VIDEO INTERVIEW TRANSCRIPT

MacLeod, Patrick: transcript of a video interview (06-Jun-2015)

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MacLeod, Patrick: transcript of a video interview (06-Jun-2015)*

Biography: Professor Patrick MacLeod (b. 1940) is a Clinical Professor of Medical Genetics in the Department of Medical Genetics University of British Columbia and an Adjunct Clinical Professor in the Centre for Biomedical Research, Department of Biology, University of Victoria, in Victoria, British Columbia. He trained in Medicine at the University of British Columbia before going on to train in Paediatrics and Medical Genetics at the Montreal Children’s Hospital under the direction of the late F Clarke Fraser PhD MD OC. He is a Fellow of the Royal College of Physicians and Surgeons of Canada, and a Fellow of the Canadian College of Medical Genetics. He has initiated research in various paediatric neurological disorders, contributed to the mapping of the gene for what is now known as spinocerebellar ataxia type 3 (Machado Joseph Disease) and the natural history of Rett syndrome in a large cohort of Canadian families.

[1]. BECOMING A MEDICAL GENETICIST

All right, let’s go. I became a clinical geneticist quite by accident. I graduated from the University of British Columbia with a career path in neurosurgery, and along the way I met a man at my internship who dissuaded me from being a surgeon. He said, ‘MacLeod, you’re not a surgeon,’ which completely changed my whole tack. So I had to take a year out and do something, so I did a year of paediatrics thinking, ‘Well, paediatric neurosurgery is still an option.’ But the more time I spent with him, the more I got interested in congenital malformations and birth defects, and he indicated this was a prime time to get into this new field. So I had two options as far as he was concerned: I could go to Boston or I could go to Montreal. So I interviewed at both, and my wife and I decided to go to Montreal. And I joined up with Clarke Fraser at the Montreal Children’s Hospital. Now back then there wasn’t such a thing as a career path in medical genetics, it was a Certificate of Special Competence in Paediatrics. So I did my paediatric fellowship from the perspective of a medical geneticist, like ‘Why are we doing this heart cath on this child, what syndrome does she have?’ Or ‘Why does this family have a collection of that or whatever?’ And then, eventually, when I qualified I was recruited back to the University of British Columbia as a junior staff person in 1973.

[2]. SERENDIPITY & JOSEPH DISEASE

Well, my story here for this career path that I’m most proud of, began in about 1976, living in Vancouver, participating in the Western Society for Paediatric Research meetings in Carmel, California, because the birth defects focus of attention at that meeting was there in Carmel every year. So after these sessions we’d meet at Clint Eastwood’s bar called the “Hog’s Breath” for an after-session beer or two. And as I was leaving to fly home, I noticed there was a TIME magazine, two-years-old, lying on the desk, I thought, ‘Nobody’s going to miss this. I’ll read it on the plane.’ So I got on the plane, had my dinner, went through it, and here was this half page story of this 40-year-old woman, who had recently buried her brother to the ‘family disease’ that she decided that she was going to do something about it. So she wrote to the National Genetics Foundation asking for assistance and they sent a neurologist, Roger Rosenberg, and Bill Nyhan, a medical geneticist, to interview her, which resulted in a family reunion of some 120 of her family members in Oakland, California, in a park where they had this family-room-come-clinic. And they were now part of what was called the “International Joseph Disease Foundation”. So I’m interested in neurogenetics, so I’ll tear this out and take it back, and I stuck it in my basket and under J for Joseph, and forget about it. Then about two years later my Department Head, who was a PhD, asked me to see this young woman because it

* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 06 June 2015, in Glasgow. Transcribed by Mrs Debra Gee, and edited by Professor Tilli Tansey and Mr Alan Yabsley.
involved a physical examination, which he wasn’t able to do. So this is a 22-year-old young woman, she’s been married, she has a two-year-old son, and she’s in for genetic counselling with her father. And I wondered, you know, why is she coming in now, if she was worried two years ago? Well, it turns out in the interval her father had come down with the “family disease” and she said, ‘Well, this goes back for ten generations.’ I said ‘So what do they call it?’ and she said ‘Joseph’s disease.’ I went over and plucked out J for Joseph and thought, ‘Oh that’s autosomal dominant, I can tell you what’s going on,’ ‘Thanks,’ end of the story. But I thought I’d just see if the people in the Foundation knew this family in Canada. ‘Oh yes, we know this family. You know, not them, but the extended families are large Portuguese families, and how would you like to be on our Medical Advisory Board?’ Like on one patient! ‘Okay, I’ll be on your Medical Advisory Board.’ So that’s fine, I never saw another patient. Another year went by and I got a phone call from the Foundation, ‘We’re having a meeting in Lisbon and we want you to come and participate in the meeting, talk about your research.’ ‘I don’t do research in this area at all, I can’t go to Lisbon and take your money for that.’ ‘Oh no…’ ‘No, I really would feel badly about this.’ So the next thing I know I get a call from Roger Rosenberg, the neurologist, who is now the Chairman or President of the American Academy of Neurology, is on the line. So we chatted a bit and he convinced me that I really should come as a medical geneticist, because there aren’t too many involved, and just sit and listen and make notes, and at the end of the three days, you know, do this particular, what we did, what we saw wrap up seminar. So I said, ‘Sure, I can do that,’ and off I went. Well, before I left I went to another meeting, and on the train I was reading the issue of the American Journal of Medical Genetics, when they were publishing the first article on RFLPs [restriction fragment length polymorphisms]. And I read this and I said, ‘Isn’t that interesting?’ and just filed it away. Got to Lisbon and said, after the three days, ‘You’ve got 200 three-generation families perfect for linkage analysis, I think you should seriously go after doing this gene.’ And they thought it was a great idea, and we wrote it up, and that was the end of the story.

[3]. JOSEPH DISEASE, MAPPING THE GENE, PROFESSIONAL DISPUTES

About a year later I got a call from the Foundation saying, ‘We want you to map the gene.’ And I said, ‘Look, I don’t have the lab, I’m a clinician. I can’t possibly do this.’ Fine. So then at this annual meeting of our Canadian College of Medical Geneticists, I was on a committee to look at manpower requirements across Canada, interviewing all the programme heads, and one of the programme heads in Kingston, Ontario, was recruiting. But she was the only person in Canada doing linkage analysis with RFLPs. In fact, she was one of the only few basic scientists in the whole country who actually was doing gene mapping with red cell enzymes, and serum proteins. Well, one thing led to another, and I came home one day and said, ‘Muriel, there’s an opportunity for me in Queens,’ and we had four young kids, and off we went to learn linkage analysis. That’s fine. The nice thing about it was I could drive down from Kingston Ontario through upstate New York to the outskirts of Boston to New Bedford, Massachusetts, where these large collections of Portuguese families who had come to the States in the fifties, because of the opening of the immigration requirements opportunity, and that was you know a great opportunity.

I’m getting ahead of myself. At that Lisbon meeting we realised that the Eastern seaboard was collecting families, and their patriarch was Machado, and our patriarch was Antone Joseph. And they were cousins. So suddenly all these pedigrees clicked, okay? And that’s what made me say, ‘You know, we should do this.’ It turns out to be a founder mutation in the Azorean population, and mass migration to the States had occurred. So going to New England was an obvious thing to do. So we could leave on Friday afternoon with a graduate student, drive down, have dinner, next day in clinic with the local neurologist, collect pedigrees and DNA samples, and bring them home to Queens. And that went swimmingly well for a while, but the politics of that early period of time in DNA mapping put the clinicians and the basic scientists on opposite sides of the equation. The basic scientists said, ‘This is DNA, this is our knowledge. Now, we’ll share it with you, but we’re running the show.’ Well, they didn’t realise that’s not how it works. And so one thing led to another, and there was a friction/fraction/dissolution, along with all my samples disappeared.

So I went through the process: Division Head, Department Head, Dean’s Office, Vice-President of Research, and got absolutely nowhere with them; that was a great disappointment to me. So I had to start all over again. So away we went again, and this taught me a lesson about the legal aspects of these things,
because although we had consent from a lawyer’s point of view, possession is nine tenths of the law. And they were reluctant to initiate anything that would bring anything down on the University from there. Now, I would have gone to the Dean and stopped there and gone to a lawyer, and for $200 I would have had a legal letter which would have changed things. But things happen for a reason. So we started all over again, and at one of these meetings in New England I met a fellow who was working with the group in Boston on Huntington’s Disease and he said, ‘Well, there’s this fellow, Guy Rouleau, who is a neurologist doing a PhD with us, and you should go and talk to him.’

