecque de la génétique des cellules somatiques et, étant donné la nature de ce domaine, c'est en grande partie pour ça que les gens à Toronto ont pu se lancer dans le clonage un peu avant les autres. Leurs outils convenaient mieux à ce genre de travail. Mais Montréal, grâce au D^{r} Scriver, et au D^{r} Fraser avant cela, était perçue comme l'endroit où aller pour étudier le métabolisme chez des patients.

C'est en raison de gens comme le D^{r} Scriver que j'ai commencé à m'intéresser à cet endroit. Pendant mes études au premier cycle, je n'ai jamais suivi de cours important avec eux. Mais il va sans dire que j'assistais aux conférences des D^{rs} Fraser ou Scriver ou d'autres personnes qui présentaient ce genre de

travail. Ça m'emballait énormément. Mais c'était toujours orienté vers les patients.

Au sein du groupe, c'était mélangé. J'étais devenu un chercheur en laboratoire, mais je tentais de cloner les gènes en cause dans des maladies génétiques chez les enfants. Mais d'autres membres du groupe, certainement les D[rs] Scriver et Rosenblatt, traitaient ces patients. C'était un autre aspect. Je crois que le fait d'avoir cette variété d'approches, des gens comme moi qui travaillaient en laboratoire jusqu'aux gens qui rendaient visite aux patients, donnait du sens à notre travail. Je n'ai jamais perçu ma science comme étant indépendante de l'application pratique pour les patients. C'est encore de cette façon que je vois les choses, mais c'était vraiment la philosophie à Montréal.

Christopher Canning : Donc, vous avez toujours eu cette approche translationnelle de votre travail en laboratoire?

Roy Gravel : Oui, mais ce n'est jamais moi qui mettais les choses en application. J'étais le gars qui travaillait en coulisse à résoudre des problèmes pour que d'autres puissent appliquer la solution.

Christopher Canning : C'est intéressant – désolé de vous interrompre. C'est intéressant que vous ayez été invité à participer aux tournées à l'Hôpital pour enfants de Toronto même si vous n'aviez pas de diplôme en médecine. C'est la première fois que j'entends parler d'un scientifique qui est intégré à l'environnement clinique.

Roy Gravel : Oui. Il y avait un chercheur là-bas qui s'appelait Andrew Sass-Kortsak. Il étudiait les troubles du foie, comme la maladie de Wilson. Je ne sais pas comment lui est venue l'idée, mais il est devenu un peu un mentor pour moi. Il m'a amené faire des tournées et, bien sûr, comme j'avais déjà participé à ce genre d'activités aux États-Unis, j'ai trouvé ça très intéressant. Peut-être qu'ils ne faisaient que me tolérer, mais j'ai beaucoup appris grâce à ça.

Christopher Canning : Dans un autre ordre d'idées, c'est une question vaste et je ne sais pas à quel point vous souhaitez en parler, mais, à votre avis, pourquoi le groupe du CRM/IRSC a-t-il connu autant de succès pendant si longtemps?

Roy Gravel : Charlie Scriver.

Christopher Canning : Pouvez-vous m'en dire plus?

Roy Gravel : Oui. Je crois que le D[r] Scriver savait où on s'en allait. Autrement dit, on n'était pas toujours coincés dans le quotidien. Quand il est question de recherche, il faut un élément de dynamisme pour « vendre » l'idée. Quand on rédige une demande de subvention, l'objectif est de mettre l'accent sur de beaux progrès et de présenter des plans d'étude du tonnerre qui permettront de répondre à des questions pour l'avenir. Mais ça ne veut pas dire que le lecteur sera très emballé par tout ça. C'est la même chose quand on lit un roman. Des fois, on commence à lire un roman et on ne peut plus s'arrêter, alors que d'autres fois, on ne dépasse pas la première page. Il y a quelque chose qui nous emballe, qui nous passionne dans ce qu'on lit et qui retient notre intérêt. Quand on rédige une demande de subvention, l'une des choses importantes est de faire en sorte

que le lecteur, c'est-à-dire la personne qui examinera la demande, soit emballé par le projet.

Eh bien, le Dr Scriver avait créé ce monde dans lequel on évoluait, ce groupe. Je ne veux pas dire sur le plan individuel; je ne le côtoyais pas nécessairement. On travaillait dans des immeubles différents à l'Hôpital de Montréal pour enfants. Ce que je veux dire c'est qu'il conférait un caractère spécial à notre travail qui le rendait très emballant.

Christopher Canning : Même après son départ du groupe dans les années 1990?

Roy Gravel : Il n'a pas quitté le groupe. [Rires]

Christopher Canning : Eh bien, j'imagine qu'il était encore dans les parages. Je suppose qu'il avait cessé de contribuer au groupe en tant que membre, mais…

Roy Gravel : Quoi qu'il en soit, Charles a été présent jusqu'à mon départ.

Christopher Canning : D'accord. Et il a eu lieu en 1999?

Roy Gravel : Oui. Comme je l'ai mentionné, j'ai été formé par Leon Rosenberg, qui a joué un rôle majeur dans l'établissement de la science des erreurs innées du métabolisme. Il a réussi brillamment dans ce domaine. Charles était fait de la même étoffe et je les percevais de la même façon. Il y a seulement quelques personnes que je peux classer dans cette catégorie.

Christopher Canning : Donc, vous diriez que le Dr Scriver a conféré au groupe une sorte d'aura qui a assuré sa longévité?

Roy Gravel : Oui. Enfin, je crois. C'est difficile à dire parce qu'au quotidien on n'aurait pas dit ça comme ça. Je crois qu'il avait cette aptitude pour la communication et une passion contagieuse qui avait assurément un effet sur les gars comme moi. Donc, en ce sens, oui. Mais ce n'est pas parce qu'il m'avait dit quelque chose de particulier ou qu'on discutait de recherche. Il ne se passait rien de différent que dans tout autre milieu de travail où ça fourmille d'activités. C'est juste qu'il inspirait vraiment… Il était la sommité dans le domaine du métabolisme au pays et c'était formidable de travailler avec lui. Je ne vois pas d'autres façons de le dire.

Christopher Canning : Fantastique. Lors du symposium de novembre dernier, le Dr Scriver a mentionné que le groupe avait toujours fonctionné comme une organisation de base, dans le sens où l'évolution était toujours venue de la base. En tant que sociologue des sciences, je trouve ce commentaire très intéressant et je me demandais si vous pouviez me dire un mot à ce sujet. Estimez-vous que le groupe fonctionnait de cette façon organique, à partir de la base, plutôt qu'à partir du sommet?

Roy Gravel : Oui. C'est une autre façon de favoriser l'anarchie. [Rires] Il ne nous disait pas quoi faire ni où on s'en allait. Je crois que l'idée était, et c'est très vrai en sciences, qu'on ne peut pas dire aux gens ce qu'ils doivent faire comme recherches. Par contre, on peut les encourager, et c'est ce que Charles faisait. Cette direction par la base se manifestait dans le processus décisionnel et les

discussions qu'on avait. On prenait nos décisions nous-mêmes. Chacun menait sa barque.

Donc, on interagissait les uns avec les autres, on se parlait d'une façon un peu chaotique, c'est-à-dire que le groupe ne définissait pas notre comportement. Il était responsable du groupe, mais il ne nous disait pas comment nous comporter ni quelle direction prendre dans nos recherches scientifiques.

Quand vous m'avez demandé plus tôt quel était mon rôle au sein du groupe, j'avais de la difficulté à vous répondre autrement qu'en parlant des subventions parce que le groupe n'avait pas d'orientation. Je n'ai jamais considéré que le groupe avait une structure d'organisation de base, mais j'imagine qu'on peut dire que c'était ça. Il évoluait simplement en suivant son propre cheminement aléatoire. Il est important de se souvenir de ça parce que, de nos jours, les universités, les organismes publics et les gens qui nous financent emploient si souvent un style de gestion du haut vers le bas. Ils nous disent ce qu'on doit faire, comment on doit le faire, pourquoi on doit le faire et ainsi de suite. Je trouve que ça mine le potentiel de réussite en sciences.

Je pense en particulier aux universités ou aux pouvoirs publics qui nous disent quelles recherches ils soutiendront financièrement, « faites des recherches sur ceci, faites des recherches sur cela »; il y a bien des façons de compter les articles ou les réussites. On en est venu à cette approche quantitative de l'évaluation par les rapports annuels. J'ai vu ça se produire ici, et cela se produit sans aucun doute ailleurs. Je crois que ça empêche les gens d'être créatifs parce qu'ils sont occupés à faire de la comptabilité. Ça n'existait pas dans le temps. Je ne veux pas donner l'impression que le groupe des IRSC était spécial. C'était simplement la façon habituelle de faire les choses et à l'époque, ces choses-là ne posaient pas problème.

Je ne me serais pas attendu à ce que Charles vienne cogner à ma porte pour me dire « Tu n'as pas publié d'article au cours des six derniers mois. Tu devrais remédier à ça. » Ce n'est pas comme ça qu'on réussit en sciences. Il faut des encouragements.

