F. CLARKE FRASER INTERVIEW
Session 1, October 27, 2004

1. Early Life, Religious Traditions, and Education

ANDREA MAESTREJUAN: It is the 27th of October 2004 and I'm with Dr. F. Clarke Fraser in Toronto for his Human Genetics Oral History Project interview. I'm Andrea Maestrejuan, and we'll start at the very beginning and I'll ask you when and where you were born.

F. CLARKE FRASER: I was born in Connecticut. Norwich, Connecticut.

AM: I know that you moved rather quickly to Canada.

CF: Well, my father was just down there temporarily on a job, so we were Canadians. He was down there selling insurance, but he moved back actually, when I was nine months old. I've lived in Canada most [of my life] – well, not really. My father eventually became a trade commissioner, so I spent a lot of my childhood out of Canada wherever he was posted. We went to Ireland when I was about four and then to Jamaica when I was about seven, and I stayed there until I was seventeen. I came back to Nova Scotia, to Acadia,[1] to go to college. My grandfather's house in Bear River is the place we had sort of a home base; we'd come back there on holidays or between postings. So I kept that connection, even though I was always living somewhere else.

AM: Are you an American citizen then by birth?

CF: I was. I had a dual citizenship till I was twenty-one, and then I was supposed to choose, I guess, between [them] – and I never got around to it. Eventually, I joined the [Canadian] Air Force and swore allegiance to the King. I thought that would negate my American citizenship, and that I would therefore be Canadian by exclusion. When I applied for a passport some five years later, they said "No, it doesn't." So I was actually citizenless for about five years. Then I finally got my Canadian citizenship by Order in Council.[2] (he chuckles)

AM: But you've always considered yourself Canadian?

CF: Yes.

AM: And you said your parents were Canadian. Can you tell me a little bit about their backgrounds? How far back are they Canadian?

CF: Oh, yes. My mother was a Clarke and they were of English stock. I think about three generations before that, Richard Clarke, an ancestor, came over. My father was Scottish. I don't know very much about his family, actually, but they were Canadian for several generations. They both graduated from college. Mother had a music degree, and I think Dad had a BA, or something like that. They met at college. Then he went off to World War I. When he came back, they got married and produced me.

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[1] Acadia University in Wolfville, Nova Scotia, founded in 1838.
[2] An administrative action of the Canadian Federal Cabinet approved by the Governor General.

AM: Any other siblings?

CF: My sister Mary, two years younger than I. She died, sad to say. She had what was called Alzheimer Pick's disease in those days, presenile dementia, in the days when they didn't realize it was the early onset of the usual kind of Alzheimer's.[3] She died at about age thirty-five.

AM: Thirty-five, wow. Your grandparents, both sets, were from Nova Scotia?

CF: My mother's parents were, yeah. My dad's were from New Brunswick, I think, right next door.

AM: Where did your parents go to college?

CF: Mount Allison, which is a small university in New Brunswick.[4]

AM: Did any of their parents go to college? Do you know?

CF: I think so. Acadia [University], probably. My grandfather was a Baptist and my grandmother was United – or Methodist as it was in those days. They had three daughters. Actually, they had four but one died young, so they alternated the church. So we went to the Baptist church every other Sunday and the Methodist church on the other Sundays, so I guess they did the same thing with college. Acadia was a Baptist college and Mount Allison was a Methodist college, so that's why my brother went to Mount Allison.

AM: Okay. How did they meld these two different religious traditions in your house? What kind of religious traditions were you raised with?

CF: Well, when I was in Bear River, I alternated Sunday schools, which was very confusing. [he chuckles] Well, there was never any – they're not too different. My parents never argued or had any conflict about which church they were going to. I don't think they went to church very often.

AM: When you were living in Ireland and then in Jamaica, did you continue to go to a church, or only when you were at home?

CF: We used to go to church in Ireland, I remember. We lived just outside Dublin. I don't remember going to church in Kingston [the capital of Jamaica]. When I was sent away to public school, which was really private school, up in the hills, they had Chapel twice a day and three times on Sunday. That was Anglican – based on the Anglican [service]. It was supposed to be non-denominational, but it was the Anglican service. So I got very accustomed to that, and it still has a lot of appeal to me.

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[3] Pick's disease is a specific type of temporofrontal lobar degeneration. Unlike Alzheimer's, personality change occurs before memory loss is evident. It was first described by Arnold Pick of the University of Prague in 1892.

[4] Mount Allison University in Sackville, New Brunswick, founded in 1839.

AM: When you kind of left the house – well, you really didn't leave Nova Scotia that much – but what kind of religious traditions have you practiced as an adult and passed on to your own children?

CF: That's a good question. I think I became quite agnostic fairly. When I was in school in Jamaica, I read about Darwin, so I had sort of a sense of holiness during the service and probably [I felt] a little sanctimonious, but I didn't really go the whole way. My first marriage, my wife was Anglican, so I then joined that church. I got confirmed. We went to that church regularly throughout my children's childhood. I think they still have quite strong attachments to the church. I'm not sure how often they go, but my son Scott sings in a church choir, and my son Allen did for quite a while. I guess that's as far as that goes.

AM: That's okay. You had mentioned in this several-page autobiography in *Issues and Reviews in Teratology* that you had at some point accepted the theory of evolution over the divine creation. How did your religious beliefs conflict to this new found faith in science?

CF: Well, it conflicted, obviously, to the point where I didn't believe some of the essential beliefs. On the other hand, I used to look at it in allegorical terms instead of literal terms so I could see where the teachings of the church were valuable and discipline was valuable. I was quite active in the Anglican church after our marriage for a while. I sat on various committees, including – I don't know, maybe I shouldn't go this far. Tell me if –

AM: No, you're doing just fine.

CF: I sat on a bishop's committee that was supposed to be revising the liturgy, and I was on the committee as the scientist. At the first meeting, I think, the creed came up, "I believe in God the Father Almighty, maker of Heaven and earth," and it ends up, "As it was in the beginning, is now, and ever shall be." And I said, "Well, what makes you think there was a beginning?" and defended that. That was the last meeting [he laughs], as far as I was concerned anyway. I don't know whether the committee went on or not, but I was not asked to return.

AM: Okay. Well, what kind of expectations did your parents have for you and your sister in terms of what you should do with your lives?

CF: They were fairly permissive, I think. I don't remember being urged that I had to do anything. But they had fairly high standards for themselves, and they were pleased when we made good marks, and they certainly made sure that we had good educations. I think we started with a governess in Ireland. My mother taught me to read. I remember still, I was trying to learn how to put syllables together in this word *chimney*. I said, "What's this word?" She said, "Well, talk it out. Chim - nee." "Oh, chimney." [he chuckles] It was a big revelation. So they obviously did value our education.

In Jamaica, we went to a small private school for a year or so. I think I spent too much time playing with my sister's little friends and my father thought I was getting to be a sissy, so he sent me to Munro College[5] up in the hills, which was also good to be out of the heat. Oops, a grammatical error. [he chuckles]

[5] A boarding school for boys in St. Elizabeth, Jamaica, founded in 1856.

AM: Don't worry about it.

CF: That was a very good school. I still remember a lot of training that I got there, and I value that because it was a real plus for my education. I liked math and physics and chemistry. They didn't teach biology, for reasons I'm not clear about. I guess it just wasn't fashionable in those days. I got a good grounding in English literature and grammar. I even spoke French better than I do now. That was a good thing for me.

Then my parents were transferred to Australia, to Melbourne. I was college age by that time, so I came back to Acadia, which is near Bear River where my aunt was living, so she sort of took care of us. Ever since I can remember, I wanted to be a doctor. I think I had a great admiration for my Uncle Lew, who was a real horse-and-buggy doctor, literally. He used to operate on the kitchen table and that sort of thing. He was a lovely man with a great sense of humor. I think that's why I wanted to be a doctor.

So I went to Acadia as premed. I entered [as a] freshie-soph because my education was about a year ahead of what it would have been if I had been in Canada. We started in Biology 101. Muriel [V.] Roscoe[6], who was at Acadia at that time, gave two lectures on genetics, and I just went for it, I fell for it. I decided I wanted to be a geneticist.

AM: Let me take you back a little bit before we get up to college. Did your parents expect both you and your sister to go to college? Was there a choice in that?

CF: I think it was just taken for granted, yeah.

AM: Okay. You had noted that your Aunt Edie probably influenced your character formation more than she knew. You spent summers with her.

CF: Well, while I was at Acadia, and sometimes earlier, depending on my father's leaves and stuff. She was quite an autocrat. She laid down the law. There was no drinking in the house, and you didn't play games on Sunday or play cards or anything. I don't know how much that influenced my character, but probably.

AM: So no drinking today and no playing cards? Do you play cards now, or do you drink now?

CF: I don't play cards. Oh, I certainly drink on Sunday. (laughs)

AM: So you spent most of your childhood in Jamaica? Or did you move around even when you were growing up? Or primarily just Jamaica?

CF: No. For some reason or other, my father stayed there longer than usual for a posting. I was there the whole time, except for trips to Canada on leave, or whatever.

AM: And your first experience with school, formal schooling, was in Jamaica? Or did you go to school in Ireland at all?

[6] Muriel V. Roscoe (1897-1988?) taught biology at Acadia 1926-1940. She was later chair of the Botany Department at McGill University, where she taught until 1967.

CF: I think there was a small one-teacher private school in Ireland. I can't remember much about that. Munro, besides being an excellent school, was mostly Jamaicans, mostly black or mulatto, so I had the experience of being in a minority, which I think was very good for me and changed my – well, I don't think I had any racist views before that, although my mother did. She wanted to be sure I got out of Jamaica before I reached marrying age.

AM: Oh, okay. Was she not particularly happy living in Jamaica?

CF: Oh, I think so [that she was happy], apart from these few hazards. She was a beautiful hostess, and she had to do a lot of – there wasn't any ambassador or anything, so my father acted more or less as what would have been an ambassador in a bigger place.

AM: Okay. So what were the backgrounds of your friends who you got to know while living in Jamaica?

CF: While I was in Jamaica?

AM: Yeah. Who did you play with? Or did you have --

CF: In Kingston, I played with the sons and daughters of various friends of my father's, I guess. [For example] the bank manager and – there were a couple of twins. I don't remember [who their] fathers were. They were all white. But at Munro, I had another bunch of friends of various colors.

AM: You had mentioned that the education was pretty well – you got a pretty good education at Munro, but more liberal arts, more general education rather than any kind of specific training in any particular area?

CF: There was a lot of chemistry, physics, and math. Most of the teachers were from England. We were studying for the Oxford and Cambridge Higher School Leaving Certificate[7]. We wrote those exams in Jamaica, but were sent out from the Oxford and Cambridge School Leaving Certificate Foundation, or whatever it was.

AM: Would it be safe to say that most of your fellow students at Munro were preparing to take the A levels or O levels and go on to college, or was that different at Munro?

CF: Yeah, I think that would probably be true. One of them became Prime Minister later on.

AM: Of Jamaica?

CF: Yeah.

AM: There's a family tradition to go to Acadia, but did you think about going somewhere else, or going to Australia with your parents to school?

[7] Equivalent to a high school diploma in the US.

CF: No. I think it was partly a matter of convenience. My Aunt Edie was there, so we had somewhere to stay during the holidays and stuff, since we couldn't go to Australia for the summer holidays. Maybe you could now, I guess, but – so Acadia seemed the logical choice for a premed.

AM: If you can recall, this had to be in the late thirties?

CF: I graduated in '40, so it was '37 I started.

AM: Would you know how common was it at Canadian universities to have actual courses in genetics?

CF: Well, Acadia didn't have one, I think. But when I got to McGill [University] – are you ready to start at McGill?

AM: Well, so you had mentioned a teacher, Roscoe?

CF: Muriel Roscoe, yeah.

AM: She taught genetics, but this was a part of –

CF: She just gave these two lectures in genetics, in Biology 101. I guess it was Biology 1 at that point.

AM: So you did get exposure to genetics. Can you recall what was it about the way she presented that – or what was it about the genetics that captured your curiosity?

CF: I think it was partly the mathematical rigor of the Mendelian laws. But also the beauty of biology which was striking me at that point, and the whole course in general, but to be able to apply this mathematical[ly] rigorous view of life really appealed to me. I thought I was good at math at that point. (chuckles)

AM: Were you good at math?

CF: No.

AM: Oh, you weren't, okay. When you became enthralled with genetics as a freshman, what happened to your interest in medical studies?

CF: Well, I'm not very clear on this, but I think – yeah, I was so enamored with genetics that I thought, “This is what I'm going to do.” I didn't think too far ahead what I would do with it, so I guess I sort of put the medical part on the back burner.

AM: Ok. How well did you integrate in with your other students? It seems to me you had a very cosmopolitan upbringing. You had moved a couple of times. You lived in Kingston, Jamaica, which would seem very exotic, I would think, and then you choose to go back to a college in Nova Scotia.

CF: Well, I think I fitted in pretty well. I got into dramatics in my first year. We did *The Importance of Being Earnest*[8], and I was Algernon. I'm sure I got that because I had a British accent. I made a lot of good friends. They were mostly Nova Scotians, and I didn't feel any different.

AM: Did you ever contemplate going into theater?

CF: No. I didn't think I was good looking enough. (chuckles)

AM: So when you decided to – when did you decide to go to graduate school, or pursue more education?

CF: Well, I think I started thinking about it fairly soon. I remember [Frederick] Banting[9] coming and giving a talk. That really turned me on, too.

AM: At Acadia?

CF: Yeah. He told about how, when he made this famous discovery, he used to have ideas in the middle of the night and he'd write them down immediately before he went back to sleep. He wrote down this thing about tying off the pancreatic duct to make the dog diabetic, or to get rid of the juices anyway. I thought this idea of writing down your brilliant ideas was great, but somehow I never got around to it.

AM: What about the tinkering part? Did you tinker a lot with things as a child growing up? Did you collect bugs or do those kinds of things?

CF: No, I wasn't a naturalist.

AM: Okay. You didn't come in through that way.

CF: No. My grandfather had a farm, so I got to know the birds and the bees that way, but I don't remember doing any experiments or anything like that.

2. WWII Service and Graduate School

AM: At what point did you see – well, let's talk about, when it came to deciding to go to graduate school, where were you looking, and at that point, how important was it to pursue a medical degree as opposed to a Ph.D. in a basic science?

CF: Well, I was going for the Ph.D. I had to make a big decision when the war started whether I would enlist or go to graduate school. General [Andrew] McNaughton[10] made a public statement that people who are in science – students – should stay here, because the country needed them in science, to go on with their education. So I accepted that, with some guilt.

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[8] A classic comedy by Oscar Wilde, written in 1895.

[9] Sir Frederick Grant Banting (1891-1941), a Canadian physician, won the Nobel Prize in 1923, for being a co-discoverer of insulin. It was his idea that led to the series of experiments that finally isolated the compound.

[10] General Andrew G. L. McNaughton (1887-1966) led the First Canadian Infantry Division, later the Canadian Army, in World War II, and served as Canadian Defense Minister 1944-45.

CF: So when I decided where to go, there was only one place in Canada that had a genetics department, and that was McGill.[11] They had started it a few years earlier, I think. [Charles] Leonard Huskins[12] started the department [in 1934], and it all arose out of an argument between botany and zoology as to who was going to teach genetics and which of them would teach genetics. Huskins got a grant from the Rockefeller Foundation to start a genetics department, so they were just underway when I got there. I still had this orientation towards humans. When I got there, they said, "You can work on corn or *Drosophila* or mice." I said, "I want to work on mice."

AM: And why was that?

CF: Because they were more like humans. It was closer to medicine, I guess, although I'm not sure I put it in exactly those terms. They were more interesting. Well, it turned out that there were two students in the mouse room at that time, so there wasn't room for another one to work on mice, so I had to work on *Drosophila*. Arthur [G.] Steinberg[13] had just – do you know that name?

AM: No.

CF: He had just arrived at McGill, so that's how I got to be *his* student. He was very good for me, too, I think. He thought I was lazy. I don't think I really was, but maybe I wasn't as strongly motivated as I should have been. I sat in his course in developmental genetics. I used to get this glassy stare when I was concentrating very hard, and I didn't take very many notes because I was good at summarizing, so I would just write little summaries, not try and write down everything, like some people do. After a few lectures, he said, "Fraser, if you must sleep, will you sleep in the back row instead of the front row?" (laughs) I meekly got up and went to the back row. But I wasn't sleeping.

He was interested in the interchromosomal effects of inversions on crossing over[14]. Somebody had discovered, in *Drosophila*, that if you had an inversion in one chromosome, it might increase the crossing over rate in the other chromosome. Now what on earth was this? At that point, even crossing over itself was still a subject of intense study. We took the X chromosome as the one to observe and then got stocks with various inversions to see whether the length of the inversion or the position of the breaks, or whatever, would make a difference. We needed a control stock, of course.

I did all these experiments on these crosses, and we had to classify – I think there were twelve hundred-some classes that you could put the little insects into. It was a lot of work. I came out with absolutely ridiculous results, and he said, "What's going on?" So he said, "All right, I'm going to do parallel experiments and we'll do them together." So we did that. He got the same results. It turned out there was an inversion in the control stock, which was upsetting everything. The control was supposed to be

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[11] McGill University in Montreal was founded in 1821. It is known for the diversity of its medical-doctoral student body.

[12] Charles Leonard Huskins (1897-1953), an English –born cytogeneticist who spent most of his career teaching in Canada at McGill University and in the US at University of Madison-Wisconsin. His best know for being a pioneer in the field of plant genetics. For more information, see the following article: http://jhered.oxfordjournals.org/cgi/reprint/45/5/249.

[13] Arthur G. Steinberg (1912-2006) was a geneticist of Latvian heritage. He is best know for his work in immunoglobins. For more information, read the article at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1867090/

[14] crossing over: when homologous portions of paired chromosomes interchange during meiosis.

normal, but it had an inversion in it. So I think he took a little more favorable view of me after that. (chuckles)

AM: So he was interpreting this as just a problem with you as an experimentalist.

CF: Yeah, I think so.

AM: Well, what did this episode teach you about progress in science?

CF: About progress in science? I can't think of anything deeply philosophical to say about that. Use good controls, I guess.

AM: In terms of your own development as a geneticist, when you're getting these results and your advisor is doubting that – it's some other problem besides you, the experimentalist, how confident were you that you were actually good at what you were doing but there was some other problem, like the control was bad?

CF: I don't remember ever saying to myself, "Well, jeez, I'm a failure." I thought, I'm doing everything right. Something's wrong but I don't know what it is. Anyway, we became very good friends, and he was a very good influence on me.

AM: You had mentioned at McGill, when it formed its genetics department, there was a kind of disagreement about who was going to teach it, botany or zoology, and when they formed the department, was there any one particular approach to genetics that predominated? Did the plant geneticists or the fly geneticists predominate?

CF: Oh, I think it was the plant geneticists. Huskins worked with Spartina, a kind of grass. And they had Bernie [G. Bernard] Wilson who was doing things with trillium[15] chromosomes, I think. And Gerhard Sander, I can't remember what he worked on. Sheldon [C.] Reed[16] had just left. He did mouse work there, but then he went to Wisconsin. Steinberg was a new boy. I guess there were more plant geneticists, and most of the conversation at tea time was plant oriented. But they had very high standards. They used to really sweat over a paper, and everybody would go over the paper and they'd talk about it at tea time and then put it away for six months to let it simmer and then take it out again. If it still looked good, they'd send it off. No more. (chuckles)

AM: Right. Well, now we have these databases that link all the different genes across all the different model organisms, and it's very easy to see if one gene has any kind of homolog in another model. But they didn't have that when you were entering graduate school. What approaches did you think you could use with mice that would be more beneficial to understanding genetics in humans?

CF: I didn't really think about that. I worked on various kinds of hairlessness when I finally did get into the mouse room the next year. I don't think I had any visions of curing human baldness or anything. It was just interesting, and as long as you could ask good

[15] Trillium: a plant commonly found on the forest floor in eastern North America. It has a tripartite leaf and has been used in genetics studies because of its genetic diversity.
[16] Sheldon C. Reed (1910-2003), a human geneticist who is best known for his work in genetics couseling. For more information, see the article at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1180572/

questions and set up incisive experiments, it was fun. I didn't really have any idealistic view of the future.

AM: How difficult was it for you to convince Steinberg to let you move from – well, how did you then move from fly genetics to mouse genetics for your thesis project?

CF: Well, I think it was understood from the beginning that if I'd spend this year with *Drosophila*, or anything else, that I would finally be allowed to get into the mouse room.

AM: Okay. Why did you choose Steinberg – or how did you choose your advisor, I guess?

CF: Well, I mean, it was either plants or *Drosophila*, and he was *Drosophila*.

AM: Then how did you choose your thesis project?

CF: Like a lot of other things, there was a lot of random choice in it. Sheldon Reed had been doing some transplant experiments with skin transplants, to study hair color and its interactions. There was a mutation that had turned up in the McGill mouse room a few years back, called Rhino[17], which has got a very wrinkled [appearance], which is because they grow a coat of hair and then it falls out and they get very hyperkeratotic[18]. So it was sitting around there. Alma [Howard][19] had gone off to England, I think, and it just seemed like a neat idea to do some transplants like Sheldon had been doing and see if you could figure out whether the fault was in the hair follicle or the skin cells or what.

AM: So basically this is a period in which there were a lot of interesting mutations, that you could just pick one? Geneticists could just pick an interesting phenotype and --

CF: I'm not sure that there were all that many, but there just happened to be this one, and then we got other hair mutations from other labs, Bar Harbor[20] mostly. And that's how it went.

AM: Okay. I know that you end up joining the air force, but as you were finishing up your project, what did you think would be your next step?

CF: Well, I guess certainly by then I was having ideas that it would be nice to do this work like I'm doing on the mice with people. I still had this medical urge inside of me, I guess. So that was certainly in my mind. I can't remember exactly how strongly or when I made the critical decision. But when I got out of the Air Force, [my] Veterans'

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[17] Rhino mutation: a genetic mutation which causes hairless-ness along with thickened, wrinkled skin, extra-long claws and cysts.
[18] Kyperkeratotic: overgrowth and thickening of the skin.
[19] Alma Howard (1913-1984) was a geneticist. Her paper on hairless and Rhino mice can be accessed at : http://jhered.oxfordjournals.org/cgi/reprint/31/11/467.pdf
[20] Bar Harbor Lab: The Jackson Laboratory, headquartered at Bar Harbor, Maine, was established in 1929, is a genetics research center. The Jackson Laboratory's goal is to both train and educate people on the genetic source of diseases and to develop effective treatments. For more information on the lab, visit their website at: http://www.jax.org/index.html.

Allowance allowed me to go back to school. So I thought if they'll pay me to go back to school, I'll go into medicine and then see what I can do with genetics in medicine.

AM: And why did you join the Air Force, as opposed to continuing with school or getting a job as a geneticist somewhere?

CF: Why did I join the air force?

AM: Yeah.

CF: Well, we were at war, and I'd made this sort of bargain that I'd stay and finish my degree and then I would do my duty.

AM: Okay. You described your Air Force experience briefly in the one article, so what impact, if any, did this stint in the Air Force have on any of your career decisions?

CF: I don't think it had any. It was just filling in time till I could get back to work.

AM: Filling in time. You know, we don't really conceive of it as like – you were a bombardier?

CF: Yeah.

AM: I mean, how aware were you that this particular position in the Air Force was highly dangerous? Some people wouldn't describe it simply as filling in time.

CF: Well, it wasn't as dangerous as gunner. (chuckles) Actually, I was chosen – when they were beginning to cut back on pilot training, they chose a few people to go to a twelve hour special training course in Oshawa[21], and I learned how to fly a small plane at that point. I really loved that. That was the most exhilarating thing I think I've ever done. But by the time I'd finished the course, they'd completely wiped out pilot training and I had to re-muster. I had a choice of either rear gunner or bombardier. Bombardier sounded more interesting. I don't think it was just the danger, but it had – well, I could have been a navigator also, but bombardier training had some of the navigating training in it, so that was a compromise between navigator or gunner.

AM: Did you ever get overseas to see combat?

CF: No, no.

3. Medical School and Early Genetics Work

AM: The war ended before that?

CF: While I was waiting to be decommissioned, I actually got seconded back to McGill and did some work in the genetics department there on DDT[22], which was new at

[21] Oshawa is a city in Ontario, Canada.

[22] DDT (dichlorodiphenyltrichloroethane) : Banned in 1972, DDT is a highly toxic insecticide commonly used to kill mosquitoes. Mosquito populations are notorious for having quickly developed a resistance to

that point. [We] didn't know much about its biology or its toxicity. We fed it to dogs and put it into mice and found out that it gave dogs the jitters. (chuckles) Very crude toxicology.

But we also – by that time, there were a couple of graduate students who did Masters theses on – we were trying to work out a bioassay[23] because they didn't know how to measure it chemically yet, so we thought we could put graded doses in the *Drosophila* bottles and then put the *Drosophila* in and get a dose response curve, and then you could learn how to assay it. Didn't work out. It was never very reproducible. But the students also selected for resistance to DDT and showed really strong differences arising by selection, which of course predicted what was going to happen with the mosquitoes, but nobody listened.

AM: Oh, okay. How was Steinberg as a mentor, as an advisor?

CF: Oh, he was, I think, an excellent mentor. He was very logical, articulate, and disciplined and imposed those values on his students. I would say he was an excellent teacher.

AM: When you got out of the Air Force and decided to pursue your medical studies, did you think about any other institution besides McGill, or was it just assumed that's where you would go?

CF: Well, it was so easy to go to McGill. I went up and talked to the dean of medicine and told him why I wanted to get in, and he said, "Okay, Clarke." (chuckles) They already had the genetics department there. I actually did some teaching and had a graduate student while I was in medical school. I had this part-time appointment in genetics. So it was a nice comfortable place to be.

I didn't do very well in medical school. I think I went in with the idea that I would just take out of it what I needed for genetics, and they didn't appreciate that. I failed anatomy in first year, and in third year I failed obstetrics and gynecology. I'm not sure whether it was because of my attitude rather than my ignorance. In the oral exam in obstetrics, the doctor, who I remember very well, posed the problem of a pernicious vomiter of pregnancy and what are you going to do with her? She's throwing up. So I made some suggestions. He said, "And she's still vomiting, Doctor. Now what are you going to do?" And I made a few more suggestions. He said, "And she's still vomiting, Doctor, *in your face*, Doctor!" And I said "What would you do?" And he said, "Wipe it off, sir." I don't suppose that had anything to do with my failure, but – d

So at that point, I took the year out and went back to sort of regain my strength. I went back to the genetics department. Huskins had just died and a new chairman had come in, Wally [J. Wallace] Boyd, who – he needed some help in teaching because most of the people who had been in the department had left for various reasons. So I taught Steinberg's courses, developmental genetics and biometrics, God forgive me. (chuckles) So I was one step in the textbook ahead of the class.

AM: Why did Steinberg leave McGill?

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the toxin, rendering the use of DDT largely ineffectual. Though banned, the toxin remains in the environment still and accumulates in creatures at the top of the food chain such as fish and birds.

[23] Bioassay: assessment of the strength of a substance by comparing its effects with those of a standard preparation on a test organism.

CF: Why? He went into the Navy as operative research of some kind. There's an interesting story about that, which is not really about me. Do you want me to [tell it]?

AM: Sure.

CF: There was a chemist by the name of Raymond Boyer[24] at McGill, who was making RDX [cyclotrimethylenetrinitramine]. He was the one that learned how to synthesize it, I think. It's a very powerful explosive. It was at the time when the Russians were being threatened by the German forces. It looked like they were loosing out at that point, (the Russians were our allies). He wanted to let the Russians have RDX, the formula for RDX. The powers that be said no, so apparently he got to know a communist, Fred Rose in Montreal, and arranged that the formula would be released to them. A few years later, there was a Russian cipher clerk [Igor Gouzenko][25] in Ottawa, who came over to our side, in effect, and confessed about all this spying he'd been doing. He mentioned Boyer, who was eventually imprisoned for this, but he also mentioned Arthur Steinberg, only as a person who was a friend of Ray Boyer's, who it would be a good idea for them to contact. And that was enough to get Arthur boycotted from – he couldn't get a job for years. This was in the McCarthy era[26], of course. That really impressed me with the power of the McCarthy-type people.

AM: Was he American or Canadian?

CF: American.

AM: Did all of this come to light while he was still at McGill, or after he had left?

CF: No, it was after. I'm not sure if he was still in the Navy or not.

AM: Okay. Well, you had mentioned that several people had left the department. Why do you think that occurred? Why did McGill have this turnover of faculty?

CF: I think it was just – I'm not sure really. Huskins died unexpectedly of a heart attack. I think they were still on Rockefeller money, so that there was not very much financial resource. It just happened that various people found various jobs elsewhere at that time, probably because Huskins was gone. He was their guru.

AM: It seems like you had some kind of opportunities to become a basic scientist working at McGill, and you weren't particularly enamored with the medical school curricula. Why was it that you felt compelled to continue in medical school? Because at least you had the medical curricula completed (maybe not well) but completed.

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[24] Raymond Boyer was a Canadian organic chemist who went to jail for two years for passing secrets to the Russians.

[25] Igor Gouzenko did indeed defect to Canada and provided information that led to the arrest conviction of 22 agents and 15 Soviet spies. The documents he provided also revealed Stalin's plans to develop nuclear weapons.

[26] The McCarthy era is named after Joseph McCarthy, a politician whose accusations led to many people being labeled as communists and communist sympathizers with little or questionable evidence produced to back up his claims. The McCarthy era occurred post WWII in the 1950's.

CF: There was a very strong sense from a lot of my mentors that you needed the ticket [of a medical degree] in order to put your hands on patients, or even talk to them and to get into records and be trusted by your medical colleagues. There was a strong sense of that given to me by various people. Besides, I liked being attached to medicine. At least, I liked working with people and helping people.

AM: So you saw a clinical practice as part of being a geneticist.

CF: I don't think I thought that far ahead. We'll talk about that when we get into early Montreal Children's [Hospital][27], okay?

AM: Okay. How many advisors did you have at McGill that were geneticists practicing medicine, who had trained both in genetics and medicine?

CF: How many at McGill?

AM: Yes.

CF: Well, there was nobody in Canada, actually. There was nobody with training in both.

AM: You mentioned in this article in *Issues and Reviews in Teratology* that you had written to James [V.] Neel[28]. How did you become aware of James Neel at [University of] Michigan, and what did he say to you to convince you that having an MD and a Ph.D. would be worth keeping going?

CF: I can't remember his words. It was the same general message, that you really needed to have the ticket to get in there. I think he might have been the first one in the [United] States with training in both genetics and medicine. He trained in *Drosophila*. When I failed the third year, I was going around to a number of people with my sob story and asking for help, or advice anyway. He certainly strongly urged me to stick with it, and so did J.S.L. Brown, who was one of my mentors at McGill, a biochemist, [in] medical metabolism, I guess. Several of the teachers at McGill – yeah. I guess during that year there were people in pediatrics – Alton Goldbloom[29] was the professor and his second in command, Allen Ross – who were beginning to see that genetics could be important in pediatrics. So I was already talking to them in an exploratory way about setting up something at the Montreal Children's [Hospital] when I got through. That was an encouragement to stick with it.

AM: How influential was that in developing a medical specialty? I mean, where was pediatrics in terms of your medical specialization, as opposed to some other medical

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[27] Montreal Children's Hospital was founded in 1904 in the city of Montreal, and was devoted to helping sick children from the beginning. In 1920 the hospital became affiliated with McGill University and became a teaching and research institution. For more information, visit their website at: http://www.thechildren.com/en/about/history.aspx

[28] James V. Neel (1915-2000) was an important geneticist specializing in genetic epidemiology. He established the first Department of Genetics at a medical school, at the University of Michigan. For more information about him, visit the website at: http://www.ibis-birthdefects.org/start/neel3.htm

[29] Alton Goldbloom (1890-1968) was a Canadian pediatric specialist. He was both a student and later a professor at McGill University.

specialty? We heard this morning at one of the sessions that everybody assumes everybody comes up in genetics because of pediatrics, but then there are other examples.

CF: Oh, I think there's no doubt that pediatrics was where the action was. That's where you see genetics acting in the beginning. I got offers from – when I was looking for a job and I was graduating – I got offers from anatomy, but most of them from pediatrics. Bruce Chown[30] offered me a job at blood groups, but the adult genetics was very, very slim at that point. Besides, what can you do with adults? (chuckles)

AM: You had mentioned that you had several job offers, including some outside of McGill. How seriously did you consider these offers, and what made you stay at McGill, that (you mentioned) didn't have much support for a medical geneticist?

CF: Well, I recall several of the letters I wrote to various people, and it was mostly, "Your offer is very attractive, but really, things are so good here that I don't feel like moving." And they were good in terms of having the people at the Children's [Hospital] supporting me and also having the basic genetics department. I didn't want to split from basic genetics because I thought a lot of the information and knowledge that we could use in medicine was coming from basic genetics, so I didn't want to set up a separate department in the university. Although there were several suggestions that I do this, go to the medical school and set up a department, but I thought, like Jim Neel thought – he was quite opposed at the beginning to forming a Human Genetics Society, because he thought we were going to cut ourselves off from a lot of basic information. *Now* it's a two-way street, but at that time it wasn't.

I was really treated very well at McGill by the pediatricians. I had a little trouble with the head of the genetics department who thought that human genetics was getting more than its share of the limelight and was sometimes quite resistant to my plans to expand. But we worked that out.

AM: And why was it getting more limelight?

CF: Well, I guess *I* was getting more limelight. When cytogenetics[31] came on board, I tried to get the cytogeneticists at McGill to come over to the hospital and take blood from these interesting patients. He wouldn't have any of that, because it was going to take them away from the really important stuff that they were doing. Dorothy Warburton[32], do you know --

AM: Yes, I know her name, yeah.

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[30] Bruce Chown (1893- 1986) was a Canadian pediatrician who spent much of his career at the University of Manitoba. He is best known for researching Rh disease (a pregnancy related blood disease) and developing a cure for it.

[31] Cytogenetics : the study of the structure of chromosomes. For more information, visit the website at: http://www.pathology.washington.edu/galleries/Cytogallery/main.php of the University of Washington School of Medicine Department of Pathology.

[32] Dorothy Warburton is a prominent Canadian cytogeneticist who currently does research at Columbia University Medical Center. She is known for her work in investigating the source of human chromosomal abnormalities. For more about her achievements, visit the webpage at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2227912/

CF: By the way, Dorothy said you ought to interview the students rather than us old fogies, because they knew a lot more about what was going on than we did and certainly will tell more of it. (chuckles)

AM: We'll get to them next.

CF: Okay. She actually set up cultures and did my chromosomes just to show that you could do it, in the McGill laboratories. But it didn't help any. The ground just wasn't receptive.

4. Creating the Department of Medical Genetics and Diagnosing Genetic Disorders

AM: Okay. Well, I want to talk a little bit about – so you create this Department of Medical Genetics. You basically just create it from scratch at McGill. I want to ask first – for twenty or thirty years now we have a track for MD-Ph.D.'s in a MD-Ph.D. program in which medical students who want training in basic science, or basic scientists who want medical training can do it simultaneously, do it parallel. It seems that you did it sequentially and you developed a reputation in basic science and then developed a reputation in clinical science. What advantages and disadvantages did this have for you and for MD-Ph.D. students now who kind of do it simultaneously?

CF: Before we get into that, maybe I should tell you about how it actually happened.

AM: Okay.

CF: When I graduated from medicine, in lieu of a clinical internship, it was possible to do a year of clinical research. Allen Ross put me on to this. So that's what I did as an internship. I set up the department on a provisional basis, not a department but a Division of Clinical Genetics, in pediatrics. So I spent the first year doing that. That meant I never did have a proper internship. I'm still very bad at drawing blood and that sort of thing. So I would get on the wards and go around and look at various patients' histories and needle the interns about how they'd taken the family history. People were looking at me as a somewhat – oh, what's the word? – [like I was] out in left field.

Gradually, they began to accept that there was something here. For instance, I made a few diagnoses from the family history, which impressed them. A person came in with bleeding from the bowel or something, and I got a family history of nosebleeds and it turned out to be the hemorrhagic telangiectasia syndrome[33]. So I presented this at rounds. Then there was a little girl who came in with rheumatic fever[34], supposedly, who had tremendous abdominal pains. It turned out that she drank enormous amounts of water and excreted the same, and I found out that that happened to her mother and her grandfather, a family history of drinkers – water drinkers! It turned out to be a pitressin deficient diabetes insipidus[35], a diagnosis that I made from the family history.

I began to get a little better accepted and people started sending me patients to counsel, or they'd call up and say, "What's the recurrence risk for this?" Eventually,

[33] hemorrhagic telangiectasia syndrome: a genetic disorder which effects the blood vessels.
[34] rheumatic fever: also known as scarlet fever, is an infection which often follows strep throat and can cause nausea, stomach cramps and vomiting.
[35] pitressin deficient diabetes insipidus: a disorder which causes abnormally high amounts of urine output, water intake, and thirst. It is caused by a lack of the pituitary hormone vasopressin.

instead of saying what the recurrence was, and them telling them [the patients], they'd send them to me to talk about what it meant. So I sort of gradually infiltrated into that aspect of it. [Pause] Where do we go from here [in the interview]?

AM: It's interesting that one man sets up this new division in pediatrics. You had mentioned in one of your works that you never did administrative posts. You were never chair of a department, you were never a dean. You kind of shied away from administrative things. But it seems to me that clearly it takes more than just putting a sign on your door saying --

CF: Well, I was director of that department.

AM: Right, exactly. Where were you drawing your model from? How did you even think about establishing your own division within pediatrics? What models were you looking at? Or was this just some idea that you had that you wanted to be able to – because it would combine your personal interests in genetics and medicine in an interesting way?

CF: Well, I admire all these people who sit down and think out everything so they have models to follow. Somehow I don't think I ever did that. I sort of stumbled along and went with whatever waves of chance led me. I was doing a parallel career in teratology[36], and I think there was a big advantage in that. Should I tell you about the teratology part of it?

AM: Sure.

CF: While I was still in medical school, I guess, I still had some mouse room space. I had a graduate student. There was a plastic surgeon, Happy Baxter, who had this idea that the embryonic organizer that initiates the neural plate was a steroid, and lo and behold, cortisone[37] appeared, which is a steroid. Nobody knew how it worked or anything about it really, except that it's very good for arthritis. He said, "Why don't you give your pregnant mice some cortisone and maybe you'll get neural tube defects[38]?"

In the mean-time, I'd been – there was a guy in Boston, Ted Engels, who was working with hypoxia, low oxygen tension as a teratogen[39] and had found out that it had caused malformations and had said that this must be the cause of Down's Syndrome[40] because all the things that happen in Down's Syndrome happen at this sensitive period for hypoxia. In fact, he won a lawsuit, or his client [did] – he testified for a client who had been in a motor accident in the third month of pregnancy and had a Down's Syndrome child and won the case on the basis of this postulate.

Then there was rubella[41] – everything was going towards environmental causes of malformations, and I thought, no, you ought to get genetics back into the picture. So I

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[36] teratology: the study of birth defects

[37] cortisone: a steroid hormone produced naturally in the adrenal cortex.

[38] neural tube defects: birth defects of the spinal cord and brain. The most common ones are spina bifida (incomplete closure of the spinal cord) and anencephaly (underdevelopment of the brain).

[39] teratogen: anything which causes birth defects in a fetus, such as alcohol, or X-rays.

[40] Down's Syndrome: a chromosomal disorder caused by the partial or complete presence of an extra 21st chromosome. The most common effect of Down's is developmental disability. To learn more visit the website at: http://www.medicinenet.com/down_syndrome/article.htm

[41] rubella: a mildly contagious disease similar to measles but capable of causing birth defects in a fetus if the mother contracts it the first trimester.

was going to use his hypoxia model on different strains of mice and look for strain differences, which he had not thought of doing, being more interested in the Down's Syndrome. While we were building the apparatus, Baxter came along with the cortisone, so I stuck some into some pregnant mice, making wild guesses as to what the dosage was and so forth. And we got cleft palates[42], not neural tube defects. We showed very early that there were mouse strain differences in frequency from the same dose at the same stage and everything. That was the first demonstration, I think. It was the first normally-used drug that would cause malformations in mice. It also was the beginning of bringing genetics into teratology.

That was influencing what I was interested in in people, and I was collecting family histories on cleft lip and cleft palates and other malformations. So that was one – there were three currents: one was the experimental teratology, and then the complex diseases or malformations, and then the genetic counseling aspects. A lot of the clinical things I did were in response to patients' questions. "I've got the BOR [branchiotorenal][43] Syndrome, which [causes] branchial cysts and ear pits and deafness. Suppose my first child just has the ear pits, what are the chances he's going to be deaf?" That sort of thing. So there were really three pathways that we directed to some extent.

AM: The basic science department of genetics – how receptive were they for you to create this division? I mean, what was their role in supporting your ideas?

CF: They supported the division in the *hospital*. They didn't want me to have too much space in genetics. But that was fine. It gave them some prestige.

AM: But you still had lab space, bench space in the basic science department?

CF: Yeah.

AM: Were you training graduate students at this point?

CF: Mm-hmm [yes].

AM: Yeah, okay. Then how receptive was the medical school [and the] hospital to having this new guy? [How receptive was] the hospital to creating this division within pediatrics?

CF: I don't remember any strong opposition. They didn't jump up and down with joy or anything, but it was the Children's Hospital's decision, and that was fine. As we said earlier, these other departments, like medicine or neurology, were not so much enamored of genetics as pediatrics was. Actually, [Wilder G.] Penfield[44] did offer me a job [to study the genetics of epilepsy] at one point, but he wanted me to show that it was all in the pelvic canal. I didn't want to do that, so --

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[42] cleft palates: a birth defect which causes an opening or "cleft" in the roof of the mouth. Corrective surgery is required to close the fissure.

[43] BOR syndrome was first discovered by Dr. M. Melnick in 1975. It is a genetic disorder which causes deafness as well as cysts in the neck and kidney problems.

[44] Wilder G. Penfield (1891-1976) was a world-renowned neurologist and brain surgeon who specialized in the research and treatment of epilepsy. For more information, visit the website at: http://etcweb.princeton.edu/CampusWWW/Companion/penfield_wilder.html

AM: You mentioned that it took you a while to get the interns and residents to take family histories. What kind of obstacles, if any, did you run into in getting the staff pediatricians to look at their patients in the ways that would be useful for you to use that information?

CF: It just gradually infiltrated, by example, and I had a lot of good friends on the pediatric staff. It was a very close-knit and loyal unit. It had a spirit that a lot of hospitals don't have – a very special place.

AM: What do you think accounted for that kind of *espirit de corps* in that particular place, in the hospital?

CF: What accounted for it?

AM: Mm-hmm [yes].

CF: I'm not sure. Maybe just a happy collection of compatible people, the fact that it was isolated up on the hill, up above the city, somewhat separated from the rest of the town, but I don't know.

AM: Okay. Well, how much of a cheerleader did you have to be to have people starting to come – patients as well, or families of patients – coming in to you for counseling or for some kind of screening?

CF: Well, I wasn't a big time operator. I didn't do much cheerleading, but I was at rounds and we'd ask questions or present cases, and gradually people began to see the light. (chuckles) Of course, I got a little frustrated with saying, "Well, the child has this and the chances are one in four that it will happen again." So when Charles [R.] Scriver[45] came aboard, that was a big satisfaction to me because here was somebody who *was* doing something about it, treating PKUs[46] and stuff.

When the medical board was debating whether to have a department of biochemical genetics and clinical genetics, one of the – I think it was the pathologist said that we couldn't have two big shots, two empire builders. I was positive I wasn't an empire builder. (chuckles) He came on board. He was very good at cheerleading, and I admired him for that – much better than I was.

AM: Geneticists who used biochemical techniques to study genetic abnormalities were able to bring a certain amount of treatment options, but you said you got frustrated by that. Initially, what did you think by becoming a medical geneticist [that] you would be bringing to the clinical table?

CF: Well, I think mainly the counseling. Some diagnoses, using the family history to make diagnoses, but mostly the counseling. Because in those days the counseling was fairly simple. You had to decide whether the risk of recurrence was big enough that you

[45] Charles R. Scriver is an important Canadian geneticist who has received many awards for his work in various fields of human genetics such as genetic testing and population genetics. An extensive interview with Dr. Scriver is available in this collection.

[46] PKU [Phenylketonuria]: a metabolic disease caused by a genetic disorder which causes a deficiency of the enzyme phenylalanine hydroxylase. The lack of this enzyme causes the build up of phenylalanine, which in turn causes mental retardation.

didn't want to take it, or that you wanted children enough so you would take it. There was no question of prenatal diagnosis, and abortion was illegal, and contraception was illegal in Quebec. So getting the recurrence risks was important, getting accurate recurrence risks, but also trying to help people with this dilemma of making the decision.

AM: What connection for you did your bench research have for your clinical observations?

CF: I could go on for a long time about that.

AM: Okay. Is this a good time to break and we can pick up tomorrow with that question?

CF: I think that would be a good idea.

AM: Well, thanks. We'll pick up tomorrow.

F. CLARKE FRASER
Session 2, October 28, 2004

5. Cold Spring Harbor Laboratory; Traveling in Europe

AM: I'm Andrea Maestrejuan and I'm with Clarke Fraser in Toronto, to continue his oral history interview for the Human Genetics Oral History Project. We'll probably spend most of our time today with understanding how your bench science interacted with your clinical work. But there are a couple of things I wanted to refer back to before we move on. You had mentioned in one of the works that I read that you had gone to a Cold Spring Harbor [Laboratory][47] meeting in between your first and second year in medical school and learned about bacterial genetics. So I want to talk a little bit about when was that, how did you get invited or why did you attend, and what significance did that meeting have for you?

CF: It wasn't a meeting and I think it was while I was in graduate school – maybe [in] '42? Arthur Steinberg arranged for me to have a fellowship, a summer studentship, so to speak. I think I had a three hundred dollar bursary or something. He knew [Milislav] Demerec[48] well. They had worked together. So he cooked that up for me; I was so lucky! That was very exciting because that was just when bacterial genetics was starting. They had just discovered that bacteria had sex, so that you could do genetics with them. They put on the first phage course[49] when I was there. There were a lot of physicists, ex-physicists, who had been disillusioned, because they had worked with the [Atomic] bomb, and they got into this because the particulate nature of bacterial genetics was very similar to the approach to physics. I think they did a lot for the field. Josh[ua]

[47] Cold Spring Harbor Laboratory: a non-profit research institute focusing on cancer, neuroscience, plant biology, genomics, and bioinformatics. For more information, visit their website at: http://www.cshl.edu/
[48] Milislav Demerec (1895-1966), Yugoslavian-born geneticist, did important research in gene mutation. He became director of Cold Spring Harbor Lab in 1943. For more information, visit the website at: http://library.cshl.edu/sp/scientists/milislav_demerec/demerec_biography.html
[49] phage course: an annual summer course offered at Cold Spring Harbor Laboratory to teach biologists about bacteriophages, bacteria-infecting viruses that are used as experimental model organisms.

Lederberg[50] was there, and Max Delbrück[51] and [Salvador E.] Luria[52] and Leo Szilard[53]. I used to play ping pong with Max Delbrück at night. He usually beat me. (chuckles)

For me, this field was pretty new and I was just beginning to get the feel for genetics. This was so exciting. I took a little experiment of my own along. I took some rhino mice with me and treated them with vitamin A while I was there. So I carried on my own research, but I also listened to the seminars and had conversations. So it was a very expanding experiment for me.

AM: And why did Steinberg think you should go?

CF: He thought it would be good for my education, I guess, to get out into the world and see some other parts of it. The mice, by the way, fitted my hypothesis by getting much thinning of their skin. They didn't regrow their hair, but their skin got much less hyperkeratotic, which is what you'd expect from vitamin A. In retrospect, I think maybe I was poisoning them and that this was a toxic effect, but at that time it was showing me that the rhino gene was influencing vitamin A metabolism somehow.

The other early important educational experience, I think, was in 1954 when I'd just gotten going at the Children's [Hospital] and my first graduate student had gotten his degree, Julius [D.] Metrakos. He and his wife Kay [Katherine], who was an electroencephalographer[54], wanted to study the genetics of epilepsy. So I went to New York to talk to the Rockefeller Foundation[55] about getting a grant to get this started. Actually, we got the grant, and it was a very good send-off for them.

But while I was there – I've forgotten his name[56]. I shouldn't forget him, he was so important. He said, "By the way, would you be interested in a traveling fellowship?" "Would I!" They ended up sending me to Europe for about four months, traveling around, meeting all the key genetics (particularly medical genetics) people.

AM: Who were they? Do you remember what labs you visited?

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[50] Joshua Lederberg (1925-2008), an American molecular biologist, was awarded the Nobel Prize along with colleagues Edward Tatum and George Beadle for their work in bacteriology. To learn more about Dr. Lederberg, visit the website at: http://nobelprize.org/nobel_prizes/medicine/laureates/1958/lederberg-bio.html

[51] Max Delbrück (1906-1981), a German physicist-turned-biologist who, along with colleague Salvador E. Luria, developed a method for quickly breeding bacteriophages.

[52] Salvador E. Luria (1912-1991), an Italian born biologist who, along with Max Delbrück, developed the breeding and use of bacteriophages, earning him and his colleague the Nobel Prize in 1969. For more about his work, visit the webpage at: http://nobelprize.org/nobel_prizes/medicine/laureates/1969/luria-bio.html

[53] Leo Szilard (1898-1964) a Hungarian physicist and molecular biologist and pioneer of atomic energy as well as the atomic bomb. He was also known for his insistence that scientists take responsibility for the consequences of their discoveries and campaigned against the use of the atomic bomb on Japan. For more information, visit the website at: http://www.atomicarchive.com/Bios/Szilard.shtml

[54] Electroencephalographer: a person trained to use and EEG machine, which is used to measures brain waves and thus diagnose and track neurological disorders.

[55] Rockefeller Foundation was begun in 1913 by John D. Rockefeller. Its broad purpose is to promote the well-being of humanity through philanthropic projects world wide. For more information, visit their website at: http://www.rockefellerfoundation.org/

[56] Alan Gregg (1880-1957) was a leader in American medical education and research for much of the early to mid twentieth century, as Associate Director of Medical Education, Director of Medical Sciences, and finally Vice-President of the Rockefeller Foundation. See the NLM profile and archival documents at: http://profiles.nlm.nih.gov/ps/retrieve/Collection/CID/FS.

CF: Well, I started in London with [Lionel S.] Penrose[57]. Cedric Carter[58], I guess, was just getting started. Harry Harris[59]. And I met JBS Haldane[60], to my great thrill. I went to Edinburgh and talked to Doug [Douglas S.] Falconer[61]. He was a mouse geneticist, but interested in multifactorial[62] things. I went to Ireland, the upper part of Ireland – I am blocking out the name – Belfast? Anyway [I met] Alan [C.] Stevenson[63], who was doing medical genetics there. Then I went to Stockholm, where my dad was the trade commissioner there, so that was nice; and saw [Erik] Strömberg, the psychiatric geneticist, and Jan Böök, who lived in Uppsala.

I went to Denmark and saw Tage Kemp[64]. He was a very important early medical geneticist. He took advantage of the fact that doctors – MDs – in order to get their MD in Denmark, had to do a thesis. Several doctors, a dozen or more doctors, came to him, and he would just assign them a disease, and they would work it up and collect family histories and produce a book for their thesis. So there was a collection called *Opera Ex Dome Hafniensis*[65], which was a series of volumes, each of which was the definitive treatise on a particular disease. [Jacob] Hallstrom, I think it was, did one on epilepsy, and [O.Z.] Dalgard on polycystic kidneys. [Bent] Harvald – I can't remember which one he did [heredity in epilepsy]. [Poul] Fogh-Anderson[66], who was a plastic surgeon, did – I'm not sure if he was in that series or not, but he did a similar kind of treatise, which was very important to me later. He had hundreds of families, all their family histories in the back, their pedigrees. Well, that gives you an idea – I can't remember them all.

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[57] Lionel S. Penrose (1878-1972), a British geneticist, pioneered the study of the genetics of mental retardation. For more information, see the article in *Genetics*, available on the website at: http://www.genetics.org/cgi/content/full/150/4/1333

[58] Cedric Carter (1917-1984) was a British geneticist who specialized in common congenital malformations. He founded the CGS Clinical Genetic Society in 1970 and worked as the director of the Medical Research Council's Clinical Genetics Unit at the Institute of Child Health, London. For more information, visit the website at: http://www.clingensoc.org/people/cedric_carter.htm

[59] Harry Harris (1919-1994) was a British geneticist and biochemist who spent much of his career teaching and researching the genetics of diabetes (among other things) at the University if Pennsylvania. For more information, visit the webpage at: http://www.independent.co.uk/news/people/obituary-professor-harry-harris-1415428.html

[60] John B.S. Haldane (1892-1964) a British geneticist was a pioneer in the development of population genetics. Educated at Oxford and taught there as well as Cambridge and University College London after earning his degree in biology. To learn more about Dr. Haldane, visit the website at: http://en.wikipedia.org/wiki/J._B._S._Haldane

[61] Douglas S. Falconer (1913-2004) a British mouse geneticist who is perhaps best know for his work in analysis of genetic traits. He wrote an important textbook entitled *Introduction to Quantitative Genetics*, first published in 1960. For more information, visit the website at : http://www.nature.com/hdy/journal/v93/n2/full/6800506a.html

[62] multifactorial genetic disorders are disorders which have multiple causes. Studies of these disorders try to determine the influence of environment as well as heritable factors.

[63] Alan C. Stevenson was a British medical geneticist who among other things, served as the director of the Medical Research Council for Population Genetics Unit at Oxford.

[64] Tage Kemp (1896-1964) was famous Danish human geneticist who did research in blood typing, bacteriology, and sex characteristics. For more information, visit the website at : http://icmm.ku.dk/klinikken/the_clinic/history/tage_kemp/

[65] *Opera ex Dome Biologiae Hereditariae* Humanae Universitatis Hafniensis, Vol. 1--128. Copenhagen: Munksgaard. For more about Tage's *Opera*, including titles and authors of each thesis, see: http://icmm.ku.dk/klinikken/the_clinic/history/tage_kemp/titles/

[66] Poul Fogh-Anderson did research on cleft palates.

We were in Norway – can't remember who I saw in Norway. [In] Paris, [I met] [Maurice Emile Joseph] Lamy[67] and I met [Jérôme] Lejeune[68], who was a young [scientist] – just getting going, before he discovered the chromosome. In my report, I spotted him as a bright up-and-coming young man. In Switzerland, I went to see [Adolphe] Francesschetti[69] and [Petrus Johannes] Waardenburg[70] in Amsterdam, I think it was. I went to Rome and saw – oh, who was the twin guy? His name escapes me for the moment, but he was well known for his work on – he had a whole institute on twins. [Luigi Gedda[71] at the Gregor Mendel Institute of Medical Genetics and Twin Studies][72] I think that was about it.

AM: This was after the war, so there was nobody in Germany.

CF: '54, yes.

AM: What differences did you note between how medical genetics was developing in England and the Continent, in comparison to what was going on on this side of the pond and/or in Canada?

CF: Well, they were way ahead, in terms of doing research on genetic medical conditions. A lot of the people I mentioned were MDs. There were not very many PhDs working in the field in Europe that I knew of. But there were so many of them and comparatively few in America. There was Franz Kallmann[73], who did a classical study of twins, one with schizophrenia and one for manic-depressive psychosis, which still provide solid data for concordance rates and so on. Lovely stuff; but he was not

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[67] Maurice Emile Joseph Lamy (1895-1975) was a noted French geneticist, trained partially in the US. He made his mark researching inherited diseases in children, especially chromosomal disorders. He was the first professor of medical genetics in Paris in 1950.

[68] Jérôme Lejeune (1926-1994) was a French cytogeneticist specializing in chromosomal abnormalities of genetic diseases. He identified the first chromosomal abnormality in humans, trisomy 21, which causes Down's syndrome, a genetic disease characterized by a range of cognitive and physical deficits. For more about Lejeune's work, see: Knudson AG Jr. (1970) Jérôme Lejeune: The William Allan Memorial Award presented at the annual meeting of the American Society of Human Genetics, San Francisco, California, October 3, 1969. *American Journal of Human Genetics* 22(2):119-20.

[69] Adolphe Francesschetti (1896-1968) a prominent ophthalmologist known internationally who spent most of his career teaching and researching at Geneva. He showed special interest in inherited disease and the genetics effecting the brain and eye. For more information, visit the webpage at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC506600/

[70] Petrus Johannes Waardenburg (1886-1979) was a genetic ophthalmologist from Holland. He is perhaps best known for his research on Waardenburg's Syndrome (named for him), but he was interested in albinism and many other genetic disorders. For more information, visit the website at: http://www.whonamedit.com/doctor.cfm/1012.html

[71] Luigi Gedda (1902-200) was an Italian geneticist who specialized in the study of twins. In 1951 he published *Studio dei gemelli* (A Study of Twins). The work was partially translated into English in 1961 as *Twins in History and Science*.

[72] Gregor Mendel Institute of Medical Genetics and Twin Studies is in Rome and functions as a database for twins studies.

[73] Franz Kallmann (1897-1965), born and educated in Germany and of Jewish descent, was a noted psychiatric medical geneticist who specialized in research on the genetics of schizophrenia and other mental disorders. Fleeing Nazi Germany, Kallmann moved to the US and there became associated with the New York State Psychiatric Institute. For more information, visit the website at: http://www.whonamedit.com/doctor.cfm/2231.html

appreciated by the psychiatrists. Nash Herndon[74] – I think you said you did him – well, he was one of the few medical people doing genetics. Madge Macklin[75], who was a Canadian, but working in Rochester, I think. I was really fond of her, she was a wonderful person, but very, very dogmatic in her counseling. Talk about directive counseling, she was one of the top examples! There was Bruce Chown doing blood groups. But that was about it.

Norma Ford Walker[76] was doing human genetics, but – well, she did a little bit on – I think Peggy [Margaret] Thompson[77] was her student, who did some work on diabetes. She had a graduate student, [Betty Curtis] who did some stuff on cleft lip and palate, and we eventually amalgamated our series to get a good series for counseling risks. That was about it for human genetics at that stage, I think.

AM: What do you think accounts for that difference between here, this side [of the Atlantic], and Europe?

CF: [I] don't know. Your collaborator – [Nathaniel] Comfort is his name?

AM: Yes.

CF: [He] mentioned the fact that they were way ahead in his history talk, I think, but he didn't suggest why, either. I haven't any idea. Really, I think medicine in general was a bit ahead.

AM: Another question – I want to go back to Cold Spring Harbor. Did you go to this meeting to learn bacterial genetics? Or you learned it while you – that's what was going on during that summer?

CF: That's a good question. I don't remember me having a goal. I was there more or less as an observer as I remember it. I took my own work along with me. I was a summer student, but they did not assign me a project or anything; I brought my own project. So I just learned by inunction.

AM: You had mentioned that you immediately went back to McGill and started teaching a developmental genetics course, and you immediately created a couple of lectures on bacterial genetics. What impact then did some of the methodology and the

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[74] Nash Herndon was a pioneer in medical genetics and genetic counseling. He worked at the Wake Forest University Baptist Medical Center. He was also associated with the eugenics movement in the US and has been accused of promoting non-voluntary sterilization.

[75] Madge Thurlow Macklin (1893-1962) as a physician and geneticist, Dr. Macklin pioneered medical genetics, and promoted the clinical application of discoveries in genetics, especially in patients with a family history of cancer. She was also a promoter of the controversial eugenics movement, which advocated selective breeding policies for humans to improve the race. For more information about Dr. Macklin, visit the website at: http://www.ferris.edu/isar/bios/macklin.htm

[76] Norma Ford Walker (1893-1968), professor of human genetics at University of Toronto known for her work on the genetics of multiple births and was director of genetics at the Sick Children's Hospital. For more information about Walker, visit the website at: http://www.science.ca/scientists/scientistprofile.php?pID=389&pg=0

[77] Margaret Thompson is a pioneer of medical genetics and specializes in muscular dystrophy and genetic counseling. She spent many years at the University of Toronto where she currently professor emerita. An interview with Dr. Thompson is available in this collection.

work going on in bacterial genetics, as you learned it that summer, have on your own ideas in mouse genetics?

CF: Nothing that you wouldn't expect, I think. They didn't influence my research very much. I never got into the molecular – well, it wasn't really molecular at that stage, was it? I was more interested in mice than bacteria. In fact, I think I remember saying that you can't study cleft palates in a bacterium.

AM: I can see where that would be a problem. What impact then, just professionally, or for your own identity as a geneticist, did going to Cold Spring Harbor have on you?

CF: I don't think it made too much difference, because I was still a graduate student. So when I started out at [Montreal] Children's [Hospital] I still had the mouse room at my disposal, and there were all these medical Mendelian diseases to work on. But each of them was rare, so it would rather depend on luck, which ones turned up at the hospital that you could study. [For] my National Research Council grants, and then later the Medical Research Counsel, I used to say, "Here are the sorts of things that I'm doing, and I can't predict what I'm going to be doing next year, because it depends on what I'm going to be seeing. But this is the sort of thing I'm doing." They bought that. I'm sure they wouldn't today.

AM: I was going to say! At least I know the NIH [National Institutes of Health] would never accept a grant like that. What was it that made this particular era so – or was it the MRC [Medical Research Council] that was different?

CF: I think it was a new thing, and they understood my problem, but they knew from what I was doing that I was likely to keep on doing interesting things. And they were broad-visioned enough to buy that. I used to sit on the [NIH] Genetics Study Section, and I think they bought a few applications like that. I can't remember which ones. Of course, the farther you got along, the harder it is to do that sort of thing.

There were these Mendelian diseases, and then there were chromosomal diseases, but there wasn't very much – we didn't have a cytogeneticist at that point. And in between, there were these familial diseases that almost everybody knew ran in the family, but they didn't fit the Mendelian pattern, and they weren't chromosomal, and they did recur. That was why I guess I went in for those diseases. There was coronary disease and schizophrenia and stuff, but they were adult and there were the congenital malformations. Then when I got the cortisone cleft palate stuff going, obviously that was what I wanted to look at in people.

AM: What was driving your scientific and clinical interests at this point? Because you mentioned a lawsuit yesterday that didn't quite make sense, and you mentioned it in some of your other writings, with the hypoxia, which was a genetic question, but it was also kind of this social question. If somebody is going to bring genetics into the courtroom – which I found it to be a fascinating story. Then you worked with Steinberg on chromosomal inversions, and now you had a clinical practice where you could also have clinical observations. So what was actually driving all this? Was it the social aspects of what genetics was becoming involved in? Or was it more basic science about the impact of hypoxia on –

CF: Well, I never did get into hypoxia. That was what I was starting to do, and I stumbled onto cortisone instead. Maybe we should follow that a little bit.

AM: Okay.

6. Career Building; Teratogens and Multifactorial Diseases

CF: So, I told you about how we found that cortisone caused cleft palates, and we very early on found strain differences which supported my idea that there was more to it than the environment. That led of course immediately to the question, will cortisone do that in people, or will anything else do that in people? So I started looking for things in the human pedigrees, taking careful prenatal histories and looking for fevers and drugs and all the things that you might imagine.

And at the same time, I was following the cleft palate story in the mouse, which created a lot of interest because it was a drug and people wondered, as I said, whether it would do anything in people, or what other drugs might. At one point, I was bold enough to say that all these teratogens that we had already, like hypoxia and cortisone and, by that time, several other things that would work in animals – 6-amino-nicotinimide, a nicotinimide antagonist – that all these things were sledgehammer blows – that you had to suffocate the mouse till it was blue in the face or give it enough cortisone that it would kill it if it wasn't pregnant, and give it enough 6-amino-nicotinimide that it would be practically paralyzed. These were way above the sort of physiological thresholds that would [be reached and] cause malformations in people, so not to worry.

Then thalidomide[78] happened, of course. That was a big surprise and raised the question immediately of – since we'd shown these strain differences in mice, it showed very clearly that you could not predict from animal experiments what was going to be teratogenic in humans, and vice versa, actually. Thalidomide, I tried to produce malformations with thalidomide, and I got nowhere. It wouldn't work in the mouse. May I digress a little bit?

AM: Yeah, go ahead.

CF: It was an interesting story, actually. I was trying to set up this thalidomide mouse model, and I had one strain, C57 Black, that had been in my lab for ten years by that time, so I knew what it did. I gave some of these mice thalidomide, and by Jove, I think the second litter produced animals with small lower jaws and cleft palates. I said, "We've got it!" We wrote a letter to the *Lancet*. I almost had sent it away when we had two or three other litters that corroborated this, and then one of the control C57s produced the same thing. And we could trace it back to a mutation that happened three generations previously. (he chuckles) Can you imagine what a coincidence that was? So you have to be careful.

Anyway, so I spent a lot of time on committees and symposia and government commissions, trying to decide how to prove that a given drug would be safe for people by testing it in animals, which they still don't know how to do, of course. That work really brought genetics into teratology, I think, for the first time. We now can even talk about teratogenetics if you'd like.

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[78] thalidomide was prescribed by doctors to pregnant women in the 1950's to prevent morning sickness and as a sleep aid. The drug caused birth defects such as blindness, deafness, and torsos without limbs. Inadequate testing had led physicians to believe the drug was safe. For more information, visit the website at:
http://salempress.com/store/samples/great_events_from_history_scandals/gefh_scandals_thalidomide.htm

In the meantime, we were going on with the multifactorial disorders in people. Sewall Wright[79], some years before, had written a paper on polydactyly[80] in the guinea pig and showed that it behaved as if there were many genes involved and a threshold. He didn't say what the genes were or what the threshold was. Then Hans Grüneberg[81] in London published a series of articles on various mouse traits, which he proposed behaved as if they were inherited, according to a continuous distribution of liability to whatever it was, and a threshold, so that you had to get enough liability genes to fall beyond the threshold, in order to actually have the trait. He called them quasi-continuous variations – the quasi-continuous variations of Grüneberg. Well, when we got this strain difference in the mouse, we wondered, of course, why the Ajax strain had a lot of cleft palates and C57s didn't have very many. To make a long story short, we showed very clearly that the Ajax palate closed later in gestation than in the C57 mouse, a normal variation in time of palate closure. So if you imagine that there's a threshold, that the shelves have to come up soon enough, so that the growth of the head doesn't carry them too far apart to meet. So there's a point of no return, so to speak, which makes a threshold. The Ajaxes are already much closer to the threshold, so it's much easier to push them over.

Then we went on and showed various factors that influenced the shape and how close the distribution was to the threshold. Like there seems to be a force in the shelves that makes them come up and push the tongue out of the way. And there's the resistance of the tongue, and there's the width of the head – the wider the head, the earlier they have to come up to meet – and the width of the shelves. The narrower the shelves, the earlier they have to come up. We had identified keys and environmental factors for each of these components, so we had a beautiful model for a multifactorial threshold pattern, which is impressive because you could deduce this from family patterns, but here we had one that you could actually work with and see.

At the same time, Cedric Carter in London was working with these common conditions in people and noted that in pyloric stenosis[82], which is much more frequent in boys than in girls, and he noticed the curious fact that the recurrence rate, that is, how likely it was to occur in the next child, was higher in the females, which had the lower frequency. That's contrary to what you'd expect, but it's explained beautifully by this multifactorial threshold model. So he started publishing papers about human conditions fitting this multifactorial threshold model.

When he heard about my stuff, he was delighted, and when I heard about his stuff, I was delighted. I showed the same sort of thing for cleft lip and palate and for isolated cleft palate in people. It's the same sort of difference and recurrence risk according to sex. We kept on sort of swapping ideas. All too often, when I would say, "I'm thinking of doing such-and-such," "Well, I just did that," he would say. (chuckles)

So I guess that's the story of how the mouse model and the human model developed in parallel lines and occasionally overlapping and interacting. I'm rather pleased with that story.

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[79] Sewall Wright (1889-1988) was a pioneer geneticist who is best known for developing the modern evolutionary synthesis, along with important discoveries in population genetics. He was educated at Harvard, he spent most of his career teaching and researching at the University of Chicago. For more information, visit the website at : http://en.wikipedia.org/wiki/Sewall_Wright

[80] polydactyly: the genetically determined condition of having extra fingers and toes

[81] Hans Grüneberg (1907-1982) , a mouse geneticist born and educated in Germany but who spent most of his career researching and teaching in Britain. He specialized in multiple expressions resulting from individual genetic mutations.

[82] pyloric stenosis: is a condition effecting infants in which the opening between the stomach and small intestines narrows, causing incessant vomiting.

AM: Okay, good. If I recall Wright's work correctly, he just did this one brief mention and then it was kind of put to the side.

CF: Yeah. I don't think he pushed that very far.

AM: Yeah. What kind of reception did you get to your work, your cleft palate work and the threshold model? How well was it received initially?

CF: Good question. The teratologists were very interested. It hadn't occurred to them that genes would have anything to do with it, so this was a big surprise, and I got a lot of attention there.

CF: I don't think the geneticists were all so greatly impressed – it was only mice [they thought]. I shouldn't say that. I'm only guessing why they didn't invite me to more symposia. Well, actually, they did. The Cleft Palate Association [American Cleft Palate-Craniofacial Association][83] was impressed. I guess it was that you couldn't put your finger on it, like you could the Mendelian diseases. There was this model and stuff, but where were the genes? We had a few genes in the mouse, but Diana [M.] Jerloff is still searching for the cleft – she found one cleft lip gene and thinks there's another one. She's located them, but not sequenced them yet, even in the mouse where you can control the breeding and stuff.

Now, just since the human genetics revolution, it's beginning to show some attention. They're now referred to as complex diseases. People are working out ways of identifying the genes, even in a multifactorial model where no one gene has a big enough effect to make it really clear. If it did, it would be a major gene and be recognized. There is this idea that, if each gene has only a small effect, even if you do identify them and correct one of them, what difference is it going to make?

I used to say that it's not much use looking for these genes. That was back then. What you need to do is look for epigenetic factors that will change the relation of the distribution of liability to the threshold. That, of course, is exactly what happened with neural tube defects and folic acid. I don't think it came out of the multifactorial model very much, but I'm sure that must be what happened. In fact, there are mouse models that show this, that the neural tube defects in some strains and with some mutants are influenced by folic acid and will come up earlier. So people began to pay more attention.

There are still, though, people who miss the significance of the peculiar family patterns that multifactorial threshold characters have, that affects difference. Also – I don't think we need to go into the details – but there are certain curious properties, like the sex ratio in families that have more than one affected [individual] is different than the ones in the so-called simplex families who only have one affected, and that is what you'd expect from this model. Also, the recurrence risk varies with the frequency of the condition in the population, which is again what you'd expect. If the frequency is higher, the distribution is closer to the threshold so that more fall over at the tail end. And I still see papers, as I said, [saying] so isn't it curious that the sex ratio in these multiplex families is more towards one than it is in the – Sewall Wright pointed this out.

[83] The Cleft Palate Association (founded in 1973) is the public service arm of the professional American Cleft Palate-Craniofacial Association. The ACPCA was founded in 1943 and has since then been active in promoting the care and well being of people with facial birth defects. For more information, visit their website at: http://www.acpa-cpf.org/

I even wrote a couple of papers on under looked qualities of the multifactorial model, but they still keep coming out. There was one important example with neural tube defects. Why is folic acid much more effective in northern China than it is in southern China? Well, it's because northern China has a higher frequency, so it's easier to push over.

But, working the other way, folic acid was a really dramatic triumph for the people who had been proposing it against the resistance of certain epidemiologists who insisted on having randomized control trials. They finally convinced people to put folic acid in the flour and pasta and that sort of stuff, and it has brought down the frequency of neural tube defects quite dramatically in various parts of the world. Great Britain didn't do it, for some reason, in spite of [Richard W.] Smith ells[84], who discovered the thing in Britain. It took Canada a while to do it. I think the reason Canadians did it – I was on a committee that considered doing this, and the nutritionist on the committee was against it, because folic acid might mask a vitamin B12 deficiency and you'd get neurological damage in little old ladies, which I didn't think was a very good reason for allowing babies to be born with anencephaly[85]. Anyway, the U.S. government mandated putting [folic acid] in [flour], and then the Canadian millers insisted that they be mandated, too, because they couldn't sell flour down there if they didn't do it. So that's how we got it in.

The frequency has fallen, but not to zero, and people are now saying, well, you should put twice as much in. We told you in the beginning you should put more in, but you didn't. It is working, but it's not working as well as it might, so double the dose. Well, I'd say, you started when you were working on this part of the curve, but now you're out on this part of the curve, so moving it another degree or so is not going to make nearly as much effect. Don't be surprised if you don't get much more lowering. People will then say, "See, it didn't work."

So I think there are implications of the multifactorial model that are important and people should be paying more attention to.

AM: Just to ask a counterfactual question. It was Hamilton Baxter[86] who brought the cortisone to you? What if he hadn't done that?

CF: (he laughs) I never thought of that. Well, we probably would have done the same thing with hypoxia, but it wouldn't have been a drug, so it wouldn't have had nearly as much impact. I suppose we might even have gone on to do the embryology stuff. But I don't think it would have gone nearly as fast.

AM: Well, there are several different directions we could go. Right now I'll just talk a little bit – we kind of brought this up and didn't really discuss it too much, that once you created your – you still had your mouse lab in the basic science department. Then you created the Medical Genetics Division within Pediatrics at the hospital. And you were continuing with your bench research. How did your relationship change with the basic science department at McGill, or did it, after you created this medical genetics division?

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[84] Richard W. Smithells is a noted pediatrician and geneticist working in Britain who specializes in the study and prevention of neural tube defects and rubella, among other things. For more information, visit the website at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1793605/pdf/archdisch00634-0007.pdf

[85] anencephaly: a neural tube defect in which an infant is born without a large portion of the skull and brain.

[86] Hamilton "Happy" Baxter is one of the founders of the Canadian Society of Plastic Surgeons (founded in 1947). His first training was as a dentist, which influenced his later career as a plastic surgeon who specialized in cleft-palate treatments.

CF: I think it didn't change significantly. We were all good friends. The chairman was still worried about me getting too much money and too much space, but we negotiated this, and I guess eventually that led to the formation of the Human Genetics Sector. I wanted authority to apply for my own grants and hire people, and with a little help from the Principal [Frank Cyril James][87] – the Principal had the idea of the Human Genetics Sector, which would allow me independence for hiring people in human genetics and grading grants and stuff, but I would still be under the aegis of the main department for teaching, and the hiring, of course, would have to be jointly approved. But I had a lot more independence with this arrangement.

That worked very well for a while; but then, as you mentioned, there were various political reasons why it was deemed beneficial for the three Departments to merge into a single Biology Department. I agreed that that was probably beneficial. I agreed to give up the Human Genetics Sector and allow this merger.

AM: What advantages would this merger have?

CF: For me, you mean?

AM: Yeah.

CF: None for me. But for the Department, the Department, well – it's too complex to get into very far, but there was strength in numbers and there was more bargaining power for Biology than there would be for any of the Departments. I can't remember the politics of it.

AM: What disadvantages did it have for you as a human geneticist?

CF: Well, I lost my autonomy and I depended on the good will of the zoologists and botanists and the chairman of the new Biology Department to continue what I was doing. That worked out pretty well for a while. Then eventually we formed our Human Genetics Department.

AM: And what happened to the Genetics Department when it merged?

CF: The Sector, you mean?

AM: Yeah. Well, wasn't there a zoology-botany-genetics and then the Human Genetics Sector that all merged?

CF: Yeah.

AM: What happened with the geneticists? Were all geneticists in the Genetics Department, or did they still have geneticists in zoology and botany as well?

CF: All the geneticists were in the Genetics Department, but they weren't all human geneticists. There were molecular geneticists and cytogenticists and –

AM: So to create a Human Genetics Sector was primarily for financial reasons?

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[87] Frank Cyril James (1903-1973) was born in England and served as president of McGill University from 1939 to 1962.

CF: To give me some autonomy, yeah, for getting grants.

AM: Okay. Then to continue with the history of genetics at McGill, the Human Genetics Sector at the hospital continued. Then why was the Center for Human Genetics created in 1979?

CF: It wasn't a Center, it was a – [do] you mean the Department of Medical? Or – sorry –

AM: Yeah, I have here some information I'd gotten on the history of McGill. From 1979 to 1993, there was what was called a Center for Human Genetics at McGill that Charles Scriver kind of created. [Actually, this was not Scriver's creation.]

CF: In '79?

AM: Yeah. Is that wrong?

CF: To?

AM: '93.

CF: I thought that was the Department.

AM: Okay. Well, maybe it was. I got this off a brief history of the Department and maybe it's different. So it would have been about ten years after they merged to create the –

CF: Well, as I said, I didn't favor leaving the basic Biology Department but did want some status in the medical school. It turned out that we created a tri-cephalic monster, which was ruled by three deans: the dean of medicine, the dean of [the] graduate school, and the dean of science. Actually, I never got to be head of that, but my colleague Leonard Pinsky[88] became the head of that, in my usual way of avoiding responsibility. (he chuckles) That worked pretty well.

Of course, in '83, I went to Newfoundland for a three-year sabbatical. I was out of it for the rest of that time. I was three years from retirement and I was beginning to get a little frustrated and overwhelmed by the administrative duties and the fact that, when you get sort of a cohort of counseling families, they keep coming back. They keep coming back more and more, so you have less and less time to do anything else. I certainly enjoyed the counseling, but – anyway, I was on the search committee for a person to go to Newfoundland and start a Genetics Service there. The chairman of the committee said, "Why don't you take it?" At that stage in my state, it sounded like an attractive proposition, a new challenge, and something to finish off with a difference. So I did that.

When I retired, McGill offered me an Emeritus Professorship if I would come back, so I did that.

[88] Leonard Pinsky became the first chair of Quebec's only Department of Human Genetics in 1994. For more information, visit the website at: http://reporter-archive.mcgill.ca/Rep/r3116/pinsky.html

7. Post-Retirement Research; Genetic Counseling

AM: Did you still have your mouse lab?

CF: In Newfoundland?

AM: In McGill, when you returned as an Emeritus.

CF: No. As Emeritus – No, I didn't feel up to getting more grants and doing any mouse work. I did counseling and I still had a few graduate students. [I] took it easy. (chuckles)

AM: To go back quite a bit and follow another strand, in the hopes that all these will meld at some point, we just talked about how your—with the cleft palate research – that there was this direct kind of feeding between your clinical work and your bench work. But you had mentioned yesterday that you were kind of frustrated, because those geneticists who could use biochemistry to effect some kind of therapeutic treatments to their patients, you didn't have that. So what was it that you thought that you could then do with your – what contributions did you think your research, your bench work, could then make in order to be of some kind of clinical assistance to these patients?

CF: I don't think it made much of a direct influence. A lot of my counseling was with multifactorial conditions, and it would give me a way of saying, "It's not that you have bad genes. There's nothing wrong with your genes. It's just that you and your husband happened – that the child got from you and your mate a collection of these genes which just made your palate shelves slow up a little bit, or something. But they weren't bad genes, just a combination that didn't quite make it." That, I think, was a comforting thought for parents, and also encouraged me to look for environmental factors. So shall we go back to the counseling aspect?

AM: Sure. What tools besides pedigree analysis and Mendelian patterns of inheritance could you bring to genetic counseling?

CF: Well, chromosomes, once they appeared, which was fairly early on in my career. I interacted with biochemical genetics, of course; I could send them for biochemical testing when indicated. What other tools? Blood groups, when indicated. That's about all there were at that point. But in the beginning when I started, most of the counseling that was done was done by physicians or medical geneticists. I mentioned the ones in Europe. There were some PhDs collecting genetic data. Sheldon Reed[89] and Larry [Laurence H.] Snyder[90] and a bunch of others, who were doing human genetics, but not with a medical degree.

Usually, they would be called up by a physician, who would say, "What's the recurrence risk for this or that?" They would tell them, and then the physician would use that information with the families. I don't think there were very many people outside of

[89] Sheldon Reed (1910-2003) was a biologist and human geneticist. A good portion of his career was spent at McGill University where he specialized in behavioral genetics and genetic counseling. For more information : http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1180572/

[90] Laurence H. Snyder (1901-1986) was a pioneer in human genetics. Educated at Rutgers and Harvard, he went on to become the President of the University of Hawaii. To learn more about him, visit the website at: http://libweb.hawaii.edu/names/snyder.html

physicians who were actually advising the families. In fact, there were some people like Alan Stevenson said that nobody without a medical degree *should* advise people about genetic conditions. And there was that aspect, not just from Alan, but it was a fairly common view among the physicians.

So when I started getting into counseling families, I didn't have any rules or principles or background to go on. I was feeling my way all the way and learning fairly rapidly that it wasn't all that simple. I think one of the first papers I gave at the American Society [of Human Genetics][91] was – the first paper was about autosomal dominant diabetes insipidus, as I remember. It caused some amusement when I called them "water babies." But one of the early papers was on the darker side of genetic counseling. I was beginning to see the problems that you run up against genetic heterogeneity. I think I coined the term [heterogeneity], by the way, in that paper in the annals of *Eugenics Quarterly*[92], was it?

AM: *Eugenics Quarterly,* yes.

CF: The term was around, of course, but I don't think the phrase was around. I mean the concept was around, but I think I was the first to use the term. But also, varying attitudes, perceptions of normality or abnormality, and severity. The same condition was terrible to one person and not bad to the other. The perception of recurrence risks. "Five percent? Oh my God, I'm just the one that would fall into that five percent." Or, "Five percent? Jeez, that's great. That's ninety-five percent normal." All these sorts of differences and things that I had not seen in the literature anywhere. I think maybe that was one of the first efforts to start talking about the personal side of genetic counseling.

AM: One thing that struck me in the *Eugenics Quarterly* article was [that] having a knowledge of genetics was only part of what could contribute to making up a good genetics counselor. There's also psychology and sociology and demography, just a whole bunch of other aspects.

CF: That was a somewhat tongue in cheek statement, by the way.

AM: Right. So how then did you go about training your own students to be good genetic counselors?

CF: Just by example, I guess, and by – they used to sit in on my interviews for a while, and then we'd talk about the problems. As I said, I didn't have any guidebooks. We just felt our way. There were all sorts of ethical problems that would come up. There weren't any bioethicists in those days, that I can remember anyway. We used to have to thrash them out. I didn't really see much need for a bioethicist. We had pretty strong ideas about what's right and what's wrong. This whole idea of do no harm – *nil nisi bonum*[93], is it? – well, that's not very practical, because anything you do, particularly in prenatal diagnosis, there's no way you can do no harm. If you *do* the prenatal diagnosis, you're harming the fetus; if you *don't* do it, you're harming the born child and the parents.

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[91] American Society of Human Genetics was founded in 1948 to provide leadership in research, education and service in human genetics. for more information, visit their website at : http://www.ashg.org/

[92] *Eugenics Quarterly* no longer exists as such, since it switched the title of its journal publication to *Social Biology* (still in print) in 1968 as the eugenics movement became less popular.

[93] Latin for "nothing except good".

It's a matter of doing the least harm that you can manage, not doing no harm. So we used to thrash these things out.

Abby Lippman-Hand[94] did a series – I think what is being referred to (if I may brag a little) as a landmark paper where she sat in on interviews and recorded them and then worked them out afterwards, established themes, and more or less crystallized a lot of the things that we had been thinking about and observing as we went along.

[On] the question of directive counseling – when I started counseling, the traditional counseling was very directive. I mentioned Madge Macklin, who said [to patients who asked], "Should I have another child?" – a resounding no! (chuckles) Or Alan Stevenson was just about as bad. Then there was this reaction that you mustn't be directive at all, which I had a little trouble with, because there are times when I myself am seeking counseling, I want some direction. I have repeatedly known families who ask for direction and obviously want it. They say, "What would you do if you were me?" I say, "I don't know what I would do if I were you, because I'm not you, but if I were me in your situation, I think I might do such-and-such. But you have to decide what you're going to do yourself." I would go that far.

Abby, in one of her interviews, had a woman – she asked them all whether they thought I was being directive or not. Most of the time they didn't, or didn't mind it if I was, but this woman said, "Well, if he thought I shouldn't have had any babies, he would have said so, wouldn't he?" So I *was* being directive. (chuckles) So I think all the kerfuffle about non-directiveness is going too far. The people who say, "Would you like a cup of tea?" That's being directive because you're forcing them to make a choice.

AM: So how does one achieve a happy medium between the absolutely-[do]-not-have-a- kid approach [and] being too directive [or] being not directive enough?

CF: I don't know. I play it by ear, and each situation is a thing of its own. I can't generalize. I certainly don't say – I never say, “I don't think you should have another baby”, or anything like that.

AM: Although I'm not really up on my Canadian history –

CF: Neither am I.

AM: (chuckles) I know that Quebec is primarily French, or has a primarily French historical background, and Catholic. How did being at McGill in Montreal influence how your attitudes toward genetic counseling developed, as well as any kind of therapeutic options that you were able to provide your patients?

CF: I don't think being at McGill influenced my attitude at all, but I was aware when I started that the Roman Church was quite strong. It was illegal to sell contraceptives, for example. Abortions were illegal unless you got special permission by going through a committee of a psychiatrist, an obstetrician, and a clinician of some sort. I used to have to write letters to this committee to say I thought the condition was serious enough and the recurrence risk was high enough so a termination would be justified. Then the committee would decide whether they accepted that or not. Sometimes they did and sometimes they didn't. I think I've written some stories about women who – one family

[94] Abby Lippman-Hand is currently teaching and researching at McGill University in the department of Epidemiology, Biostatistics and Occupational Health. She specializes in genetic counseling.

where this woman had three hemophiliac sons because of this sort of obstruction [from getting an abortion].

And the family sizes were tremendous, which made genetics a lot easier, but then the so-called quiet revolution took place and the Church lost a lot of its power over the people quite rapidly, and the family size dropped precipitously. I would have women who would say, "Is the priest going to look after my sick child?" when they were thinking of not aborting.

I did testify to a parliamentary committee – I'm not sure whether I wrote about that or not – who were drafting a law about abortion. I testified and I took it on myself to take pictures of some of these children and give them an idea of how serious the conditions were that we were talking about. I think I probably made an impression. One Roman Catholic parliamentarian accused me of being a murderer afterwards because of advocating termination of pregnancy. But then the law finally came out making abortion not a criminal offense. So things are much easier now in that respect. Is that what you were getting at?

AM: Yeah. Before abortion had become available in Quebec, was it available in other provinces in Canada? And if so, could you suggest to a patient that she --

CF: No. This was a federal offense.

AM: Okay. And what was the impact of amniocentesis on your own approach to being very declarative or not?

CF: I was never very declarative. I don't think it influenced that aspect that I can think of. It became, in some ways, simpler because, as I said, the woman before that had a choice – do you want a baby enough to take this chance? Or, if you don't want a baby enough to take this chance, you're going to get sterilized. Or at least keep on the [birth control] pill, which is not entirely safe. When I started there wasn't any [birth control] pill. Or if you're already pregnant, do you want me to apply to a committee for a termination? Is the risk high enough and the burden high enough that you would like to do this? Go home and think about it for a few days. Not just that, but we would talk about the pros and cons and how she felt about it and how her husband felt about it. Sometimes they got very complicated situations. The parents would end up in tears in the office. So you can't generalize.

But having prenatal diagnosis made it a lot clearer in that you could – it wasn't just a probability that you had to deal with but yes or no. The child had it [a genetic disorder] or not. Even then, of course, there was still the question of was it severe enough to justify termination or not? Of course, there are all the complications of variable expressivity. This child has an anencephaly, but the next child might have a spina bifida with a repairable defect, or this child had a severe neural fibromatosis and the next child would have café au lait spots, and you have to make that sort of decision. So I was never declarative, but I spent a lot of time talking out these sorts of aspects.

AM: Genetic counseling increasingly became a profession unto itself. In 1995 – or was it earlier – that McGill developed a Masters of Science in genetic counseling?

CF: It was earlier than that, I think.

AM: In '85?

CF: It was just when I was leaving for Newfoundland. Did you say '85?

AM: '85, yes. I first said '95, but it was '85. How involved were you in this, and what led to this idea that genetic counselors did not have to have an MD degree or a PhD in genetics in order to be good counselors?

CF: Well, I was fairly involved. I mean, a lot of my graduate students did counseling under my supervision. Some of them did research on genetic conditions, human conditions, and had to interview the families by themselves and got into counseling that way. I was strongly for – when the CCMG was formed, the Canadian College of Medical Geneticists[95], I fought for admitting PhDs as well as MDs into the college, which I thought was a good thing. Now even the Royal College [of Physicians and Surgeons][96] has recently decided that they would let PhDs use their accreditation, their educational program to maintain their status, which is a great step forward.

I used to sit in on the selection committees that were selecting the students to come, and sit in on some of the training sessions, or give some of the training sessions. We talked to Joan Marks[97] quite a lot before we started. Am I answering your question?

AM: Yes. And what disadvantages does it have where a genetic counselor does not have an advanced degree in medicine?

CF: There's a question of responsibility, for one thing. Some of the MDs would say "They are patients, you can't handle patients if you're not an MD." But apart from that, somebody has to take responsibility. Suppose they [genetic counselors] give wrong advice, for example, or fail to give advice that they should have given? Somebody's legally responsible for that. It's not going to be them, it's going to be whoever is in charge. So they're working that out, I think. I'm not sure what the current status is.

AM: So in 1995, there was an American Board of Genetic Counseling[98], and the genetic counselors had their own kind of distinction within the American Society of Human Genetics. What were the advantages and disadvantages of separating the two groups?

CF: Which two groups?

AM: Well, somewhat separating the genetic counselors from the main organization of the Society of Human Genetics.

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[95] Canadian College of Medical Geneticists is an organization committed to providing high quality medical genetics services. It was founded over 25 years ago. For more information, visit their website at : http://www.ccmg-ccgm.org/cred_info.html

[96] Royal College of Physicians and Surgeons of Canada is an organization which aims to promote the highest standards of medical education of specialists in Canada. It was founded in 1929, by an Act of the Canadian Parliament. To learn more, go to their website at: http://rcpsc.medical.org/about/history_e.php

[97] Joan Marks was the first director of the genetics counseling program offered at Sarah Lawrence University. She is a foundational figure in the field of genetics counseling, including its psychological aspects, and has a degree in social work as well. Currently Dr. Marks is the Co-Director of The New York Breast Cancer Study associated with Sarah Lawrence College in New York. To find out more about her, visit the webpage at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1182251/

[98] American Board of Genetic Counseling was formed in 1993 and its mission is to bring the highest standards of care to the genetic counseling profession. For more information, visit their web site at : http://www.abgc.net/english/view.asp?x=1

CF: Well, it's a question of professional services, I think. You don't have to be qualified to provide professional services to join the American Society. Anybody can join. But for having professional status, I think you need some kind of body that ensures quality control. We have a Canadian Association of Genetic Counselors[99], too, on very similar sorts of lines.

AM: And was that created at about the same time as the American Board?

CF: I'm not sure. I think it was just about the same time. The Canadian College was created several years before the American College.

AM: Of Human Genetics?

CF: Yeah.

AM: Oh, okay. I didn't realize that. I'm sure you were instrumental in the creation.

CF: Not as much as I should have been probably. (chuckles) I didn't get in the way anyway.

AM: Why don't you tell me a little bit about the history of the Canadian College and what advantages and disadvantages it had for the development of human genetics and medical genetics in Canada?

CF: My memory isn't too clear on this, but I think it started when there was a genetic counselor, who I will not name – or a cytogeneticist in a city that I will not name, who took it on herself – oh, I mean her or himself --

AM: Okay --it's too late for that! (chuckles)

CF: (chuckles) – to provide genetic counseling for her cytogenetic clients, and she gave some really off-the-wall advice to people. The word spread around, and we said we've got to do something to stop this. There may have been other examples, too, but this is the outstanding one. The Toronto Sick Kids [Hospital][100] has a foundation that supports beginning research or pilot-sort of projects, who funded a meeting that we had in Toronto, just up the hill a bit, all of the people that were practicing medical genetics. We decided it was a good time to start a bootstrap organization and give ourselves a way of accrediting people and maintaining quality control.

Unlike the American Board, it really was a bootstrap operation in which we had a grandfather clause. Some of us didn't have to write exams. I think I would have – I faced the idea of taking months off to study for exams rather hardly. So we formed a group who were – we decided nobody would disagree [that] we're capable counselors. And this group made up a list of the other people who they thought were creditable. That's the way it started.

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[99] The CAGC was formed in 1987.

[100] Toronto Sick Kids Hospital, aka Sick Children's Hospital, aka The Hospital for Sick Children aka Sick Kids, founded in 1875 in Toronto by a group of women, is now one of the leading pediatric teaching-hospitals in Canada and is associated with the University of Toronto.

There was some hard feeling, of course, by those who weren't – and some people who didn't get in by grandfathering or mothering never did get in. They couldn't be bothered to write the exam. Eventually, those phased out, and we now have, I think, a pretty healthy and strong organization. It was easier to do because it's a smaller country, at least population-wise, and there was a fairly close-knit body of people who all knew each other well, because they would meet at the meetings and correspond. So that's the way that happened.

AM: I know in the history in creating the Board in Medical Genetics in the United States, there was a lot of reluctance, not only by the American College of Medical Specialties to create yet another medical specialty, there were also medical geneticists who thought that creating just another specialty would detract from the strength that having specialties in other areas, whether it's pediatrics, cardiology, internal medicine, so that it would just further divide specialized people and detract from a general approach to genetics issues in medicine. Was there that same reluctance in Canada to create a medical specialty?

CF: I don't think so. Maybe there weren't enough of us to worry about being split up. (chuckles) Of course, the Royal College was reluctant to have another specialty. That's why we had to set up an independent organization, and it took quite some years after *we* set up to convince the Royal College that medical genetics was worthy of being a specialty, but they finally did. Recently, the Quebec College agreed that people who pass their exams will be accepted into the CCMG. So it's now a big fat happy family. (chuckles)

8. Closing Comments

AM: When you retired, you were the Molson Chair and Professor of Human Genetics and Professor of Pediatrics at McGill, and you were also the Director of the Department of Medical Genetics at the [Montreal Children's] Hospital.

CF: Division.

AM: Division of Medical Genetics.

CF: Within Pediatrics, yeah.

AM: Within Pediatrics at the Montreal Children's Hospital. What difference did it make to be called a human geneticist and a medical geneticist?

CF: Well, as I see it, human genetics includes all conditions, normal as well as abnormal, and medical genetics is a subset that deals with medical conditions. So medical genetics is part of human genetics, but being qualified in medical genetics gives you certain privileges that non-medical geneticists don't seem to have. I'm not sure how big these differences are. I kept telling my PhD students that they didn't need a medical degree. Look, you're doing what you want to do. But they all seemed to think it was better to have a medical degree. Most of them didn't get one, but they resented not having one.

AM: That's interesting because when you were having your wandering-in-the-wilderness [experience] through medical school, James Neel had said – and you were convinced by this argument – that you should have an MD degree.

CF: Yeah.

AM: What had changed over the course of your lifetime that you thought having an MD degree *was* important and later when you were advising your own students that it wasn't that important?

CF: I guess it was that there was a department, that they had the protection of the head of the department, or other MDs, if they were doing – actually, it's a question of responsibility. I don't remember it ever coming up in the days when we were starting. It was only when there were Bachelor or Masters type genetic counselors that this even began to come up, as far as I know. So I don't know what the difference was.

AM: You had also mentioned yesterday that when you created the Division of Medical Genetics within the Pediatrics Department of the hospital it was met with a little reluctance by the Department of Genetics on the campus. You had mentioned that, was it necessary to have both human genetics and medical genetics in the same institution. How has the development of this field changed your attitude toward this separation? Has it been beneficial, or has it been detrimental?

CF: I think the Department of Genetics regarded the Division of Genetics as a sort of fieldwork, so they didn't resent it as long as it wasn't in their space. In fact, took some credit for it, took some pride in it probably, some of them.

AM: Yesterday I briefly mentioned, and we discussed something else in order to understand – you did your Ph.D.-MD sequentially because there was no other way to do it, and now they have these programs in which you can do the Ph.D. and MD simultaneously. What's your attitude toward these programs that try to do both at the same time, to teach both basic science and medical science, train people in both?

CF: Both basic science – do you think that MD-Ph.D.'s do basic science?

AM: Well, supposedly that's what they're supposed to do.

CF: Okay. Well, McGill has a program like that, and it seems to work out very well for a very select kind of student.

AM: What kind of student does that work out well for?

CF: Well, they have to be brilliant, I guess, probably. I had a number of students – Alasdair [G.W.] Hunter[101], for example, who did his Masters degree with me in the summers of his medical school. That was not exactly a combined program, but he did three summers of research and got a Masters thesis out of that while he was doing his medicine, so he got his Masters degree and a PhD at the same time. I had quite a few

[101] Alasdair G.W. Hunter is a prominent medical geneticist who has numerous publications in many aspects of medical genetics. He currently teaches and researches at the Children's Hospital of Eastern Ontario, Canada.

students who got Masters degrees, either just taking a year off in between their studies or just before they went into medicine, or sometimes concurrently. Not Ph.D.'s, though.

AM: How successful do you think you were in combining a productive mouse laboratory and an effective practice in medical genetics, in counseling and collecting family pedigrees?

CF: (chuckles) How successful do I think I was? Well, I always felt that I wasn't doing a good job in any of them, because they all took up so much time. I was always pressured. But it seems to have worked out fairly well.

AM: Do you think that's still possible, to combine a productive basic science career with a productive clinical practice?

CF: Yeah, I think so. I mean, some MDs do bench work of other kinds, molecular or – it's getting easier and easier to study mice, make mouse models for medical conditions. If you have time for research at all, why not genetic research?

AM: Okay. Speaking about molecular impact on mouse genetics, in your ASHG Presidential Address in 1962, you kind of warned about the danger of being over-equipped in a laboratory, because it was just the – what Horace Judson[102] has called the molecular revolution was just beginning to take off, and now most labs spend as much on personnel costs as they do on equipment costs, if not more. The human genome project could not have been done without huge pieces of equipment. How has your attitude changed since 1962 about this kind of thing – and I've talked to other scientists about it – the things that you used to have to do by hand and think through is all done by machine now. What impact – do you still feel like there's this danger of being over-equipped in genetics?

CF: Well, you have to be over-equipped, I guess, to do molecular genetics. I still admire the English [scientists], at least as I knew them, who had time to sit down for tea twice a day and chat. I'm not sure how much of that goes on in the average molecular genetic world. I think maybe the danger is still there that you get so much stuff to do that you don't have time to sit down and think. But I can't speak from observation or anything. Certainly people seem to be doing a lot of very successful thinking.

AM: I know we're jumping around a bit, because we're coming to the end. There's just a few more questions I have, but they're probably not all that connected. You just mentioned England has a little bit different tradition of some aspects of science. Would you say that there is a distinction between Canadian and American approaches to genetics? Or specifically science in general?

CF: No. I don't see that. I think Canadians rate fairly well on the North American genetics scale, maybe more per capita than the U.S., but I don't see any fundamental differences that explain that.

AM: Okay. Well, one area that we just kind of briefly mentioned was one of the many identities that you have assumed is that of teratologist. Looking over your work and

[102] Horace Judson is a journalist and an historian of the revolution in molecular biology. His book *The Eighth Day of Creation* was one of the earliest scholarly works on the subject.

trying to figure out where all these paths lead, is it kind of inevitable that a pediatrician interested in genetics becomes a teratologist?

CF: No. I think it would be more likely it would be an obstetrician.

AM: Okay. And why is that?

CF: Because teratology happens before birth.

AM: But you only see the consequences afterwards.

CF: Yeah. So the pediatricians would be syndromologists, say, but I don't think they're as interested in the embryology, the origins of the defects as a geneticist would be.

AM: I did read – your name appeared also as a syndromologist. Do you consider yourself a syndromologist?

CF: No. I think some people do. My wife was much more of a syndromologist than I was. She had an uncanny knack for recognizing faces. She could spot a Down's Syndrome that had been sitting on the ward for three days that nobody had picked up [on the disorder]. Or she'd pick up a case report of a child and say, "Hey, that looks just like Billy that we saw three years ago," and it would turn out to be the same condition. Uncanny. She did some very classy work, I think, developing – she used numerical taxonomy to develop indices whereby you could classify a person as either having or not having a particular syndrome. She did one for Down Syndrome that tests better than any other test except chromosomes. It's not so important for Down Syndrome, but there are lots of syndromes that don't have a chromosome basis or a known basis where you have to do it on physical appearance. Largely underappreciated work, but I thought it was very good work.

AM: I interviewed Robert Gorlin[103], who does consider himself a syndromologist.

CF: Yes, I would agree with that.

AM: I'll ask you the question, are syndromologists born, or can they be trained?

CF: Well, I think my wife would say [they are] born, and I'd probably agree with that. I did do some work in syndromology, and I didn't make too many mistakes. But I don't have that pattern recognition thing that she does, so I have to work harder at it. I think Bob [Robert Gorlin] has that, too. There are some so-called syndromologists that I know who don't have it. (chuckles)

AM: Well, of all these hats that you wear, all these identities that you've carried, how do you describe yourself?

CF: (laughs) I don't have a term that incorporates all of me. (chuckles)

[103] Robert Gorlin (1923-2006) was an oral pathologist and geneticist who specialized in cranio-facial birth defects and wrote the definitive work on the subject entitled *Syndromes of the Head and Neck*. He spent most of his career at University of Minnesota. An interview with Dr. Gorlin is available in this collection.

AM: How would you prefer to be identified?

CF: Never thought of it. (pause) A medical genetic teratologist.

AM: There you go. Okay. A couple more questions and I think I'll be at the end. Where is normal for you in genetics? It seems like you've studied the abnormal aspects of genetics all your life. Where is the normal?

CF: Normal is what you have to measure to know what's abnormal.

AM: You've mentioned in a few of your publications this movement that before the fifties, malformations were considered genetic, and then in the 1950s, it moved away from that in that malformations were seen as caused by environmental factors. For a while, at least through the sixties, that really became the public view as well, with people like Rachel Carson and *Silent Spring*[104], and DDT and thalidomide. But with the molecular revolution, it seems now that again the pendulum has swung back to where everything is genetic and it's happening within the genome, that errors are induced between transcription and translational errors, and that the environmental factors of understanding malformations has taken a back seat. How would you characterize that?

CF: I think it may have happened during the early days of the human genome project. But I think it's now beginning to swing back again. A lot of the papers I hear here [at the conference] are talking about networks and epigenetics. Epigenetics involves the environment. In fact, did you hear Charles Scriver talk today?

AM: No.

CF: He talked about environomics. Particularly with the complex diseases, people are certainly acknowledging that there are environmental interactions, maybe not identifying them so much but acknowledging their presence.

AM: So that there is much more of a balance now between understanding genome genetics and environmental genetics.

CF: Yeah, particularly the proteomics[105]. Well, epigenetics[106] is the word, I guess, that's beginning to bring it back.

I'd just like to add one thing about the genetic counseling and the pleasure I got out of working with these families, particularly in the opportunities where I was able to get into their homes and really interact. In Newfoundland, for instance, we did a study that actually showed that folic acid deficiency was present in the mothers of neural tube

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[104] *Silent Spring* was a ground-breaking work published in 1962 which brought a new level of awareness both in the US and globally, of the growing crisis of environmental pollution, especially through pesticides like DDT. The work was written by Rachael Carson (1907-1964), an ecologist and marine biologist as well as nature writer. *Silent Spring* is considered by some to have launched the contemporary world-wide environmentalist movement. For more information, visit the website at: http://www.rachelcarson.org/Biography.aspx

[105] proteomics: the study of proteins structures and functions.

[106] epigenetics: the study of inherited changes in phenotype or gene expression caused by mechanisms other than changes in the DNA.

defects, again, an underappreciated study. But I had the opportunity to get into their homes and see these pitiful little creatures and their parents and how lovingly they were taken care of. I just loved that.

AM: In your career as a geneticist, how have you brought – you had mentioned that you were frustrated when you saw the biochemists effecting treatment. How far have you come in helping now these people that you know quite well and become very – how much of their problem can you alleviate now than say when you first started?

CF: Well, I guess we know a lot more about recurrence risks, and we can make better diagnoses of genetic syndromes, and there's prenatal diagnosis. I don't think I said that I was frustrated by the fact that biochemists could do this. I said that I was frustrated by the fact that I *couldn't* do it and that I was glad when Charles Scriver could enlarge the area where we could help. I didn't help in any very practical ways of curing people, but I think I – well, I have a number of letters of appreciation for sympathy and sensitivity, being able to help them through crises.

AM: And how well have you been able to carry this sensitivity and appreciation of these families to the next generation? Since you were such a pioneer in Canada and McGill, there weren't that many medical geneticists. How successful have you been to instill this same kind of attitude in your students?

CF: Can't measure it. I don't know whether it's by example, or maybe you're just born that way. I can think of a lot of fellows and students who do have tact and compassion and sensitivity. A few who don't.

AM: Okay. Well, I don't have anymore questions. Is there anything that you'd like to talk about that we haven't so far?

CF: I don't think so really. We've covered quite a lot.

AM: Okay. Well, I really appreciate you taking your time out of the meeting here to sit down with us.

CF: Oh, a pleasure for me.

END OF INTERVIEW