So I did, and he was going to go back to Montreal so we began a collaboration. So all the samples were dropped off in Boston then and he went to Montreal, and he started this Institute for this group in Montreal, and away it went. And we had young people from Portugal and Brazil coming to his lab to learn this new-fangled thing of genetic analysis and he grew a great, big programme, which was great. Eventually the gene was mapped, although we didn’t do it, the Japanese did it by searching through for just repeats. They found a repeat and then a disease - bing, bang, boom - solved. We published all our data which confirmed that.

[4]. JOSEPH DISEASE, JORGE SEQUEIROS, PORTUGAL & CUBA

So there was an opportunity to go back home to Victoria this time because the lab was without a Director and there was nobody there, and this is perfect for me because I wanted to, you know, build something. And so off we went. And I would commute to Vancouver for clinics and I persuaded the molecular lab there to set up testing for SCA3, as it was called then, and that included SCA1 and eventually SCA2. My colleagues who were involved in all of this were initially Jorge Sequeiros, who is here, who was training with Victor McKusick and his team in Baltimore, at Hopkins, and he would come to these clinics and that’s how we got to know one another, and we collaborated on a number of issues. And we involved some other people. One of them was Marie Boutté, who was a medical anthropologist and she had done some nursing in Brazil, and was fluent in Portuguese. So she came to see what we were doing in these clinics, and one thing led to another, and she decided to do her PhD in anthropology on stigma about genetic disease. This was the first large-scale study of what it means to be from “the family” of the afflicted. It was really seminal work that she did.

Jorge Sequeiros goes to Porto to start his Institute and five years later, 10 years later, I guess, we had a series of five yearly workshops on Machado Joseph disease. And at that meeting was a young PhD-candidate who had come from Cuba to do her genetic counselling PhD in Porto. And at this casual, you know, interview, we were chatting and she said, ‘You know, we have this meeting in Cuba on ataxia, you should come.’ And I said, ‘I’m there, you know, what do I need to do?’ She said, ‘You need to submit an abstract.’ And this is where providence comes into the telling of these stories. I came home from that meeting and the first patient I saw on Monday morning has SCA2! Well, what sign do you need to go to Cuba? So off I went with my other brother, and we presented, and that was fine, and I thought it would be in and out, goodbye. Well, one of the students approached me and started e-mailing, and one thing led to another, and now 10 years later and 20 visits to Cuba, we’ve been very much involved in helping them set up presymptomatic and diagnostic testing for hereditary ataxias. And the latest thing that should be on that list of good things was a young MD there who wanted to do her PhD, and so she selected this large cohort from this large cohort of Cuban families, the paediatric cases. And she just recently published successfully her PhD Thesis on paediatric onset Friedreich’s ataxia. And so our efforts, you know, sort of were winding down, only just nicely winding down when the lab tells me, ‘We went through this and we found nine families who have SCA3.’ So this thing keeps going on and on and on and on. So when I give this talk to the students I say, you know, ‘Early on in your career, get a disease and stick with it, you know, and see the world.’ And here I am at 75, enthusiastic about working part-time, and I was in Cuba in November again, you know, so I would really encourage young people, there’s a wonderful career path outside of the lab.

I was commuting between Vancouver and Victoria once every three months to provide some clinical supervision there. And the Department Head, new Department Head, didn’t want to have anything to do with any other programme in the province, and so it was either I stop doing that, or leave. And so one day I got this idea in my mind, ‘Jeez, I’m going to have to leave Vancouver. That’s heresy, nobody leaves
Vancouver.' And that led to the snowball effect of recruiting in Kingston, and it just fell into place, effortlessly fell into place. And when those things fall into place like that, I mean you’re on the right road, so I just go with the flow. So the two people that really, three people that really I had issues with were the Department Head and then my biochemist, my biological chemistry, biochemistry colleague, sorry, my biology colleagues, who thought DNA was their thing. And this is in the very early days and eventually things fell apart for them, and the collaboration with Guy Rouleau took off, and it happened for a reason that there was a falling out, because that collaboration with Rouleau would have never taken place and we would have ground along, ground along in this other relationship and not gotten anywhere. So those are two big setbacks or disappointments, both of which I’ve been able to get around.