Christopher Canning : Donc, en ce sens, le groupe fonctionnait exactement comme il l'a dit, soit d'une façon organique, à partir de la base.

Roy Gravel : Oui, sauf que lui donner cette étiquette, ce n'est probablement pas la bonne chose à faire.

Christopher Canning : D'accord. Ça se défend.

Roy Gravel : Le groupe s'est simplement occupé de ses affaires et, grâce à cela, on a eu la chance de survivre aussi longtemps.

Christopher Canning : Ma prochaine question peut vous sembler étrange comme enchaînement, mais qu'est-ce qui faisait de cet ensemble de personnes un véritable groupe? Qu'est-ce qui vous unissait?

Roy Gravel : Eh bien, laissez-moi vous dire qu'à chaque évaluation de subvention, et sans contredit à toutes celles auxquelles j'ai participé, on nous posait toujours la

question. Et elle comporte deux facettes, n'est-ce pas? Tout d'abord, notre groupe n'avait pas de visée précise. On se demandait pourquoi on était un groupe, pourquoi on avait le sentiment d'être un groupe, ou si on pouvait réaliser quelque chose de mieux en groupe plutôt qu'individuellement. C'était le côté intéressé de la chose. Ensuite, il y a le point de vue des examinateurs. Ils nous demandaient « Quel est le ciment du groupe? Que faites-vous pour souder le groupe? ». Je crois que c'est comme ça qu'on a perdu le D[r] Skamene, parce que [le CRM] ne comprenait pas son rôle au sein du groupe.

Mais ce que j'ai appris de certaines des personnes avec qui j'ai travaillé c'est que le milieu dans lequel on travaille nous influence vraiment. Ce que je veux dire, c'est que le fait de côtoyer Rima Rozen et David Rosenblatt quand je travaillais à Montréal m'a amené à m'intéresser au métabolisme de la vitamine B_{12}. Ça n'aurait pas été le cas autrement. J'ai commencé à faire des modèles murins grâce à [Jaquetta] Trasler, qui a pris les rênes de l'Institut après Rima. Son bureau était près du mien et elle travaillait sur des modèles murins. C'est comme ça que j'ai pu en apprendre plus sur les souris.

Quand je suis arrivé à Calgary, le gars dans le bureau à côté du mien était un microscopiste. J'ai donc commencé à beaucoup utiliser les microscopes. Vous voyez où je veux en venir?

Christopher Canning : Absolument.

Roy Gravel : La nature du groupe, le hasard des interactions professionnelles… Quand un groupe est soudé, il est plus facile de se parler. Mais ce qui est important dans les interactions en sciences, ce sont les gens que vous croisez. Mes travaux de recherche ont été très influencés par les gens que je côtoyais. Quand j'étais emballé par ce que les autres faisaient, je me disais « pourquoi je ne ferais pas ça moi aussi? ».

Christopher Canning : C'est la même chose dans mon domaine, la sociologie. Dans des endroits différents, les gens ont des idées différentes. On loge à la même enseigne. Selon vous, quelles sont les découvertes ou les avancées importantes en génétique médicale que le groupe a réalisées durant son existence? Autrement dit, vers quoi nous dirigeons-nous maintenant si l'on se fie aux recherches menées par tout le monde, évidemment remarquables à bien des égards? Quelles seront les prochaines avancées médicales en génétique humaine?

Roy Gravel : Eh bien, je crois que le domaine progresse plus vite que les gens. Donc, même si ce groupe a été très productif, il n'est qu'une partie d'un plus grand tout. Il a apporté une contribution au domaine qui, grâce aux efforts de certains de ses membres, a été majeure. Je constate aussi que l'apport de certaines personnes – je pense en particulier aux D[rs] Fraser et Scriver – va au-delà des expériences et aborde ce que la génétique signifie pour nous en tant qu'êtres humains. Leur contribution a été beaucoup plus grande, en d'autres mots; elle a dépassé le cadre du laboratoire.

Et, bien sûr, traiter des patients atteints d'une maladie génétique n'est pas évident parce qu'il s'agit d'un problème intrinsèque. Ce n'est pas un bras cassé qu'on peut réparer. Et ce qu'on a constaté au fil du temps, et assurément durant

ma carrière en génétique, c'est que, étonnamment, la capacité de traiter les patients atteints de maladies génétiques a vraiment évolué.

Cela étant dit, ce que je vous décris est un groupe de scientifiques spécialisés qui ont contribué au savoir d'une certaine façon pendant de longues carrières dans leur domaine respectif. Je pense qu'on peut dire sans se tromper que ça créait des synergies et que, par l'entremise du groupe, ça a fait progresser la science. De mon côté, j'ai plus tendance à penser que l'existence du groupe a donné une orientation à la science. Dans mon cas, ce n'est pas ce qui s'est toujours produit. Notre intérêt pour la vitamine B_{12} découlait de mes interactions avec Rima et David.

Donc, où tout ça nous mène-t-il? Je crois que c'est la grande question. Les percées en technologie et en science, et le projet sur le génome humain, sont les grandes réalisations qui ont complètement transformé la science et en ont changé notre perception. Elles modifient très rapidement la prestation des soins. On ne peut pas attribuer le mérite de cette réussite à un seul groupe ou à un seul scientifique; tous les acteurs du domaine y sont pour quelque chose.

Christopher Canning : Excellent. Combien de temps vous reste-t-il avant la retraite?

Roy Gravel : [Rires] On me pose tout le temps cette question.

Christopher Canning : [Rires]

Roy Gravel : J'aurai 65 ans cette année.

Christopher Canning : O.K.

Roy Gravel : Il y a quelques jours, j'ai reçu une lettre officielle. On aurait dit qu'elle provenait du fisc, mais en fait l'expéditeur était une entité nommée « Services ». Je me demandais bien ce que ça pouvait être. Je l'ai ouverte et elle disait que je pouvais maintenant commencer à toucher mes prestations de retraite. [Rires] Je trouve ça un peu prématuré. J'ai quelques subventions de recherche en cours. L'une d'elles se termine l'année prochaine et l'autre, en 2014. Je profite donc de la présente tribune pour dire à mes employeurs que quelque part dans ce laps de temps, je tirerai ma révérence, mais ça reste indéterminé. Donc, j'ai encore quelques années devant moi.

Par contre, j'ai opéré un changement dans mes recherches. L'autre chose qui rend la science vraiment passionnante, c'est que c'est un peu une partie de plaisir qui ne se termine jamais. Le vrai défi pour les scientifiques est de répondre à la question ou de résoudre le casse-tête. Mais on ne travaille pas tout le temps sur le même casse-tête. L'objet de l'étude change et la façon de l'étudier change aussi. La beauté de mon travail, c'est que la technologie a tellement évolué au fil de ma carrière qu'il n'y a jamais eu de moment creux. Il y a toujours de nouvelles choses à apprendre ou de nouvelles façons de travailler à essayer, et la même chose s'applique en recherche. Nous avons cloné plusieurs gènes dans différents champs d'expertise, et c'est le défi de résoudre un casse-tête qui nous stimule.

Donc, quand je vous ai dit que j'avais décidé de me concentrer sur la vitamine B_{12}, c'est en partie parce que ma carrière tire à sa fin. Mais je voulais aussi me concentrer sur la vitamine B_{12} parce que je voulais pousser mes recherches. J'aimerais vous dire que mon but est de contribuer à la science, mais le fait est que c'est tout simplement un travail passionnant. Et je vous ai aussi mentionné que mes voisins m'influençaient. Eh bien, à cet endroit, j'ai de nombreux voisins qui travaillent avec des organismes modèles, comme les mouches à fruits, les poissons zèbres et les *C. elegans*. En clonant les gènes de la vitamine B_{12}, on s'est rendu compte que *C. elegans* – un nématode, c'est-à-dire un vers microscopique – avait une voie métabolique de la vitamine B_{12} comme les humains. Ils ont des gènes dont la séquence est homologue à celle des gènes humains.

Christopher Canning : Wow, c'est très intéressant.

Roy Gravel : Ils ont tous les gènes de la vitamine B_{12}, sauf un. Et ce que j'aimerais vraiment savoir, c'est s'il y a d'autres gènes en cause dans le métabolisme de la vitamine B_{12} qui nous auraient échappé. Parce que pendant l'existence du groupe, on a pu voir tous les gènes identifiés chez l'humain. Enfin, non, je ne devrais pas dire ça comme ça. Les gènes en cause dans toutes les catégories de maladies liées au métabolisme de la vitamine B_{12} au niveau cellulaire ont été identifiés. David Rosenblatt a joué un rôle dans le clonage de chacun de ces gènes, par exemple. Et donc, mon questionnement était « Maintenant qu'on n'a plus de patients, comment fait-on pour savoir s'il y a d'autres gènes en cause? Que doit-on faire? Où trouvera-t-on des réponses? »

Comme on avait constaté que *C. elegans* avait une voie identique à la voie humaine et qu'on pouvait en tirer des extraits en recourant à des méthodes qu'on ne pourrait pas imaginer utiliser avec des cellules humaines, on a eu la brillante idée de chercher d'autres gènes dans *C. elegans*. Donc, ma dernière subvention, celle qui se terminera en 2014, est très axée sur l'utilisation de *C. elegans* comme organisme modèle pour la mise au jour des mystères du métabolisme de la vitamine B_{12}. Alors, on élève des *C. elegans* depuis quelques années et, grâce à eux, on a découvert de trucs intéressants sur cette voie métabolique.

Ça veut donc dire que la recherche a encore fait un autre bond en avant, et je veux vraiment mener ce projet à bien avant ma retraite. Donc, je vais rester jusqu'à ce qu'on ait suffisamment analysé *C. elegans* pour qu'il livre tous ses secrets.

Christopher Canning : Ça a l'air extraordinaire. Donc, vous avez découvert de nouvelles voies dans le métabolisme ou de nouveaux gènes qui pourraient nous aider à comprendre la vitamine B_{12}?

Roy Gravel : Eh bien, autrement dit, ce sont leurs parties manquantes. Ce sont les gènes à identifier; ce sont eux, en fin de compte, qui définissent le métabolisme de la vitamine B_{12}, c'est-à-dire comment nous traitons cette vitamine pour qu'elle devienne un cofacteur utile dans notre corps. Ce qui est intéressant dans les vitamines, et sans conteste dans la vitamine B_{12}, c'est qu'elles ne vous servent à rien si vous ne faites que les avaler. Elles n'agissent pas sous la forme sous laquelle vous les ingérez. En fait, elles doivent être métabolisées; elles

prennent différentes formes et sont envoyées à différents endroits, et il y a une multitude de gènes qui interviennent dans ce processus.

Christopher Canning : Je vois.

Roy Gravel : Et, donc, le défi chez l'humain – étant donné mon intérêt et celui de David pour la voie métabolique – est de déterminer toutes les étapes en jeu. Les catégories auxquelles j'ai fait référence et dans lesquelles les patients ont été classés sont appelées des « groupes d'hybridation ». David a joué un rôle important dans ce travail. Chaque groupe d'hybridation présentait le gène. Une catégorie de patients était définie par le fait qu'ils avaient tous des mutations dans le même gène.

Et on a donc pu identifier environ huit gènes de cette manière, et d'autres le seront. Nous, on regarde les trous dans la voie métabolique, c'est-à-dire les endroits où on n'a pas identifié de gène. On peut supposer qu'il y en a un, mais on n'a pas de patients qui peuvent nous aider à le déceler. On s'est donc demandé comment on allait faire pour trouver ces gènes. Alors, on a décidé d'utiliser *C. elegans* comme cobaye chez qui on pouvait perturber les gènes. On réalisait des expériences sur lui pour tenter de trouver ces autres gènes.

On essaie de trouver les gènes dans la voie métabolique qu'on n'a pas encore identifiés. On pourra ensuite utiliser les séquences d'ADN pour trouver leurs équivalents dans les cellules humaines. À ce moment-là, on pourra retourner étudier des sujets humains et comprendre le rôle de ces gènes.

Christopher Canning : Formidable. Eh bien, voilà, c'est ce qui conclut notre entrevue. Merci beaucoup de m'avoir accordé de votre temps, M. Gravel.

FIN DE L'ENTRETIEN

H. Susie Tenenhouse, Ph. D., le 8 février 2011

Christopher Canning : Nous sommes le 8 février 2011. Ici Christopher Canning en compagnie de Susie Tenenhouse. M[me] Tenenhouse, je suis honoré de pouvoir m'entretenir avec vous de deux grands sujets relatifs à la génétique humaine. J'aimerais d'abord que nous parlions de votre formation, qui a contribué à l'avancement de la génétique médicale au Canada et ailleurs dans le monde. Ensuite, et surtout, je m'intéresse à votre participation au groupe sur la génétique médicale des IRSC[1] – anciennement le CRM[2] – auquel vous vous êtes jointe à titre d'étudiante postdoctorale en 1972, puis de chercheuse principale en 1981, et dont vous avez été membre jusqu'en 2004. Vous avez d'ailleurs été l'une des personnes qui ont fait partie de ce groupe le plus longtemps pendant ses 37 années d'existence.

Mais avant de parler du groupe, parlons un peu de vous, si vous le voulez bien. Pouvez-vous nous parler de votre lieu de naissance et de votre parcours?

Susie Tenenhouse : Je suis née à Montréal, au Québec, et j'ai fréquenté la Strathcona Academy. J'ai ensuite obtenu mon baccalauréat en sciences avec spécialisation en biochimie en 1961, puis ma maîtrise en biochimie en 1963, à l'Université McGill. Je dois préciser qu'après mon baccalauréat, j'ai été admise à l'école de médecine de McGill, mais que j'ai préféré m'inscrire à la maîtrise en sciences parce que j'ai épousé Alan Tenenhouse en 1961 et que je croyais qu'une carrière en recherche serait plus compatible avec ma vie de femme mariée. Notre première fille, Lee, est née en 1962.

Après ma maîtrise, qui portait sur l'allergène actif présent dans les grains de café verts et que j'ai faite sous la supervision d'Alec Sehon, mon mari et moi avons déménagé à Madison, au Wisconsin, puis à Philadelphie, en Pennsylvanie, où Alan a poursuivi sa formation postdoctorale auprès du D[r] Howard Rasmussen. (En 1965, nous avons suivi le D[r] Rasmussen à l'Université de Pennsylvanie, où il est devenu directeur du Département de biochimie.)

À l'Université du Wisconsin, j'ai été adjointe à la recherche dans le laboratoire d'immunochimie d'Harold Deutsch pendant deux ans. À Philadelphie, j'ai été adjointe à la recherche dans le laboratoire d'immunochimie de Fred Karush. C'est à Philadelphie, en 1965, que j'ai ensuite donné naissance à notre cadette, Ruth.

Christopher Canning : Je vois dans votre CV qu'il doit s'agir de la période entre 1963 et 1968.

Susie Tenenhouse : Lorsque nous avons déménagé aux États-Unis, nous avons obtenu nos cartes vertes d'immigrants. Nous nous disions que si l'occasion se présentait, Alan pourrait accepter un poste dans ce pays. Mais c'était l'époque de la guerre du Vietnam, et comme il avait un diplôme en médecine, Alan a été recruté par l'armée américaine. Nous ne savions pas qu'en tant qu'immigrants, nous avions le privilège de pouvoir servir le pays.

[1] Instituts de recherche en santé du Canada
[2] Conseil de recherches médicales du Canada

Nous avons donc quitté les États-Unis à ce moment-là. Des avocats de l'Université de Pennsylvanie ont pu aider mon mari à quitter le pays en toute légalité. Alan a ensuite eu la chance d'obtenir un poste de professeur adjoint au Département de pharmacologie de l'Université McGill. C'est à ce moment-là que j'ai décidé de faire un doctorat à McGill. À l'automne 1968, mes filles ont fait leur entrée à la prématernelle et en première année, et moi au programme de doctorat du Département de biochimie.

Pendant mon doctorat avec Murray Fraser, je me suis intéressée à la caractérisation de l'activité ribonucléasique de deux nouvelles nucléases de *Neurospora crassa*, l'une présentant une activité exonucléasique et l'autre une activité endonucléasique. Ces enzymes jouaient un rôle important dans la détermination des structures primaires et secondaires de l'ADN[3] et de l'ARN[4] à une époque où la biologie moléculaire en était à ses débuts. J'ai donc acquis des connaissances dans un nouveau domaine de recherche et j'ai obtenu mon diplôme en 1972.

Pour ma formation postdoctorale, j'avais envie de faire des recherches dans un domaine plus axé sur les applications cliniques. Je devais aussi rester à Montréal. Le groupe de biochimie génétique du Dr Scriver me semblait extrêmement intéressant. Après une rencontre avec le Dr Scriver, j'ai été acceptée comme étudiante postdoctorale dans son laboratoire, où je suis arrivée en septembre 1972 avec ma propre bourse du CRM.

Christopher Canning : Revenons un peu en arrière. Qu'est-ce qui vous a attirée dans l'aspect médical de la génétique, alors que vous aviez un bagage en chimie et en biochimie? Pourquoi avez-vous eu envie d'étudier la génétique dans un contexte médical?

Susie Tenenhouse : Même si l'équipe du Dr Scriver travaillait en génétique, elle se servait de méthodes utilisées en biochimie pour répondre à ses questions de recherche. J'allais donc utiliser une technologie que je connaissais pour trouver des solutions à des problèmes pertinents sur le plan clinique, ce que je trouvais très intéressant.

Quand je suis arrivée en 1972, le laboratoire du Dr Scriver se trouvait au deuxième étage de l'Hôpital de Montréal pour enfants. Nous y étions très à l'étroit, mais l'ambiance était stimulante et amicale, et il y régnait un bel esprit de collaboration. Peter Hechtman et Renny Gold, qui étaient des chercheurs principaux dans le groupe de génétique médicale du CRM, travaillaient dans le même laboratoire, et le Dr Clarke Fraser, qui passait une partie de son temps dans l'hôpital, n'était pas bien loin. C'est dans ce groupe que je suis arrivée.

Le Dr Scriver, mon superviseur, m'a intégrée à un projet de recherche qui lui tenait à cœur. Il traitait de nombreux patients atteints d'une forme héréditaire de rachitisme appelée « hypophosphatémie liée à l'X » (XLH). Ces patients souffraient de rachitisme même s'ils avaient une alimentation normale. De plus, cette maladie était héréditaire et liée au chromosome X,

[3] Acide désoxyribonucléique
[4] Acide ribonucléique

mais la nature de l'anomalie n'était pas connue. Des études cliniques réalisées par le Dr Scriver ont révélé que les patients atteints de XLH avaient un faible taux de Pi[5] dans le sang et une trop grande quantité de phosphate dans l'urine, ce qui semblait indiquer un défaut de réabsorption rénale du phosphate. Autrement dit, chez ces patients, le taux de phosphate dans la circulation sanguine était trop faible pour assurer une formation osseuse normale. À la lumière de ces découvertes, nous avons émis l'hypothèse que la XLH était un trouble génétique du transport du phosphate.

Dans le cadre de mon premier projet, je devais déterminer si le transport du phosphate était déficient dans les globules rouges de ces patients. Nous avons choisi d'étudier les globules rouges parce qu'ils étaient facilement accessibles chez les patients et les témoins. Nous avons découvert que les globules rouges des patients se comportaient de la même façon que ceux des sujets sains, ce qui signifiait que l'anomalie n'était pas présente dans les globules rouges. Je ne sais pas si vous voulez que j'entre dans les détails à ce sujet.

Christopher Canning : À vrai dire, j'aime beaucoup les détails, et vous pouvez en parler autant que vous le voulez. Je voulais aussi vous dire que je me suis récemment entretenu avec Reynold Gold et qu'il m'a demandé de vous passer le bonjour.

Susie Tenenhouse : J'ai rencontré Renny Gold pendant le projet XLH, puis j'ai eu la chance d'étudier avec lui des souris atteintes d'un trouble héréditaire du métabolisme de la kératine (protéine présente dans la peau et les poils). Des souris nude étaient incapables de produire un pelage normal, ce qui semblait indiquer une anomalie dans la synthèse de la kératine. L'étude réalisée avec Renny Gold a été très instructive et productive, et elle a donné lieu à quelques publications.

Christopher Canning : Je vous interromps brièvement pour vous dire que M. Gold a dit de vous que « vous étiez une expérimentaliste extraordinaire ».

Susie Tenenhouse : C'est très gentil de sa part!

Christopher Canning : Il a également dit que pendant votre collaboration, il a ajouté un petit côté théorique à votre esprit d'expérimentaliste futée. Qu'est-ce qu'il voulait dire par là, à votre avis?

Susie Tenenhouse : Il avait un esprit mathématique brillant et je possédais l'expertise technique nécessaire pour produire les données. Il a mis au point une méthode qui permet d'estimer la composition des protéines de kératine chez des souris nude et des souris saines de la même portée. Nos données ont révélé que les souris mutantes présentaient une anomalie importante dans la synthèse d'une famille de protéines de kératine, connues comme étant des protéines riches en glycine et en tyrosine. Nous formions une bonne équipe : il avait des connaissances dans un domaine et moi dans un autre.

À propos du projet XLH, le Dr Scriver a appris qu'Eva Eicher, généticienne spécialiste de la souris au laboratoire Jackson, situé à Bar Harbor, dans le

[5] Phosphate inorganique

Maine, avait découvert une souche mutante de souris, désignée *Hyp*, qui présentait toutes les caractéristiques cliniques de la XLH observée chez l'humain. Fait intéressant, la mutation chez la souris était également liée au chromosome X, ce qui donnait à penser que la souris *Hyp* constituait un modèle parfait pour élucider les bases biochimiques et moléculaires de la XLH chez l'humain.

Connaissez-vous le laboratoire Jackson?

Christopher Canning : Je n'en ai jamais entendu parler. Si vous pouvez m'en dire un peu à son sujet, ça serait bien.

Susie Tenenhouse : Le laboratoire Jackson est un établissement de recherche de renommée internationale et une ressource précieuse de souches mutantes de souris, dont nous nous servons comme modèle pour étudier et mieux comprendre les troubles génétiques chez l'humain.

Christopher Canning : Il est donc question des systèmes de transport rénal, n'est-ce pas? C'est bien le sujet que vous avez étudié pendant la majeure partie de votre carrière?

Susie Tenenhouse : C'est exact. J'ai changé de modèle expérimental et j'ai mis en place une colonie de reproduction de souris *Hyp* à l'Hôpital de Montréal pour enfants afin de déterminer la nature et le siège du défaut de transport du phosphate dans le rein des souris mutantes. Les souris *Hyp* m'ont été très utiles jusqu'à ma retraite, et pendant la majeure partie de mes travaux, j'ai cherché à expliquer les mécanismes des anomalies du transport rénal du phosphate et du métabolisme de la vitamine D chez ces souris.

Mon groupe a fait les constatations suivantes :

- Les souris *Hyp* présentent un défaut de transport dans la membrane de la bordure en brosse du tube proximal, principal siège de réabsorption du phosphate.
- Les souris *Hyp* présentent également une anomalie dans l'activation rénale de la vitamine D et une dégradation accrue de la forme active de la vitamine D (1,25-dihydroxyvitamine D).
- Le gène qui conditionne la synthèse du principal transporteur de phosphate dans le rein n'est pas situé sur le chromosome X ni chez la souris ni chez l'humain; il n'est donc pas le gène mutant chez les souris *Hyp* (XLH).
- Chez les souris *Hyp*, on observe une délétion importante dans le gène *PHEX*[6]. (Il y a aussi une mutation de ce gène chez les patients XLH, et le gène est situé sur le chromosome X.)
- Le gène *PHEX* est exprimé dans l'os et non dans le rein. Toutefois, nous ne comprenons toujours pas précisément comment le gène *PHEX* se comporte *in vivo*.

Nous avons aussi constitué une base de données sur les mutations du gène *PHEX*, accessible en ligne. Je suis sûre que grâce aux travaux du Dr Scriver, vous mesurez pleinement l'utilité d'un outil comme celui-là.

[6] Gène responsable de l'hypophosphatémie héréditaire

Christopher Canning : Et, plus globalement, quelles étaient les retombées de ces recherches sur la santé humaine?

Susie Tenenhouse : Il faut bien comprendre les mécanismes sous-jacents d'un processus pathologique pour mettre au point une stratégie de traitement efficace. Dans le cas de la XLH, le traitement comprend la prise orale de suppléments de phosphate et de la forme active de la vitamine D (1,25-dihydroxyvitamine D). Cette approche n'est pas idéale, car elle est difficile à gérer et nécessite une surveillance constante. Nous espérons que de futures études sur la fonction du gène *PHEX* mèneront à la découverte de nouvelles cibles pour la mise au point de médicaments efficaces dans le traitement de la XLH et d'autres troubles hypophosphatémiques.

Christopher Canning : Vous étiez donc en train de faire votre postdoctorat avec le Dr Scriver à un moment qui doit correspondre à l'ajout de la vitamine D dans le lait. Vos travaux ont-ils contribué à la recherche fondamentale et aux actions menées pour mettre ces études au service de la santé humaine?

Susie Tenenhouse : En fait, la majeure partie du travail que je viens de décrire a été réalisée après mon postdoctorat et bien après l'ajout de la vitamine D dans le lait au Québec. Je dois préciser que le métabolite de la vitamine D ajouté au lait n'est pas la forme active de la vitamine D. Il doit être modifié *in vivo*, d'abord par le foie, pour devenir la 25-hydroxyvitamine D, puis par le rein, qui le transforme en 1,25-dihydroxyvitamine D, afin d'avoir un effet biologique.

L'ajout de la vitamine D au lait a eu des effets bénéfiques énormes pour la population en général, et surtout pour les peuples des pays nordiques et les patients atteints de rachitisme nutritionnel. Toutefois, il n'y a eu aucune retombée bénéfique pour les patients atteints de XLH ou d'une autre forme de rachitisme héréditaire.

Après mon postdoctorat, j'ai eu l'immense chance de poursuivre mes recherches dans le laboratoire du Dr Scriver en tant qu'adjointe à la recherche. Ça me convenait tout à fait, et ce n'est que plus tard, une fois la dynamique familiale bien huilée, que j'ai pu voler de mes propres ailes.

Christopher Canning : J'ai remarqué que vous vous étiez jointe au groupe en 1981. Il s'est donc écoulé neuf années entre la période où vous avez été étudiante postdoctorale et adjointe à la recherche, et le moment où vous êtes entrée dans le groupe et avez obtenu un poste de professeure qui menait à la permanence.

Susie Tenenhouse : C'est exact. En 1981, j'ai obtenu un poste qui menait à la permanence dans le Service de pédiatrie. Juste avant, j'ai occupé un poste de professeure adjointe qui ne menait pas à la permanence et un poste d'adjointe à la recherche. Pendant ce temps, j'ai obtenu des bourses salariales de l'Université McGill (Harry Bagley et Fraser Monat).

Christopher Canning : J'ai une autre question à ce sujet. Elle m'est venue à l'esprit pendant mon entrevue avec Reynold Gold parce que je sais que vous avez travaillé en étroite collaboration à cette époque. M. Gold a laissé entendre qu'il y avait des querelles au sujet des postes permanents au sein du groupe. Il a dit qu'il cherchait aussi à obtenir un poste permanent et qu'il y a eu des discussions

entre vous et le Dr Scriver, et entre lui et le Dr Scriver, au sujet de l'obtention d'un poste permanent protégé plutôt que d'un poste sous la coupole du groupe et des recherches du Dr Scriver. Pourriez-vous me parler de ça?

Susie Tenenhouse : Oui, mais je peux parler uniquement en mon nom. Lorsque j'ai décidé de demander ma première subvention dans le groupe du CRM et de mettre en place mon propre programme de recherche, je voulais obtenir une forme d'engagement de la part du Service de pédiatrie. Cette situation touchait également Reynold Gold. Finalement, grâce à l'aide du Dr Scriver et parce que mes recherches étaient productives et que j'avais réussi à obtenir des subventions salariales, j'ai eu un poste de professeure adjointe qui menait à la permanence dans le Service de pédiatrie.

Christopher Canning : Et c'était en 1981?

Susie Tenenhouse : Oui.

Christopher Canning : C'est intéressant que vous ayez obtenu un poste au Service de pédiatrie même si vous n'aviez pas de diplôme en médecine. Vous étiez donc une biochimiste en poste dans un service de pédiatrie.

Susie Tenenhouse : D'après mes souvenirs, un certain nombre de chercheurs fondamentalistes, soit des titulaires de doctorat, occupaient des postes qui menaient à la permanence dans les services cliniques à cette époque. Il y avait donc un précédent à McGill, et le Dr Scriver avait beaucoup d'influence au sein du Service de pédiatrie.

Christopher Canning : Bien. Et que saviez-vous des activités du groupe avant d'être invitée à vous y joindre en 1981? Vous participiez déjà aux travaux du Dr Scriver, mais connaissiez-vous les autres membres, notamment le Dr Fraser, Peter Hechtman et le Dr Rosenblatt?

Susie Tenenhouse : Je connaissais très bien les programmes de recherche des membres du groupe du CRM à l'Hôpital de Montréal pour enfants, notamment ceux du Dr Scriver, de Peter Hechtman et de Reynold Gold. J'aimais particulièrement nos séminaires de recherche, pendant lesquels les professeurs, les étudiants aux cycles supérieurs, les adjoints à la recherche et les boursiers en recherche clinique se réunissaient pour des présentations et des discussions sur des sujets qui touchaient la recherche clinique ou la recherche fondamentale. Il y régnait un bel esprit de camaraderie.

Évidemment, les rencontres étaient moins fréquentes avec les personnes qui ne travaillaient pas à l'Hôpital de Montréal pour enfants, comme les Drs David Rosenblatt, Leonard Pinsky et Clarke Fraser, mais nous entretenions de très bonnes relations et échangions souvent avec eux.

Dans les dernières années du groupe du CRM, certains membres ont entretenu des collaborations très prolifiques. Ce fut le cas pour Rima Rozen, Roy Gravel et le Dr David Rosenblatt, qui travaillaient dans des domaines similaires.

Christopher Canning : C'est le groupe qui s'intéressait aux folates?

Susie Tenenhouse : Oui. Ils travaillaient tous dans le même établissement et avaient des champs d'intérêt communs. Cette collaboration a donné naissance à un programme de recherche productif et à de nombreuses publications importantes. Et les membres qui, comme moi, n'avaient pas noué d'association au sein du groupe ont établi d'excellentes relations avec des scientifiques à l'extérieur de l'Université et du pays. Au fil des ans, j'ai participé à de nombreuses collaborations fructueuses.

Ce n'est que peu de temps avant que je quitte le groupe qu'une personne aux intérêts de recherche proches des miens est arrivée : le Dr Andy Karaplis. Lui avez-vous parlé?

Christopher Canning : Oui.

Susie Tenenhouse : Le Dr Karaplis s'intéressait au métabolisme osseux et minéral. Il avait beaucoup d'expérience en biologie moléculaire, et nous avons travaillé ensemble à la production d'une souris *knockout* chez laquelle nous avons inactivé le principal transporteur de phosphate dans le rein. Nous avons ainsi pu étudier le rôle de ce transporteur de phosphate *in vivo* et comparer le phénotype de notre souris *knockout* à celui de la souris *Hyp*. Ce projet a donné une toute nouvelle dimension à mes recherches, et ce fut vraiment enrichissant de travailler avec un membre du groupe.

Christopher Canning : Cette technique d'inactivation a de toute évidence été rendue possible grâce aux méthodes de biologie moléculaire mises au point pendant les années 1970 et 1980. Avez-vous appris de nouvelles techniques de biologie moléculaire après vos travaux en biochimie?

Susie Tenenhouse : Absolument. Dans ce domaine, il faut continuellement actualiser ses connaissances. À l'époque, si vous n'appliquiez pas les méthodes de biologie moléculaire en génétique, vous n'étiez plus dans la course pour les subventions de recherche. Je suis d'ailleurs très reconnaissante envers Roy Gravel, qui est devenu directeur du groupe et directeur scientifique de l'Institut de recherche de l'Hôpital de Montréal pour enfants, affilié à l'Université McGill, pendant les années 1990. Il nous a tous encouragés à acquérir des connaissances en biologie moléculaire et nous a bien épaulés.

Roy Gravel a aussi fait un grand pas en avant en créant un processus interne d'évaluation des subventions. Chaque chercheur principal devait soumettre sa demande de financement à un comité interne avant de la présenter à un organisme subventionnaire externe. Nous avons beaucoup appris sur la demande de subventions et avons nettement amélioré notre dossier de financement.

Dans mon cas, j'ai eu la chance de pouvoir compter sur un financement continu de la part du CRM et des IRSC de 1981 à 2004. Au fil des ans, j'ai aussi reçu des subventions d'autres sources, comme la Fondation canadienne du rein, le gouvernement du Québec et le secteur pharmaceutique.

Christopher Canning : J'aimerais revenir sur ce que vous avez dit sur la compétitivité du groupe en biologie moléculaire. Selon certains documents que j'ai obtenus, il y a eu quelques désaccords internes vers les années 1985 à 1987 concernant

l'orientation et la compétitivité du groupe, particulièrement en biologie moléculaire. C'était un peu avant que Roy Gravel se joigne à l'équipe. D'après ce que j'ai compris, lui et Rima Rozen ont été formés et recrutés pour apporter cette expertise au groupe.

Comme vous avez fait partie du groupe pendant longtemps, pouvez-vous me parler du changement et des discussions qui ont eu lieu pendant les années 1980 afin de rendre le groupe plus compétitif en biologie moléculaire?

Susie Tenenhouse : Je ne me rappelle pas avoir participé à des discussions officielles sur l'amélioration de notre compétitivité et sur un virage vers la biologie moléculaire, mais j'avais l'impression que c'était la seule chose à faire pour faire avancer nos recherches. C'est pourquoi le Dr Scriver essayait de recruter dans ce domaine. Il a embauché Ken Morgan, qui n'était pas un chercheur principal dans le groupe, mais un généticien qui avait les compétences en statistique dont nous avions besoin pour trouver des gènes liés à des maladies chez des patients atteints de troubles héréditaires. Il a également recruté le Dr Golder Wilson, un généticien clinique venu des États-Unis qui n'est pas resté très longtemps, et Rima Rozen, qui avait fait une formation en biologie moléculaire pendant ses études postdoctorales aux États-Unis.

Christopher Canning : Je crois que c'est lorsqu'elle est allée faire ses études postdoctorales à Yale.

Susie Tenenhouse : C'est exact. Ensuite, Roy Gravel est arrivé. Je suis d'accord pour dire que nous devions effectivement acquérir de nouvelles compétences pour conserver notre compétitivité.

Christopher Canning : Pour que le groupe reste compétitif dans le domaine de la génétique humaine, c'est bien ça?

Susie Tenenhouse : Oui. Nous avions besoin de cette technologie pour trouver des réponses à nos questions sur les types de mutation à l'origine des troubles génétiques, leur localisation dans le génome, leur mécanisme d'action, etc.

Christopher Canning : Et croyez-vous que le groupe a réussi à faire ça après le virage effectué dans les années 1980?

Susie Tenenhouse : Tout à fait. Rima Rozen et Roy Gravel étaient des chercheurs très productifs et ont apporté une contribution importante à leur domaine. Et avec l'arrivée de nouveaux membres dans le groupe, comme Eric Shoubridge et les Drs Mark Trifiro et Andy Karaplis, l'expertise en biologie moléculaire a atteint un sommet. Et il y avait beaucoup d'entraide.

Christopher Canning : Dans un autre ordre d'idées, où le groupe travaillait-il et quel effet l'espace dont vous disposiez a-t-il eu sur le rôle de chacun?

Susie Tenenhouse : L'espace est toujours un sujet épineux, et c'était tout particulièrement le cas dans les premiers temps du groupe du CRM. Lorsque je suis arrivée en 1972 pour mes études postdoctorales, nous étions vraiment à l'étroit dans le laboratoire et je n'avais pas de bureau ni même de poste de travail à moi. La situation s'est nettement améliorée au milieu des années 1970 lorsque nous avons emménagé dans l'aile A de l'hôpital. Nous avions le septième étage au

complet, et tout le monde avait suffisamment de place pour travailler.

Christopher Canning : Je vois.

Susie Tenenhouse : Il faut toujours se battre pour avoir de la place.

Christopher Canning : Et quelles étaient vos installations? Qu'est-ce qui a été ajouté lorsque vous avez quitté vos petits locaux des premières années?

Susie Tenenhouse : La majeure partie du matériel dont nous avions besoin était sur place et l'environnement de travail était beaucoup plus agréable. Chaque personne avait son propre bureau et son poste de travail. De plus, les installations pour les souris dans le sous-sol de l'hôpital ont été grandement améliorées : il y avait plus de place, mais aussi plus de personnel pour veiller sur les colonies de reproduction.

Au début des années 1990, mon groupe a déménagé à la Place Toulon, un immeuble de bureaux situé sur la rue Sainte-Catherine, à deux coins de rue de l'Hôpital de Montréal pour enfants. L'institut de recherche de l'hôpital y avait loué plusieurs étages afin d'augmenter le nombre de locaux de recherche. Rima Rozen et Roy Gravel, ainsi que plusieurs autres chercheurs de l'hôpital, avaient installé leurs laboratoires dans cet immeuble. Il y avait beaucoup de matériel commun, des services de secrétariat, une petite bibliothèque et une salle de conférence, mais surtout plus de place pour les animaux, ce qui était très important pour moi.

La réglementation sur l'utilisation d'animaux à des fins expérimentales et les exigences sur les installations pour les animaux se sont nettement resserrées au fil du temps. Il fallait obligatoirement se conformer à la réglementation et justifier le nombre d'animaux hébergés par chaque chercheur. L'amélioration de nos installations pour les animaux à l'Hôpital de Montréal pour enfants et à la Place Toulon est arrivée à point et a grandement facilité la tâche de nos chercheurs.

Christopher Canning : Le Dr David Rosenblatt m'a remis une lettre qui a été envoyée au groupe au sujet des locaux, parce que le CRM voulait rassembler tous les membres du groupe au même endroit. Vous souvenez-vous de discussions sur la nécessité de regrouper tout le monde?

Susie Tenenhouse : Je n'en ai qu'un vague souvenir. Je ne peux pas vous dire grand-chose à ce sujet.

Christopher Canning : Je vois.

Susie Tenenhouse : Je n'ai jamais participé à ce genre de décision.

Christopher Canning : Je comprends.

Susie Tenenhouse : Je pourrais vous dire ce que je pensais de l'espace que nous avions à l'époque. De façon générale, ce que j'avais me convenait bien.

Christopher Canning : Mais ce n'était pas un problème pour vous que les membres du groupe

travaillent dans différents endroits?

Susie Tenenhouse : Dans d'autres installations, vous voulez dire?

Christopher Canning : Oui.

Susie Tenenhouse : Mais même au début, les Drs Pinsky, Rosenblatt et Fraser travaillaient dans d'autres locaux.

Christopher Canning : Oui, et le Dr Pinsky a fait partie du groupe jusqu'en 1990. À cette époque, de nouveaux membres se sont ajoutés, mais tout le monde n'était pas au même endroit. Je pose cette question simplement parce que je m'intéresse à la façon dont le groupe se définissait. Autrement dit, est-ce que tous les membres doivent travailler au même endroit pour qu'un groupe fonctionne bien en génétique médicale?

Susie Tenenhouse : Je ne crois pas. Il est toujours possible d'accomplir beaucoup de choses même si les chercheurs travaillent à des endroits différents. Bien entendu, c'est beaucoup plus agréable si tout le groupe est réuni.

Christopher Canning : Oui.

Susie Tenenhouse : Malheureusement, c'était impossible.

Christopher Canning : Je vois.

Susie Tenenhouse : Et je crois que nous avons su tirer le meilleur de la situation.

Christopher Canning : Vous rappelez-vous la façon dont le groupe était dirigé pendant les premières années? Le Dr Scriver a assumé cette responsabilité au début, puis Roy Gravel et Rima Rozen ont pris le relais. Quel était le rôle du directeur d'un groupe comme le vôtre?

Susie Tenenhouse : Lorsque le Dr Scriver était directeur, le groupe était beaucoup plus petit. Il était un excellent dirigeant et il faisait beaucoup de choses avec nous. Il nous accompagnait pour les repas à la cafétéria, les séminaires ou encore les conférences nationales et internationales. Notre groupe était beaucoup plus soudé à cette époque. Les choses ont changé lorsque des personnes travaillant dans des domaines différents se sont jointes à nous. Je trouvais que Roy Gravel entretenait de très bonnes relations avec tout le monde et qu'il était un excellent directeur. Même chose pour Rima Rozen lorsqu'elle a pris les commandes. Je ne peux pas vraiment vous en dire plus que ça.

Christopher Canning : Très bien. Vous rappelez-vous comment la structure de financement du groupe fonctionnait? Autrement dit, comment se passaient le financement individuel et le financement de groupe?

Susie Tenenhouse : Je ne m'intéressais pas beaucoup à l'administration du budget du groupe. Au Département de génétique humaine, et auparavant au Centre de génétique humaine, c'est Fran Langdon qui s'occupait du budget. Elle nous aidait beaucoup et était une personne très agréable à côtoyer. Ça fait longtemps et je ne me souviens pas des détails.

Christopher Canning : Aucun problème. Je peux vous poser quelques questions plus générales sur le groupe? Comme je vous l'ai mentionné, vous êtes le 14e membre que j'interviewe. Et pendant toutes ces discussions, nous avons parlé de la relation entre les scientifiques fondamentalistes et les scientifiques cliniciens. Pourriez-vous me parler de la dynamique du groupe du point de vue de chaque type de scientifique et me dire comment les membres du groupe réglaient les différends, s'il y en avait?

Susie Tenenhouse : Quand je suis arrivée comme étudiante postdoctorale, je m'intéressais beaucoup aux discussions cliniques. Comme je l'ai dit, le groupe se réunissait régulièrement pour discuter de recherche fondamentale ou des aspects cliniques de notre travail. Je trouvais que c'était une excellente idée. Mais finalement, les aspects cliniques étaient secondaires parce qu'en fait, nous formions un groupe de recherche fondamentale. Dans le groupe, certains cliniciens avaient des responsabilités cliniques, mais elles n'étaient pas reliées à leur programme de recherche. Et d'après mes souvenirs, les questions touchant les patients étaient rarement abordées avec les scientifiques fondamentaux.

Christopher Canning : Je vois.

Susie Tenenhouse : Les Drs Scriver et Rosenblatt sont des cliniciens, tout comme les Drs Pinsky, Fraser, Karaplis et Trifiro. Leurs champs d'intérêt cliniques étaient souvent à la base de leur programme de recherche fondamentale.

Christopher Canning : D'accord.

Susie Tenenhouse : C'est comme ça que je voyais les choses.

Christopher Canning : Vous n'avez donc jamais participé de près à l'établissement de diagnostics et au traitement des patients, mais vos recherches y ont contribué d'une certaine manière.

Susie Tenenhouse : Même si mes recherches ne portaient pas sur les diagnostics et les traitements, les échanges sur le sujet m'intéressaient. Je crois qu'il est important d'avoir une vue d'ensemble. Et je trouve qu'au fil du temps, l'aspect clinique de la recherche a pris moins de place.

Christopher Canning : Pensez-vous que le groupe est parvenu à embrasser cette vue d'ensemble?

Susie Tenenhouse : À mon avis, les chercheurs non cliniciens du groupe n'étaient pas intéressés par l'aspect clinique.

Christopher Canning : Dans l'une des demandes du groupe, on indique que l'équipe a atteint un certain niveau d'interdisciplinarité. Pourriez-vous me dire un mot à ce sujet? Croyez-vous que parce qu'il réunissait des connaissances en génétique des cellules somatiques, en cytogénétique, en biochimie et en biologie moléculaire, le groupe pouvait être considéré comme une unité interdisciplinaire?

Susie Tenenhouse : On peut dire que le groupe était interdisciplinaire dans une certaine mesure, ce qui peut être une caractéristique très positive. D'un autre côté, une équipe est

souvent plus productive lorsqu'elle compte plus de membres qui travaillent dans une même discipline. Ça dépend de l'orientation qu'on veut lui donner. Nous menions beaucoup de projets en même temps, mais il y avait aussi de petits sous-groupes qui étaient très productifs parce qu'ils partageaient les mêmes objectifs, comme le groupe des folates.

Christopher Canning : Je vois. Et pourriez-vous me rappeler avec qui vous avez travaillé en particulier?

Susie Tenenhouse : J'ai travaillé avec le Dr Karaplis sur un seul projet. J'aurais aimé davantage de collaboration, mais ça n'a pas fonctionné. Il avait un grand esprit de compétition, et il était en concurrence avec moi. Nous sommes tous confrontés à des compétiteurs qui ne veulent pas tout dévoiler. C'est terrible, je sais, mais c'est comme ça.

Christopher Canning : Pouvez-vous m'en dire plus là-dessus?

Susie Tenenhouse : Avant de se joindre au groupe du CRM, le Dr Karaplis a travaillé de nombreuses années avec des chercheurs du Laboratoire de recherche sur le calcium, dirigé par le Dr David Goltzman. Ce groupe était déjà reconnu pour ses recherches sur le métabolisme et les troubles osseux et minéral, ainsi que pour ses recherches en biologie moléculaire. J'ai voulu collaborer avec cette équipe, mais ça n'a pas fonctionné. Finalement, tous mes collaborateurs se trouvaient dans d'autres universités, et nous avons été très prolifiques.

Christopher Canning : Vous avez donc travaillé avec plus de personnes de l'extérieur que de membres de ce groupe?

Susie Tenenhouse : Oui. J'ai travaillé avec le Dr Scriver au début, mais il était mon superviseur pendant mon postdoctorat. Nous avons aussi réalisé des travaux intéressants ensemble pendant les années qui ont suivi. Mais lorsque je suis partie de mon côté, je devais absolument devenir indépendante et définir ma propre identité afin de pouvoir obtenir des fonds du CRM. Il n'y a pas de solution parfaite. Il faut s'adapter à la perception des organismes subventionnaires. Il faut être indépendant des autres groupes et des autres chercheurs. De nos jours, on recherche de plus en plus la collaboration et on regroupe des personnes ayant diverses compétences : statisticiens, épidémiologistes, cliniciens et fondamentalistes.

Christopher Canning : Je vois. On semble vouloir étudier un problème en particulier d'un point de vue interdisciplinaire. Tout le monde s'intéresse à un seul problème, c'est bien ça?

Susie Tenenhouse : Exactement.

Christopher Canning : Donc, contrairement aux groupes d'aujourd'hui, les membres de l'équipe de McGill s'intéressaient à un grand nombre de sujets différents. C'est bien ça?

Susie Tenenhouse : Oui. Beaucoup de projets différents dans beaucoup de domaines différents. Les choses ne fonctionnaient pas du tout de la même façon à cette époque.

Christopher Canning : Qu'est-ce qui faisait que ce groupe était effectivement un groupe? Comment les efforts de collaboration, ou d'autres aspects de votre travail, définissaient-ils

ce groupe du CRM, puis plus tard des IRSC?

Susie Tenenhouse : Je crois que le succès du groupe est principalement attribuable aux qualités de dirigeant du Dr Scriver. C'était une personne charismatique et intelligente qui s'exprimait bien et qui possédait les compétences nécessaires pour former ce groupe, le diriger et le représenter auprès du CRM. Les chercheurs principaux étaient tous des personnes accomplies et prolifiques dans leurs domaines respectifs et, étonnamment, seuls les trois chercheurs principaux qui s'intéressaient aux folates travaillaient en collaboration.

Christopher Canning : Et vous dites qu'il y avait de petits groupes dans le groupe.

Susie Tenenhouse : Oui, un en particulier.

Christopher Canning : Et il arrivait que des membres travaillent ensemble, mais c'était rare. Comme vous le dites, il n'y avait pas de collaboration dans l'ensemble du groupe, contrairement à aujourd'hui.

Susie Tenenhouse : Comme je l'ai dit tout à l'heure, ce n'était pas comme les équipes d'aujourd'hui, qui sont composées de personnes ayant des formations et des compétences très différentes, comme des cliniciens, des chercheurs fondamentalistes, des épidémiologistes et des statisticiens. Notre groupe n'avait pas une telle composition.

Christopher Canning : À votre avis, qu'est-ce qui a contribué à assurer la longévité du groupe, de 1972 à 2009? Il s'agit tout de même du groupe de recherche en santé qui a été financé le plus longtemps dans l'histoire du Canada.

Susie Tenenhouse : Je dirais que le Dr Scriver a eu une influence considérable sur la longévité du groupe. Il a une grande crédibilité et une vaste expertise, et il a fait un travail remarquable pour faire connaître les réalisations du groupe. Il fait bonne impression et est très doué pour parler aux politiciens. Je pense que c'est grâce à lui que le groupe a pu exister pendant aussi longtemps.

L'ouvrage intitulé *The Metabolic and Molecular Basis of Inherited Disease*, qu'il a dirigé puis rendu disponible sur Internet, ainsi que sa contribution à la génétique et sa passion pour ce domaine ne sont pas étrangers à cette longévité. Enfin, les réalisations personnelles des membres du groupe ont aussi joué un rôle important.

Christopher Canning : C'est donc beaucoup une question de doigté. Vous aviez une personne qui avait un talent particulier pour maintenir l'unité du groupe, trouver du financement et préserver une certaine structure.

Susie Tenenhouse : Le Dr David Rosenblatt tenait aussi beaucoup à garder le groupe uni et à travailler au sein de la structure de ce groupe. Il a donc toujours été en faveur du groupe, tout comme Roy Gravel.

Christopher Canning : Vous parlez de la structure du groupe, mais comment peut-on dire que la structure en place était celle d'un groupe? Désolé d'insister sur ce point, mais comment définit-on la structure du groupe?

Susie Tenenhouse : C'est un mystère pour moi. C'était simplement un groupe de personnes qui travaillaient en génétique et qui se sont réunies pour des questions de financement. Cette composition était un peu artificielle. Nous estimions qu'il était très avantageux pour nous de faire partie d'un groupe en raison du financement de nos recherches, mais aussi parce que nous recevions des fonds pour les installations et le matériel. Le salaire des chercheurs principaux et des stagiaires était également pris en charge. C'est tout ce que je peux dire à ce sujet. Nous avons simplement réussi à garder le groupe vivant.

Christopher Canning : Oui. D'après les discussions que j'ai eues avec les autres membres, tout le monde semble du même avis. Tout le monde travaillait dans son domaine tout en faisant partie d'un groupe qui lui permettait d'obtenir du financement. Et ce financement permettait à chacun d'effectuer ses recherches individuellement.

Susie Tenenhouse : C'est ça. Et comme je l'ai dit plus tôt, jusqu'en 1996, le salaire de tous les chercheurs principaux était payé par les subventions du groupe. C'était extrêmement avantageux pour les départements des universités dans lesquels nous occupions des postes. Mon salaire de chercheuse principale a été versé à même les subventions du groupe de 1981 à 1996.

Christopher Canning : Wow. Le département devait vous aimer, parce que vous fournissiez votre propre salaire.

Susie Tenenhouse : Tout à fait. Je dois mentionner que bon nombre de chercheurs principaux recevaient aussi un supplément de McGill, mais je n'en sais pas plus à ce sujet.

Christopher Canning : Je vois. Vous rappelez-vous que vers 2000, lorsque le CRM a fait place aux IRSC, les membres devaient trouver leur propre financement avant d'être invités à se joindre au groupe? Les membres ne pouvaient plus être financés par le groupe et devaient obtenir leurs subventions individuellement.

Susie Tenenhouse : Je pense que les chercheurs principaux, nouveaux ou non, ont toujours dû faire évaluer leurs propositions de recherche individuellement. L'acceptation au sein du groupe dépendait de cet examen ainsi que de la pertinence de la personne dans le groupe.

Christopher Canning : Une personne qui désirait faire partie du groupe devait d'abord obtenir sa propre subvention des IRSC, et ensuite être acceptée dans le groupe.

Susie Tenenhouse : Oui, c'est ça. Je sais qu'une personne qui n'obtenait pas son financement ne pouvait pas être membre du groupe.

Christopher Canning : À votre avis, quelles sont les avancées scientifiques ou cliniques en génétique qui ont profité des travaux du groupe?

Susie Tenenhouse : Je crois que l'apport clinique le plus important du groupe du CRM en génétique est le travail de Charles Scriver pour le dépistage néonatal du statut de porteur dans les familles à risque de maladie génétique. La découverte des mutations chez ces familles et la capacité à établir un diagnostic prénatal sont également très importantes. À cet égard, Peter Hechtman a fait de grands pas avec ses recherches sur la maladie de Tay-Sachs.

Malheureusement, les bienfaits de la recherche fondamentale mettent des années à se concrétiser. Autrement dit, la découverte du gène touché par la mutation ne mène pas toujours à un traitement efficace. La fibrose kystique, une maladie génétique courante, en est un bon exemple, même si elle n'a aucun lien avec le groupe du CRM. Le gène responsable de la fibrose kystique a été découvert à la fin des années 1980, mais nous n'avons toujours pas de remède pour cette maladie dévastatrice. Il nous faut encore plus d'information sur le comportement du gène *in vivo* pour trouver de nouvelles cibles médicamenteuses et mettre au point de nouveaux traitements.

À cet égard, le projet Génome humain a été décevant. Beaucoup de gens estiment qu'il n'a pas été à la hauteur de l'investissement. D'après Francis Collins et Eric Landers, il faudra investir encore plus de travail et de temps avant de récolter les fruits de ce projet qui a coûté extrêmement cher en argent et en main-d'œuvre.

Christopher Canning : Et quelle est votre opinion à ce sujet?

Susie Tenenhouse : Je crois que le projet Génome humain est très important, mais qu'il faudra plus de temps pour que les données produites puissent être utilisées pour prédire une prédisposition à une maladie. Les choses sont un peu plus compliquées qu'on le croyait au départ. Bon nombre d'études d'association pour la détermination des risques génétiques ne sont pas fiables, et on manque de connaissances pour interpréter ces données. Le projet prendra beaucoup plus de temps que prévu, mais en fin de compte, je crois que les bienfaits seront énormes.

Christopher Canning : Croyez-vous que la génétique humaine finira par avoir des effets positifs pour des maladies comme la fibrose kystique ou aura d'autres retombées thérapeutiques?

Susie Tenenhouse : Oui. On nous dit qu'un jour, chaque personne aura sur elle une petite carte, semblable à une carte bancaire, qui renfermera des données sur son statut génétique et sa prédisposition aux maladies. Mais ce jour n'est pas encore arrivé.

Christopher Canning : Quelle est l'opinion des autres chercheurs principaux au sujet de la contribution du groupe?

Susie Tenenhouse : Vous voulez savoir ce qu'ils en pensent?

Christopher Canning : Oui, l'avis des autres chercheurs principaux.

Susie Tenenhouse : Je pense que ça ressemble à ce que vous avez déjà dit. Pratiquement tout le monde parle des premiers travaux du D^{r} Scriver sur le métabolisme de la vitamine D et les erreurs innées du métabolisme. Dans l'histoire de la recherche sur la génétique au Canada, il s'agit sans contredit d'une découverte très importante. Et je pense que beaucoup d'autres personnes disent simplement qu'il y a encore beaucoup de travail à faire.

Christopher Canning : En effet.

Comme vous l'avez dit, la recherche fondamentale n'a pas nécessairement de retombées thérapeutiques immédiates.

Susie Tenenhouse : Je suis d'accord.

Christopher Canning : Oui.

Susie Tenenhouse : Comme je l'ai déjà dit, j'ai vu une entrevue télévisée pendant laquelle on a posé des questions très difficiles à Francis Collins et Eric Landers au sujet du projet Génome humain. Comment se fait-il que nous n'ayons toujours pas plus de réponses? Ça prend du temps; c'est très complexe.

Christopher Canning : Et on dirait que plus les généticiens savent de choses, plus les choses se complexifient et sont difficiles à expliquer.

Susie Tenenhouse : Oui, mais on finira par tout savoir.

Christopher Canning : Oui.

Susie Tenenhouse : Peut-être pas de mon vivant, mais les réponses arriveront un jour.

Christopher Canning : Vous tenez-vous au courant des études en cours? Vous avez pris votre retraite, mais faites-vous toujours de la recherche? Lisez-vous toujours des ouvrages de génétique ou coulez-vous simplement des jours paisibles en Arizona?

Susie Tenenhouse : Je prends du bon temps en Arizona pendant l'hiver, mais je continue à m'intéresser au domaine. Pendant un certain temps, j'ai révisé des manuscrits soumis à des revues, mais je trouvais que je ne pouvais pas faire un travail optimal. Il faut rester à jour dans la littérature scientifique pour pouvoir juger de l'originalité et de la validité des travaux décrits dans ces manuscrits.

Je consulte le site *PubMed* de temps en temps, mais je lis surtout sur d'autres sujets, ce que je n'ai jamais eu le temps de faire avant de prendre ma retraite.

Christopher Canning : On peut donc dire que vous avez délaissé le rein pour vous intéresser à d'autres domaines?

Susie Tenenhouse : [rires] Oui, mais j'aime bien en entendre parler de temps en temps.

Christopher Canning : Quels sont vos projets pour l'avenir?

Susie Tenenhouse : Nous espérons simplement rester en forme et passer nos hivers ici, continuer à lire, à voyager et à faire de la randonnée. Nous aimons beaucoup faire des choses que nous n'avons jamais eu le temps de faire auparavant. Et bien entendu, nous aimons passer du temps avec nos petits-enfants; nous en avons deux à Toronto et trois dans la région de Boston. Je suis très proche de ma mère, qui habite à Montréal. Elle aura 100 ans en avril. Nous nous parlons tous les jours et je la vois régulièrement. Elle est en grande forme pour son âge, et nous avons bien hâte de fêter cet anniversaire important avec elle.

Christopher Canning : C'est formidable.

Susie Tenenhouse : J'ai parlé à ma mère aujourd'hui, et elle n'arrive pas à croire qu'elle va avoir 100 ans. Je lui ai dit qu'elle devrait être fière d'elle, mais elle m'a répondu qu'elle ne se sentait pas comme si elle avait 100 ans. Elle m'a aussi dit qu'elle espérait que j'aie ses gènes. Je l'espère aussi. [rires]

Christopher Canning : C'est fantastique. Et votre mari est médecin, n'est-ce pas? Il est donc à la retraite également?

Susie Tenenhouse : Alan [M.D., Ph. D.] a pris sa retraite de l'Université McGill, où il dirigeait la Division du métabolisme osseux. En 1993, il a mis en place une vaste étude épidémiologique, l'*Étude canadienne multicentrique sur l'ostéoporose* (CaMos). L'équipe suit un groupe de Canadiens et de Canadiennes âgés de 16 ans ou plus, choisis au hasard, pour évaluer leur santé osseuse et le taux de fractures. Cette étude est unique pour plusieurs raisons, et elle est l'une des plus importantes études épidémiologiques dans le monde. Elle est toujours en cours, et un nouveau financement des IRSC a été obtenu récemment. Alan continue de participer aux conférences téléphoniques avec les directeurs des centres, et il est très fier de l'efficacité de cette étude. Il aime aussi les voyages, la randonnée et la lecture.

Christopher Canning : C'est bien!

Susie Tenenhouse : Toutes les personnes que je rencontre ont une perception différente de la vieillesse et de ce qu'ils vont faire pendant cette étape de leur vie.

Christopher Canning : Oui. Je pense que vous devriez profiter de cette période et, comme vous l'avez dit, faire les choses auxquelles vous ne pouviez pas accorder de temps auparavant.

Susie Tenenhouse : Avant de prendre ma retraite, je me sentais coupable de lire des romans ou des documents qui n'étaient pas liés à mon travail. Je savais qu'il était beaucoup plus productif pour moi de lire des textes scientifiques. Aujourd'hui, je rattrape le temps perdu. Alan et moi avons chacun une liseuse Kindle, et nous adorons le fait d'avoir un nombre incalculable de livres au bout des doigts. C'est fantastique!

Christopher Canning : Maintenant, vous pouvez profiter du soleil, votre Kindle à la main.

Susie Tenenhouse : Exactement.

Christopher Canning : Une dernière question. Avez-vous encore des contacts avec des membres du groupe?

Susie Tenenhouse : Très rarement; environ une fois par année. J'essaie de rester au courant du déroulement de leur carrière.

Christopher Canning : Comme je vous l'ai dit, Reynold Gold vous transmet ses salutations. Il a beaucoup d'estime pour vous, surtout lorsqu'il parle de vos travaux en laboratoire.

Susie Tenenhouse : J'ai beaucoup aimé les retrouvailles du groupe de recherche du CRM/IRSC en novembre 2009. C'était formidable de voir toutes les personnes qui ont fait

partie de ce groupe au fil des ans.

Christopher Canning : Oui, et c'était une très belle journée.

Susie Tenenhouse : Je vous souhaite beaucoup de succès avec votre projet. J'ai bien hâte de lire vos publications.

Christopher Canning : Merci! Je vais maintenant éteindre l'enregistreur. Merci beaucoup de m'avoir accordé de votre temps.

FIN DE L'ENTRETIEN