[5]. GENETIC TESTING, FRAGILE X SYNDROME, RETT SYNDROME & HUNTINGTON’S DISEASE

Well, thinking about the major changes over the last 40 years in my career, I arrived home in Vancouver in 1973 just after the first successful amniocentesis results were coming out. And so we started, it was a very long involvement with women who were at risk by virtue of age. As much as we tried to divest ourselves of this and give it to the obstetricians to do, the counselling fell upon us for advanced maternal age. But, eventually, that morphed into other things. This is before we had what is now standard practice in the biochemistry lab, the ability to study various inherited diseases, lysosomal storage diseases, Tay-Sachs disease, those kinds of things. Now it’s a routine matter. So I witnessed the birth of genetic testing for Tay-Sachs disease in Montreal. We brought it back to British Columbia and screened the Jewish community with their assistance. Then it snowballed into more and more sophisticated cytogenetic techniques, more and more sophisticated biochemical genetic techniques, and then about 1985/86, this business of DNA for fragile X came about, in Kingston for some reason. I don’t know the history there, but there was no end of families with fragile X, and I remember seeing this video yesterday of Stephanie Sherman, who is now in Honolulu, and Sherman’s paradox about fragile X. And she came to Kingston to review the files of my colleague there, Michael Partington, who had about 38 families.

So we were having lunch one day, and I chatted her up and I said, ‘Have you ever seen a patient with fragile X?’ There’s a PhD, basic science researcher, working at the cutting edge of fragile X who had never been in the same room as someone with fragile X in them. Well, as serendipity had it, I was seeing a family that afternoon, so Stephanie came with me and that was sort of a little thing for me with other PhDs who were so welded to the lab, who never got out and saw the patients. And I have witnessed the most profound change in their behaviour. So I’ll give one example; in Montreal we did a project on this other syndrome, and there was a young PhD-candidate who was going to work on this Rett syndrome thing. And she came and spent the day with me at the children’s hospital; I’m not sure why I had a clinic there when I was travelling. And two weeks later, two months later I visited her lab and pictures all over the wall of these kids. You know she really hadn’t understood what this was about, and did she get motivated then. So I insisted that anybody doing a PhD on a human disease got to spend some time with the family, at least one time. So Stephanie started that.

Then molecular genetics just became more and more. We were doing linkage analysis for Huntington’s disease and this was in the mid-eighties. Michael Hayden had started this big institution in Vancouver and he had 17 sites across the country that were sending samples and linkage analysis and that became much more precise with actual gene testing. That then set up a really interesting dynamic. He had done such good work with his team in the whole concept of presymptomatic testing and guidelines and things you should follow, that he and I were approached by the BC Cancer Agency then to do the same kind of protocol for testing for BRCA1 and, eventually, BRCA2. So they really essentially took the Huntington’s protocol and made it into BRCA1, and away we went. So we had a real growth in presymptomatic testing for these cancer diseases. I witnessed the time when the potato blight theory was rampant for spina bifida; I heard something about that yesterday. Well, it wasn’t the potatoes, it was the ink in the paper that the potato chips were wrapped in thing, and eventually the trials and tribulations that led to folic acid.
[6].  **SPINA BIFIDA & FOLIC ACID, OTHER CONGENITAL MALFORMATIONS**

And with that sort of this plummeting reality of spina bifida just was a disappearing nightmare. So I watched that. I also watched some of the interesting politics of that. As a group we petitioned Health Canada to support the introduction of folic acid into the prenatal thing, and that went on and on and on and on, back and forth, back and forth. Well, some little old lady might be pinching pennies and take prenatal vitamins to save money and there’s B12 in, sorry, there’s folic acid in her vitamin, and that suppresses the fact that she’s got B12 deficiency and she’ll get this terribly anaemia, and she’ll get neuropathy. Well, supplement the pill with both, sort of thing, you know. Finally, the Spina Bifida [and Hydrocephalus] Association of Canada called this, ‘Enough already. Ladies, take folic acid.’ Then in 1999 the American powers that be legislated that folic acid be mandatorily added to flours, cereals, food grains and things like that, but not Canada. Oh no, we couldn’t do that. And then one day, just like that, overnight there was a law passed and that was because of free trade. Prime Minister Mulroney had negotiated a free trade alliance with the United States, and we were sending massive amounts of wheat products into the States. And they said, ‘Wait a minute! No folic acid, no trade.’ That was fun to watch that happen.

Then, with the decline in congenital malformations, came an increasing awareness of families’ concerns about the genetics of behavioural issues, the autism, autism spectrum disorder type family, started to come to the genetics clinic. For one primary reason, that was for diagnosis, because with the diagnosis the school board would provide you with an aid, okay? So they flooded in at the beginning just to get in the programme, and then of course with the advent of some of these newer genetic techniques, particularly the deployment of microarray testing, and all the different findings we are, were coming across, there’s a wonderful website in this country called “Unique”. I don’t know if you know about it but if you just Google “Unique” and there’s a “Unique” chromosomal website. If you go on there and click the right button, up comes a listing of all these different chromosomal deletions and all the syndromology, and these wonderful seven, eight page reviews for parents. And this is written by parents for parents, but it’s vetted by medical authorities. This wonderful source, you can put that out.

[7].  **NEUROGENETICS, SCREENING & EXOME SEQUENCING**

I’ve had much more success using microarrays with adults, which is problematic because children’s hospital, ‘this is not an adult hospital, it’s a children’s hospital’, but we’ll sneak them around. Everybody is right now juggling until the Government decides they are going to fund microarrays. So I snuck a few things in. Primarily in my neurogenetics thing, which is probably 75% of what I do now. And finding some really interesting things, that takes me back to the ataxia story. So after seeing many patients with ataxia, my reputation as ‘I’m an ataxia guy,’ a physician, who’s now retired, moved to Victoria concerned about his family history, not so much for himself, but for his daughter who is in her forties and has schizophrenia. And he wants to know if they need to make provisions for her. And that taught me a second or third thing, I’ve lost track of how many things: the neurologists take a neurological family history, medical geneticists take a genetic family history. So when you take a genetic family history you learn all kinds of things about these other non-neurological phenotypes, and this was not a family history typical of schizophrenia, and it was not a family history for typical ataxia, let’s do an array. Bingo! He has a deletion on chromosome 3, he has spinocerebellar [ataxia] type 15, probably the first person in Canada to be diagnosed as SCA15. But in this country and in Europe, which is so far ahead of Canada in many of these things, the rule is after you do the panel, you do a microarray, because it’s 10% of autosomal dominant spinocerebellar ataxia, it’s a big number.

Now we’re on the verge of having access to exome sequencing - and still in British Columbia it’s considered a research priority - but there are ways that you can persuade the provincial insurance people to allow us to send a sample to one of the American labs for exome sequencing. And we’re making all kinds of diagnoses now, which takes me into the future, which I’ll talk about in a minute. But the most recent thing, to bring the spina bifida, the prenatal diagnosis to its origins, I was just looking at television last night about this country’s decision to have a pilot study of non-invasive prenatal diagnosis. So that’s been available to us for a year now, a year and a half in Canada. You have to pay for it, it’s about $800 which is roughly €400 and
400, but the population that’s asking for that are primarily couples who have gone through a great deal of effort to become pregnant, because of infertility issues. They spend $20,000 becoming pregnant, they’re 40 years of age, they’re at risk for chromosomal abnormality, the last thing they want to do is an invasive amnio, and so they’re happy to pay that kind of money.

The people in Vancouver who run the provincial prenatal screening programme have signalled that they’re going to persuade the Government to swap out ultrasound and maternal serum screening and all of that, in favour of non-invasive prenatal diagnosis, because then we won’t be doing amnios, we won’t have the lab culture costs, so we’re in that kind of transition.

[8].  EXOME SEQUENCING & GENETIC ECONOMICS

Well, the future’s here. It very much is here. Here’s an interesting story of two young women that I knew in their pre-teen years with some terrible neurological disorder that none of us could figure out. I did all the biochemical genetics things I could do at the time. They became young adults, they exited the paediatric system, and they didn’t come back. But a year ago the wife, sorry the husband, of the, sorry, I’ve got to get this straight. These two girls have a mother and a father. This mother has a cousin and she’s married. And they have a child who is three. And dad thinks that she has what they have. Don’t think so. But he approaches the medical genetics people and they say, ‘She’s got something, but I think the only way to answer that is to do exome sequencing.’ So he gets on the blower, he gets hold of GeneDX, 5,000 Canadian dollars, bang! Diagnosis. And it’s treatable. It’s an inborn error of vitamin B2 metabolism, which is treatable. So the two-year-old, three-year-old, is now on treatment and improving, we’re about to start when I get back treating these two. Similar stories are now appearing frequently in the New Yorker magazine about families who have done the same. Or they see a geneticist who calls them up three or four years later saying, ‘I’ve got this experimental thing called exome sequencing. Do you want to participate?’ Bang! Diagnosis.

So much so that the American Society of Medical Genetics, the American College of American Genetics meeting was in March, I think, in Utah, there was a whole half day on exome sequencing for newborns. So that’s the future and that is coming. And then finally getting back to my interest in neurogenetics from these repeat diseases, because any autosomal dominant disorder that has a neurogenetic phenotype, is likely to be a repeat. We’ve heard about Huntington’s, we’ve heard about fragile X, we’ve heard about Kennedy’s disease, but there are several others. In Portugal there is a second disease called “Portuguese amyloidosis”, which is a point mutation rather than expansion. It misfolds the protein and accumulates in the liver, but also in the peripheral nerves, and it causes just a devastating peripheral neuropathy, a sensory neuropathy, so you’re not aware that you’ve injured yourself and you get these terrible leg ulcers. And then you have to have a liver transplant. Well, this time last year back-to-back articles in the New England Journal of Medicine talked about the safety and efficacy of RNA interference to knock down that mutant allele.

Why that’s so exciting is because it takes you off into the Alzheimer amyloid story, but also if you look at big pharma, they have done everything in their power to make a new statin for hypercholesterolaemia and they’ve bent the molecule seven days to Sunday and they can’t, the patent’s off. So they’re looking for some other way to block that enzyme and they’ve very much heavily invested in RNA interference. So you’re going to see Huntington’s fall; clinical trials are underway now in North America using RNA interference. And when it goes a whole bunch of other diseases will go. And hopefully, I’ll live long enough to see some of the things happen. But on a more sobering note, I was at a meeting a couple of weeks ago in Banff about these children with these lysosomal storage diseases. And there are 14 children in Canada with this one disease and they’re all on enzyme replacement and as they get older they need more enzyme by weight, and some of these children are consuming $600,000 a year, that’s £300,000 a year, for one patient. They’re covered with some kind of orphan disease thing, but how long can that last?

So I’m a bit concerned about the future, with health economists saying this is not a good use of money, etc. etc. I can see why somebody would make that argument. So I see that as a future problem. But on the other hand, being an Irishman my optimism and all that, more and more people are going outside the medical system and spending money. I mean $5,000 is not a lot of money to get a treatable diagnosis on your child.
Canadians spend a billion dollars a year outside of the country for personalized medical care. It can be anything from a knee to an MRI [magnetic resonance imaging] [scan] to whatever. And the politicians are very frightened by that so we’re seeing the slow, steady rise of two-tier medicine in Canada, where you can get an MRI 10 days from now for €400. That’s not a lot of money. It’s cheaper to get an MRI than fly to Toronto, for example, you know? People fly to Toronto all the time, and don’t think much about it. So if you’ve got some terrible thing and need MRI, that’s what I see. So I see these pushing and pulling. I was going around with my brother in Ireland, and now in your country, and was looking at the headlines in the newspapers and the headlines in newspapers here are exactly the same as the headlines in the newspaper: education and healthcare. The doctors are yelling and screaming about the bureaucracy, there’s downsizing of their attempts to help with the patients, and the schools are all in trouble.

You can go to The Globe and Mail or the National Post or The Times columnist, and get the same headline, same old, same old.

[END OF TRANSCRIPT]

Further related resources: