Norman Nevin

Personal Details	
Name	Norman Nevin
Dates	
Place of Birth	
Main work places	Belfast
Principal field of work	Medical Genetics
Short biography	See below

Interview	
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Biography

Norman Nevin trained in Medicine and Pathology in Belfast, where he worked with Alan Stevenson, epidemiological geneticist, before coming to London in 1965 to do a training Fellowship in Human Genetics at the Institute of child Health with Cedric Carter, also working with Alan Stevenson, now in Oxford. On his return to Belfast in 1967 he established a comprehensive medical genetics service and research unit, making a particular contribution to the prevention of neural tube defects, and also playing a major role in the setting up of the UK Clinical Genetics Society.

Interview with Professor Norman Nevin, 4th November, 2004

PSH. It's Thursday 4 November 2004 and I'm talking with Professor Norman Nevin at his home in Hillsborough, Northern Ireland. What I would like to do to start off, which is what I've been doing with all the people I have seen, is to ask what got you interested and involved in Genetics in the first place?

NN. I began medicine in 1953 and during the course in medicine I had the opportunity to do an intercalated BSc. Now in those early days in 1957, at Queen's University Belfast, we'd only the option of either doing it in anatomy or doing it in physiology. I did it in anatomy and the Professor of Anatomy, Jack Pritchard, as part of the training and as part of the course, sent me every Friday morning to the Department of Social and Preventive Medicine. The Head of Department of Social and Preventive Medicine was Alan Stevenson and his second in command there was Eric Cheeseman, a medical statistician. Now both Stevenson and Cheeseman had done a lot of the research into diseases like muscular dystrophy, tuberous sclerosis, achondroplasia and deafness and they had a deep interest in genetics, and in population genetics, and as a result of that was my first contact with genetics and the way they made the subject was indeed so fascinating that one could almost capture their enthusiasm for it. So I then qualified in 1960 and after doing a houseman's year I went into Pathology and for 3 years I studied in Pathology.

PSH. That was still in Belfast?

NN. That was still in Belfast and one of the interesting things in Pathology in those days is that you had a lot of post-mortems to do. I can remember doing a post mortem on a baby, a stillbirth that had thalidomide and I became interested in congenital abnormalities at that stage. So I did my doctorate of medicine in pathology.

PSH. That was a thesis?

NN. That was a thesis and my subject was indeed the pathology of cerebral concussion and head injuries.

PSH. So nothing to do with genetics?

NN. Nothing to do with genetics whatsoever. In those days we were all encouraged to come into pathology before we began to think of membership. I then went into medicine for a year and this desire to do genetics as a specialty was very strong with me at that stage, but the problem was there was no opening in northern Ireland for this at all. No opportunities to train, so my professor of medicine was Sir Graham Bull, who actually later headed up the MRC unit at Northwick Park in London, and he encouraged me to apply at that stage for an MRC clinical fellowship, at which I was successful, so I had a clinical fellowship for two years. So in 1965 I went off to the Institute of Child Health to study at the MRC Clinical Genetics Unit, which was headed at that time by Cedric Carter.

PSH. Now before we get on to that, I would just like to just backtrack a little bit and you to tell me a little more about Alan Stevenson's unit, because in talking with other people, they have spoken about Alan Stevenson during the time his unit was in Oxford, but I have heard nothing about how he began in Belfast and the kind of work he was doing. I mean you, along with Peter Frogatt, are the people who can tell me more than anyone else about that.

NN. Yes, Alan Stevenson worked with Eric Cheeseman in the School of Tropical Medicine and Hygiene in London and a position for a Chair in Social Medicine came up, that would have been about I think in 1949/1950, and Alan Stevenson was appointed to that chair. I understand that one of the conditions that he made for his appointment or indeed for his acceptance at that post was that Eric Cheeseman, the medical statistician, should come with him. So indeed the two were in Belfast at that early stage. Alan Stevenson's interest was single gene disorders, but really from a population genetic point of view, so that as far as Northern Ireland's concerned, which at that time had a population probably about 1.4 million, fairly compact, very little emigration or immigration, so a reasonably stable population, it was ideal for this type of study. So he set out to do studies such as population study of achondroplasia, population studies of tuberous sclerosis, muscular dystrophy, myotonic dystrophy and these papers all were published in the Annals of Human Genetics, and particularly the work on deafness, and Annals tended to publish all the pedigrees, so that you could go back to these and look at those and I can remember even going back to Stevenson and Cheeseman's paper on deafness and demonstrating very clearly how indeed two deaf people can marry and have perfectly normal children, and identifying the possibility in those early days of multiple alleles causing deafness.

He also did a very important piece of work which is still quoted to this day and that is he decided he would then look at all the possible genetic diseases that existed in Northern Ireland, try to work out the frequency of these and also to collate them, to try and get a picture of the burden of genetic disease in the community. Now those
were early days, because for example when you go back and look at his original data, he'd only one case of Huntington's disease, so quite clearly they were very much under-ascertainments and indeed when you were doing this sort of study with achondroplasia his stillborn achondroplastics were much more likely to be thanatophoric dwarfs, so in fact, although you know you could fault them for those areas yet I think at the end of the day they did come down with a figure which has held up today in terms of most of the population studies of the burden of genetic diseases in the community. So Alan really I think almost interpreted social preventive medicine in population genetics.

PSH. Was he trained in genetics, because I mean he was essentially an epidemiologist wasn't he?

NN. No.

PSH. Would he, as far as you know, have spent any time either at the Galton or any other place where he would have got formal genetic training.?

NN. No, he never had formal genetic training whatsoever. As you say, he was an epidemiologist and was involved in social and preventive medicine but never had formal training, but had this almost as a hobby, an interest in single gene disorders, and indeed when Peter Frogatt was appointed as a lecturer in his department he was given the task to carry out a population survey of albinism in Northern Ireland and Peter Frogatt carried that out and got very interested; for example he got very interested in the possibility that the heterozygotes in a recessive disorder might show manifestation. He invited Waardenburg over, because Waardenburg had described the test where you shine a light onto the sclera and if you look in a darkened room you can actually see spots of light coming through the iris so, to confirm this he invited Waardenburg over to look at this and Waardenburg came over with his wife. I think Waardenburg at that time must have been in his eighties, and not only that, Peter was also interested in the reflectance of light from the hair and took examples of hair from all the parents of the patients that he had identified. Indeed I think he sent these to Barnicott who was an anthropologist, but nothing materialised from that, but all of Alan's work was in fact, and his major publications were in terms of population genetics, burden of genetic disease and I think that paper on the burden of genetic disease, published in Mutation Research, is still looked upon as a classic. I think then the World Health Organisation then asked him to look at the genetic distribution of disease in various countries and the WHO published a report of the frequency of genetic diseases, and that was Alan Stevenson's work at this stage.

PSH. This was before Cedric Carter had done his population studies wasn't it?

NN. It was.

PSH. It must have been about 10 years before?

NN About a decade before Cedric's work. And then I was with Alan in Belfast doing my intercalated BSc. That would have been 1957. Shortly after that, Alan Stevenson was approached by the MRC to set up a population genetics unit and he decided that he would establish that at Oxford and that's how the MRC unit in Oxford came into being at that time.

PSH. That is interesting and I can quite see in terms of developing genetics as a whole that would have been the right decision, whereas for the continuing population studies it was probably not such a good decision.

NN. No, I think you are probably right. I mean it was nice when I was appointed in '67 and wanted to do studies, lets say frequency of spina bifida in Northern Ireland and the neural tube defects, it was easy to do it because you had a confined population, and I know Laurence did the same for Cardiff and South Wales, but going to Oxford it just wasn't possible to do that type of study.

PSH. But I can see now, which is something I haven't seen before, I had been wondering before now, why did the MRC approach Stevenson to create this new unit, but I can see that his track record of this research and perhaps the WHO must have made him the obvious person if one wanted to develop that kind of . . .

NN. I think you are absolutely right, because he really had the quality first of all as an epidemiologist. I think secondly his epidemiology, so to say, was in fact involving single gene disorders and his WHO work on congenital abnormalities and genetic disease made him the obvious candidate for that. But I think he had a third forte and that was the fact that since the time in London at the School of Tropical Medicine his associate had been Eric Cheeseman, a medical statistician and one of the earliest medical statisticians in the UK.

PSH. Did Cheeseman work with people like Fisher or anyone, do you think, or Karl Pearson?

NN. No he wouldn't have worked with Karl Pearson, but he would have been in contact certainly with Fisher. He was a statistician and as I say published with Alan in terms of deafness, and I think with his background, because in those days when you published a paper on population genetics, you had to do heterozygote frequencies, frequency of mutations. Hardy-Weinberg and everything had to be done and Cheeseman was very much involved in that.

PSH. So really in those days statistics and genetics were much more closely connected. He really would have been able to function as a statistical geneticist alongside Stevenson as a more clinical and population geneticist.

NN. Absolutely and when I was appointed as lecturer in human genetics in 1967 at the Queen's University Belfast, my appointment was in the Department of Medical Statistics.

PSH. So Norman, we have finished talking about Alan Stevenson and we interrupted your own career to the point where you left Northern Ireland to go to the Institute of Child Health. Am I right that John Fraser Roberts had retired by then and Cedric Carter was head of that Unit?

NN. That's right. John Fraser Roberts had retired and Cedric was head of the Department at that stage and those were certainly early days. I can remember vividly attending Cedric's counselling clinics.

PSH. Tell me about them.

NN. Well Cedric's counselling clinics were certainly very brief and to the point. Now lets say for example there's been a family who had had a child with cystic fibrosis. All the counselling involved was taking the pedigree, usually on a card and deciding what the inheritance was and then giving a risk of 1 in 4 and that was it. Very brief but one saw a lot of patients with single gene disorders through that particular clinic.

PSH. I mean Cedric was always very interested in genetic counselling but it struck me that he was a man of very few words and, would I be right that in terms of the family on the receiving end, he wasn't really a very receptive....

NN. What I was going to say in fact that there was no empathy that developed between Cedric and the family and indeed it was always very brief. I know when I was counselling families back in Belfast, I would be spending half an hour maybe to three quarters of an hour with each family. You'd be trying to build up a rapport and a relationship with the family and trying to break to them the news of a high risk and what could be done, but in those days all you could do was just say well, this is cystic fibrosis, it's recessive and you have a 1 in 4 risk of it happening again, and very very little coming and going about the disease or how it affected the child. Indeed even with something like Down's syndrome, as you know there was no cytogenetics in those days. That was 1966. there was no cytogenetics at Great Ormond Street and we usually had to call for a technician from Paul Polani's unit at Guy's and they would come across, take the blood sample and go away again and that's all there was in terms of Down's syndrome. But one certainly saw, because of the institute, one saw a wide variety of interesting single gene disorders, and he had a social worker with him at that time who would visit the families, get pedigrees and so forth, Kath Evans, she really was Cedric's right-hand man. Indeed in the research projects that Cedric was doing at that time, Kath did a lot of the leg work in going out, visiting the families, getting the pedigrees, getting the details.

PSH. Would it be fair to say that Kath was the person who really explained things or listened to or related to the families?

NN. Very much so, she was a very caring person and had a good personality and could sort of elicit from the family details and so forth, and obviously she passed on a lot of information to these families.

PSH. How about you yourself, were you involved in the clinics or not really?

NN. Well in a sense you were acting as an observer, you just sat and observed really, and you had little opportunity of actually participating, although if it was an interesting genetic disease you had the opportunity of examining the patient and learning in that particular way.

PSH. What was your own specific project for this studentship?

NN. When I went to the Institute of Child Health, Joan Slack was working there at that time. She was interested in genetics obviously, but she was interested in the genetics of ischaemic heart disease, one of the early pieces of work which was attempting to try and look at what was the genetic component of ischaemic heart disease. And I remember I linked up with Joan, because we were interested in familial hyperlipidaemias and I had the opportunity to visit various hospitals, such as the Middlesex, and actually collect data and pedigrees from 55 families with hyperlipidaemia. As far as the classification of the hyperlipidaemias were concerned at that time, it was based on the level of the cholesterol, the triglycerides and a combination of those, and this became known as the Frederickson classification, and I

published that work in the Journal of Medical Genetics and we were able to show that there were different types of familial hyperlipidaemias. Obviously the large one was the familial hypercholesterolaemia one, but we identified triglyceride families and mixed triglyceride families. At that time it was one of the early papers on the familial side. At the same time, Joan Slack was publishing work on why is it that women develop ischaemic heart disease about a decade later than men, and she was working this out from the mortality figures and showed indeed that women had this ten year protection. So that was the area, hyperlipidaemias, but it was interesting that one could do that work, collect all the data and then get it written up and I remember one of Cedric's strong points was, that obviously you could submit a paper say 55 cases of hypercholesterolaemias, but the editor wasn't going to accept 55 pedigrees because of the space, but Cedric had ways in which you would say let's just record here on a line, the number of sibs, male and he put in the date of birth, female, date of birth and so forth so you could have the sibs, then you could have the parents, male, father, date of birth so forth, and you could build up the pedigree from this and you could go back and do the analysis of the work. So you know, I completed that work and had two papers published from that on hyperlipidaemias.

PSH. I mean, that tradition of publishing raw data

NN. Yes.

PSH. It was very strong at the time and hugely beneficial. I remember someone [Bette Robson] who I was seeing talking about Penrose, said something very comparable and I think Penrose had asked her to look at a paper and then came back the next day and said "What do you think?" She said "well I haven't had time to read it or read the text fully" and Penrose had replied "Oh don't worry about the text. You should just look at the tables". And I mean everything is there in these tables.

NN. That's right and you can go back and you can do a further analysis on it and indeed if you go back you can compare it with other collections and pedigrees that have been done. So I worked with Cedric for probably the best part of a year and a half.

PSH. Who else was there at the time in terms of genetics, with Cedric. Was Sarah Bundey there then or . . .?

NN. No Sarah had left by then. There was an American called Anne Child was there. There was Joan Slack, who was mainly in the lipid disorders and there was someone else, and his name eludes me at the moment, who had done quite an extensive twin study and I'm sure it will come to me.

PSH. Marcus Pembrey was not there yet. That was later.

NN. Marcus wasn't there. Michael Baraitser wasn't there at that stage. That came later.

PSH. It was quite a small unit.

NN. It was a very very small unit at that stage.

PSH. It always strikes me that if you compare that unit with say the Galton, in the Galton there were always lots of people coming for a few months from here there and everywhere, whereas Cedric's unit was very focused and very compact.

NN. Michael Laurence was liaising with Cedric at that time and again, one of Cedric's interests was in the neural tube defects, as was Michael Laurence, and I think that drew them together initially in '65/'66, but certainly I saw quite a bit of Michael when I was there. But it was a very small unit, very productive unit, in the sense that Cedric always ensured that if you started a piece of work you completed and got it published as quickly as you can, and I learned a lot from that unit.

PSH. Was it up in the little attic?

NN. No, it wasn't, it was actually on the first floor of the Institute of Child Health.

PSH. That's the new building.

NN. That was the new building; Tanner the paediatrician and growth expert was on the next floor and I know that Cedric and he also had liaisons together in terms of research.

PSH. Were there any labs attached to that unit or not?

NN. Only the research lab which was mainly geared around Joan Slack's work which was the lipidaemias

PSH. No chromosomes.

NN. No chromosomes or blood groups at that time. That came later. Certainly when I left there was no chromosomes. They were still using Paul Polani's unit to undertake chromosome analysis.

PSH. When you were in London during this time, how much did you see of the other London people like the Galton or Paul Polani's unit?

NN. I saw quite a bit at the Galton because C. A. B. Smith, statistician, was there and he ran a course in statistics for geneticists. It was every Monday afternoon that course and Cedric arranged for myself to go along and to participate in that course. Paul Polani's unit, I knew Paul and I saw him quite frequently, but that was early days for genetics, so you didn't have the multiplicity of units that you have today in London,
and we were quite close to Queen's Square [Institute of Neurology] and Queen's Square ran lectures, I think every Tuesday evening, on aspects of neurology like epilepsy or muscular dystrophy. I was encouraged to attend those regularly as well. But certainly it encouraged me to continue a course in genetics.

PSH. So can I ask, by that stage were you fairly definite that medical genetics was going to be your career as opposed to just an interest?

NN. Yes, I actually set out and that's why I applied for the MRC Fellowship at that time. I wanted to go into a career in genetics. I didn't know what it was going to lead to, because obviously the question of positions, posts and so forth is something that's . . . but then having finished with Cedric, that was 18 months, I had arranged to do the final 6 months in Oxford with Alan Stevenson and I had been communicating with Alan Stevenson for some time, trying to set up a project, so when I went to Alan's unit, my project in fact was to look at the population of tuberous sclerosis in Oxfordshire and I linked up with an ophthalmologist who was at that time working in the Radcliffe, Bill Pearce, Canadian, and we would go out together to see a family. Now Bill had a little portable fundus camera and one of the things we really wanted to do was not only just a population study to look at the families' genetics, but also to try and look at the frequency of the tuberous sclerosis lesions on the fundi. So he would take photographs of the fundi and indeed we would dilate the pupils and take photographs. Now that was interesting because at that stage we knew that Van der Hove had described the fundal lesions and he had described it in 6 out of 6 patients.

I think our study in fact showed that, if you do dilate the pupils, and you do have a good look and perhaps if you have an expert ophthalmologist on board, that the frequency is very much higher than 80%, and again that study was published in the way that Cedric had taught one, in terms of being able to record the pedigrees of those families and to record the clinical details. So that took me up to the end of my clinical Fellowship.

PSH. Can I ask, on that study, did you have any concept that germline mosaicism might be something to watch out for or . . .?

NN. It was something that didn't even cross one's mind at that time, and it is interesting that later on, with the introduction of molecular genetics, indeed I published a family with tuberous sclerosis and it was the first family in which we convincingly showed that from a normal female in the family, that obviously the mutation had been in the germline and she had passed it on to, I think four out of seven of her children. But in those days, none whatsoever, and indeed even when looking at those pedigrees from the Stevenson, yes you could see anticipation
for example, but it was always explained in those days that this was the consequence of better diagnosis and the family knowing about the existence of the problem. But there were a lot of those concepts in genetics which only appeared later as the specialty developed.

PSH. Can I also ask you, when you were looking at these families, did you do things like skull X-rays or anything, or was it a home-based study very largely?

NN. It was a home-based study, but where there was an opportunity to take X-rays one took skull X-rays, hand X-rays and certainly you could demonstrate the skeletal changes, but it was amazing I think, in those days of

doing studies like hyperlipidaemias and tuberous sclerosis and the Stevenson work, just how much you could do without the sophistication of technology.

PSH. Yes, I remember that from my myotonic dystrophy work. You could take a lot around with you, couldn't you, and do things in the home.

NN. Yes. Yes. Yes.

PSH. Who was at that time, remind me which year are we? About 1960?

NN. We are about 1966.

PSH. So who was in Stevenson's unit?

NN. Well at that time in Alan Stevenson's unit I can remember Martin Bobrow. Martin Bobrow was working in cytogenetics at that time. I remember Peter Pearson. Peter Pearson was working on, again cytogenetics and cytogenetics of the horse at that stage, and I remember Clare Davison. Clare Davison had been working on mental handicap, particularly the X-linked variety, and had published a monograph

PSH. I remember that.

NN. On mental handicap, and that's just another sideline, because she and Alan Stevenson wrote one of the early books on genetic counselling and risk. I think that was before the publication of yours.

PSH. It was.

NN. Because there was nothing really available for clinical geneticists at that time apart from Stevenson and Davison's book, and then yours obviously changed the whole face of clinical genetics.

PSH. I remember they were one of the first to bring Bayesian calculations in, because I remember that was at the same time as Tony Murphy at Johns Hopkins was teaching that, where I was at the time.

NN. Yes indeed, if you go back to Davison and Stevenson's book they had appendices at the back on Bayesian calculations to try and work out, I think it was one of the first clinical genetic books that tried to address the issue of calculating risk, and I know it was one that I used quite a bit in those days. Charles Wells had just left before I arrived, just left Stevenson's department. Charles was a dermatologist and he had been working with Alan Stevenson on the population genetics of ichthyosis and I think he had published. He had an MD thesis, two volumes actually, I can remember it now on X-linked ichthyosis. So a lot of the early geneticists came through Alan Stevensons's department in Oxford. John Edwards had been there. I think Jim Renwick had been there for a very short time and Marco Fraccaro had been through that unit as well and George Fraser was another one who had been there. But when I went there it was Martin Bobrow and Peter Pearson and Clare Davison were the main ones present at that time.

PSH. Was there any particular area of research that was Stevenson's own at that time, or was he by then more or less running the unit and other people doing most of the projects?

NN. No, I think that he had an interest, which I find quite strange in the sense that when he was in Belfast it had been population studies. Yes, that was continued when he went to Oxford, but he took an interest in cytogenetics which really indeed hadn't been his forte because wasn't a laboratory person. But when I was there, most of the work was being done by his research fellows, although he still was retaining an interest in radiation and chromosomal breakage at that time.

PSH. One or two of the folk who I talked to said that Stevenson was a very cyclothymic person, he had phases of being depressed and phases of being manic, and that created quite a few difficulties in terms of promises of things made when he was manic which didn't quite turn out.

NN. Didn't materialise.

PSH. I mean did you see anything of that?

NN. Oh no, you are quite right, he had his ups and downs and indeed during his ups, full of enthusiasm and, but there were periods when he could be quite down with it. Yes, I know that from conversation around coffee time that there were quite a number of people who it's hard to believe, because of the sort of personality, although I know my daughter was, that would have been '67, my daughter would have been about 4 and yet when I brought her in Saturday morning he would take her into the tutorial room and draw for her on the board and you know really was very warm in terms of that, but I look back on him and certainly he was one of the early pioneers as far as population genetics was concerned.

PSH. Norman, we have reached a point now where you returned to Belfast and remind me again, which year was it you came back to Belfast?

NN. I came back on 1st October 1967. Having completed with Alan Stevenson, I was looking around for a post to continue a career in genetics. At that time the number of units in the UK were quite small, because I can remember when I went over to work with Cedric Carter in '64/5, one of the first things he got me to do was to act as a tutor to a British Council course for potential European geneticists and rather than sort of set this up as a series of talks day after day, I decided that the best thing to do was to take them round the existing units which were involved in genetics at that time. Clinical genetics. So I took them to Liverpool, to Cyril Clarke's department of medicine, which indeed was focused at that time on rhesus disease and leukaemias and genetic disease and the other person was David Price-Evans, doing pharmacogenetics at that time.

PSH. It's interesting that people now talk as if pharmacogenetics was completely new, but it started nearly 50 years ago.

NN. Not at all, in those days he was leading the field in this exciting area, anti- tuberculosis drugs which produced peripheral neuropathy in people was due to the fact that it was slow metabolism and the ground work for pharmacogenetics was laid at that time, so they were able to get exposure to these aspects and then from there I went to Professor Ferguson-Smith's unit in Glasgow, and Jim Renwick was also professor at that time and Jim was working on linkage. Ferguson-Smith was working on cytogenetics and indeed those were the early days of culture of amniotic fluid cells. From there I went to Alan Emery's department in Edinburgh and then to Alan Stevenson's unit at Oxford and then back to London, so indeed the number of units then were very small, so the chances of getting a post were very limited at that time. But fortunately a position came up for a lectureship in human genetics in the Department of Medical Statistics, Queen's University Belfast, so I came back to Belfast, 1st October into the Medical Statistics Department which was Eric Cheeseman, who now had his own department at that stage.

PSH. He had stayed in Belfast after Stevenson had gone to Oxford is that right?

NN. After Stevenson went to Oxford he stayed in Belfast. With Stevenson going to Oxford and a new Professor coming to the Department of Social and Preventive Medicine, John Pemberton, the Department split and Medical Statistics became a separate department. I think one of the early medical statistics departments in the UK. Cheeseman's research then went away from genetics, and he was involved mainly in a lot of the early work on record linkage and that proved to be a valuable background, but when I came to Belfast into Cheeseman's department, his advice was to me: "develop genetics as you want to develop it as a clinical speciality. I will not interfere with the direction in which you take it".

PSH. That was very nice.

NN. Well that was very, very good advice, because I said to myself, really what one wants to do at that stage is to build up a strong clinical base, so that clinicians - paediatricians, obstetricians could see the relevance of clinical genetics within a medical environment, so that was good advice and I had the freedom to do so. It
wasn't easy when you are single-handed. One of the first things I managed to do was get a grant to employ a health visitor and that was Wendy Johnston, who in fact had been with me until her retirement from 1968, and so she was one of the early people involved in the genetic nurses' development and society. She was involved in the genetic counselling and also helping with research projects which we subsequently developed in Belfast, but we built up a very good clinical genetic unit and we initially had clinics in the hospital in which we were based but eventually spread out and had satellite clinics in every major hospital within the province.

PSH. At what stage did you develop a cytogenetics lab in Belfast?

NN. When, in 1957, when I was doing an intercalated BSc course, the Reader in embryology, Dr Reynolds Morton, was interested in cytogenetics. That was'57 and he was trying to develop techniques. Initially his work

involved looking at samples of animals that had died at the zoo or what have you, then eventually he moved in to look at human chromosomes. When I came back in 1967 he was providing, not a service, but if people with Turner's syndrome or Klinefelter's syndrome required chromosome tests, he was doing it at that stage and also looking at Down's syndrome. I had only been there about a year when Dr Reynolds Morton had a heart attack and died and so I took over the cytogenetics laboratory at that stage.

PSH. Was that in the department of pathology?

NN. No, it was in the department of Anatomy and I had one technician, Ann Foster, and then there was an anatomy technician who was also doing some work there, a chap called Bernard McLaverty. Bernard McLaverty actually came to me once and said "you know I don't like this work. I want to be a writer" and indeed went off to Queen's, qualified, got his degree in English literature and is a very famous Irish writer at the moment, and he has written books like Cal, and these have been made into film and into stage plays.

PSH. Does he ever bring his early chromosome work into his plays?

NN. Oh yes, very much, he brings in his anatomy and early works, into his plays but I took it over at that stage and obviously with the development of technology, sort of brought it along. We were fortunate in Belfast in that it was all under one umbrella, the clinical side, the cytogenetics side, eventually the molecular side and then, also before I left in 1996, I didn't leave in 1996 but in 1996 I also established the genetic cancer clinics at that stage, and we had it all under the umbrella, which makes life a lot easier I think for geneticists, but there weren't many units that had that. Your unit was one very similar.

PSH. Manchester

NN. Manchester and Glasgow I think had this but now it tends to be a bit more fragmented.

PSH. So when you came back did you have any specific research plans in mind, or were you more concerned with just getting the infrastructure going?

NN. Well I think first of all, getting the infrastructure going and getting funding in those days, which was extremely difficult and indeed to try and persuade people that this was a developing service, but I was also very much interested in research at a number of levels. First of all, quite clearly as a clinical geneticist you see interesting problems, you see interesting families, interesting diseases, so I always made it a rule to investigate them and hopefully maybe publish some of these. But the big challenge really coming back to Northern Ireland was the situation with neural tube defects. We had, from early work that I was doing, we had a prevalence of 1 in 100 babies born either with anencephaly or spina bifida, indeed like South Wales we had one of the highest incidence in the United Kingdom and indeed in the world, so that was a big challenge. So one of the first things I started to do, having had the experience with Cedric Carter collecting pedigrees and documenting the information, was to carry out first of all an epidemiology study. How common were these problems? Now the advantage of Northern Ireland is that

population in those days of 1.5 million and very good records. The children with spina bifida who would eventually have to have surgery would have to come to the one paediatric hospital for surgery. Children born with neural tube defects, there are only about 5 major obstetric hospitals and I had good liaison with all the people there, so we did a very good ascertainment of the neural tube defects and then we moved into the study of the families and we collected pedigrees of all these families and then published them to try and work out what were the recurrence risks of neural tube defects. In those days, that was the early seventies, we were having families with 3 and 4 children with neural tube defects and today we just don't see that at all. It is one of the very positive developments that has come out from clinical genetics.

PSH. Did you find a lot of stratification? I'm thinking again, the South Wales situation was that up the valleys, where there was a lot of deprivation, again there was a frequency of up to 1%, whereas in Cardiff and some of the more prosperous areas, much lower. Did you find those same differences, or was it more widely spread?

NN. No, I found exactly the same sort of differences, because I can remember that taking the data and looking at them in terms of what was the old registrar general's social classification 1-5, and when you break into that stratification there is no doubt that social classes 4 and 5 had the highest incidence of neural tube defects, whereas social classes 1 and 2 had the lowest incidence of neural tube defects. So quite clearly in those early days there was evidence that in the "underprivileged areas of poverty", you had the highest prevalence of those abnormalities.

PSH. Can I ask, with all the epidemiology work that had gone on in Northern Ireland, had people already looked specifically about possible environmental factors and neural tube defects, or hadn't it been studied in its own right?

NN. No, I think in terms of looking at environmental factors one would only examine the sort of environmental factors that one found in any epidemiological study that you were looking at, factors such as social class, occupation. From that point of view, but in terms of looking, let's say specific details from nutrition or areas of pollution,
because we know that living near landfill sites you've got an increased incidence of neural tube defects or other congenital abnormalities. No, that hadn't been looked at specifically. What we had done up to that stage was to look at the epidemiological prevalence of the conditions, look at the family structure and when you were looking at the family structure you were looking at other sibs, other members of the family, uncles and cousins and also looking at whether there was any consanguinity. Just using those factors at that early stage.

PSH. So when was it you got involved in the various nutritional studies of neural tube defects?

NN. Well I think we always had this gut feeling that when you looked at social class 4 and 5 they were certainly the highest prevalence, then one began to ask the question about could there be a relationship with diet and I remember one of the early theories, which was Jim Renwick's. Jim Renwick was

interested in the concept that, if you look at some potatoes which tend to be green, the solanin is just under the skin and he was wondering whether or not this could act as a poison on the foetus, and we know that Northern Ireland for example, when you looked at the consumption of potatoes per head of population, we had the highest level of potatoes and then you know that Ireland always suffered from blight and infected potatoes, so Jim had put forward that idea that is because mothers ingested infected potatoes, or potatoes that had solanin. Now I think the only paper that was ever published, as it were, to refute the concept at an epidemiological level, was one that we did ourselves. Because of the high incidence of neural tube defect, we had access to many mothers who had had a previous one, so we knew these mothers were at risk. So we saw a lot of patients at our Genetic Counselling clinics because of neural tube defects. Now I never discouraged this, because it was an interest, and I know certainly many geneticists would leave this in the hands of the obstetricians or the paediatricians, but we encouraged these families, so I had access to these patients and I remember getting a group of these patients and saying to them, well look, I want you to collect dietary information, and they kept diaries and they were very meticulous, and then we moved on and said well lets ask a group maybe to avoid eating potatoes, which is not an easy thing to do, but these mothers did it and eventually what we ended up with was certainly demonstrating very clearly that avoidance of potatoes made no difference to the recurrence risk of future children.

PSH. Was that a prospective study?

NN. That was a prospective study and it was published, and I worked with a medical statistician at that time called Desmond Merritt and we published that work and it certainly refuted Renwick's, but Jim at that stage I think had just moved to the School of Hygiene and Tropical Medicine in London and he still held onto his theory. I can remember him at a clinical genetics meeting actually speaking on this and he was
adamant about his theory and found all sorts of ways of actually trying to refute any evidence that was put up against this, and then I think he got involved in mouse work and trying to feed mice and so forth, and then tragically Jim died, but certainly what he did, even though his idea was totally erroneous, what it did it began to focus people's minds on the importance of diet in neural tube defects. I then became involved with Dick Smithells at Leeds. Dick had moved from Liverpool to Leeds, and his interest was in neural tube defects and Dick had done an experiment whereby he had taken samples of blood from a thousand women before the 12th week of their pregnancy and these samples were analysed for a wide spectrum of vitamins and he waited then until all the babies had been delivered and out of the thousand there were 6 infants born with neural tube defect. When he then in retrospect went back and looked at the vitamin levels in these 6, they turned out to be the individuals who had the lowest folic acid level. They also had low B12 and they also had low vitamin C.

At that stage we decided to recruit, and Dick contacted me so I was happy to go in with them. Rodney Harris' Liverpool group as well and we decided we would try and see if we could prevent neural tube defects by supplementing those at risk in terms of their diet. Now because folic acid, B12 and vitamin

C, basically what we did was to pick up a MIMS, look through it to see if there was any medication that could give all of those and the only one was Pregnavite 40F. Pregnavite 40F provided the mothers with .364 milligrams of folic acid a day. So we actually took a group of mothers and we put them on to Pregnavite 40F, one tablet, 3 times a day before they conceived and continued it through until they had missed their second period. And we demonstrated that the risk of recurrence could be reduced from 4.6% down to 0.8%. And that work has been published over a series of papers. Indeed when I took the Belfast data alone, we had by far the largest number in the multi-centre study. Our data held up exactly the same. So it was quite clear that this was beneficial, but the criticism of this was that it hadn't been done as a double blind trial. Now the reason for that is that one ethics committee stated that you couldn't withhold vitamins from a mother who was pregnant. Another ethics committee said it was wrong to give it as early as we had planned and because of that we couldn't pursue this in an ideal way. Now Mike Laurence in Cardiff had also been working on neural tube defects and also on nutrition, and he had been giving his patients folic acid rather than the multivitamin preparation. And Mike also demonstrated that if you give pre-conceptional folic acid that you can reduce the risk of recurrence. Now his work too was criticised. Again because he had tried to design his as a double blind trial but because patients dropped out and so forth, he was criticised. But those were two early pieces of work that were pointing very strongly to the fact that neural tube defects and vitamins were related and that you could prevent the recurrence by actually supplementing pre-conceptionally a mother's diet. It wasn't really accepted and I think it took, I can't remember exactly, but I think it took probably the best part of 10 years from that early work, before the MRC set up its trial, and the MRC trial convincingly showed that by supplementing with folic acid, that you could reduce the recurrence of neural tube defects. So the field moved on from that and it became accepted. I can remember attending a Government committee on the whole question of folic acid supplementation, it was chaired by June Lloyd and she made the recommendations eventually to government that you could prevent neural tube defects by supplementing with folic acid. So that was a lovely piece of work to be involved in, because you know Cedric had always taught us in a sense, that you know, the work, these common birth defects which were multi-factorial, there probably was a genetic background, but there was also an environmental influence and I think this clearly was the first congenital abnormality in which it was demonstrated that you can manipulate the environmental arm of the causation and actually reduce the recurrence risk. Then, as you know, eventually it moved into the area of being able to try and prevent recurrence. Now I can remember, when I came back and began this work on spina bifida, you'd see something like 260 children admitted to the paediatric children's hospital a year because of neural tube defects. Now when you walk into a paediatric surgical ward, you rarely see a child with spina bifida and I think that is one of the big developments in clinical genetics, because many of the people who were involved in that work were really clinical geneticists. Rodney Harris was involved from the Manchester point of view. Mary Seller from Guy's hospital was involved also on the London side of that.

PSH. It always interests me how for many of these major developments, which go way beyond medical genetics, it's been medical geneticists who

have been the instigators, in much the same way as Cyril Clarke was with the rhesus, when you might have expected it was the obstetricians or the immunologists, and there have been a series of things like this where
NN. Absolutely

PSH. Medical geneticists have been right at the centre.

NN. Well certainly Cyril Clarke's work on the rhesus is a very good example. I can remember coming back to Belfast in 1967, I established in November 1969, as it were my first prenatal clinic. I was very keen on developing joint clinics, joint clinic with the obstetricians, I had a joint clinic with the ophthalmologists. I had a joint clinic with the dermatologists, but I can remember when we started that clinic, Professor Charlie Whitfield said you know you can use the rhesus clinic, and you would go along there and there would be 30 or 40 women waiting for an amniocentesis for rhesus disease. And now you don't see one at all. Again, as you say Peter, interesting to see that developing from a medical clinical geneticist perspective initially.

PSH. And also important that it's put on record, because people coming into medicine now don't see it and they forget this ever was a huge problem, both neural tube defects and rhesus, and it's almost taken for granted.

NN. No, I think you are absolutely right and all they've got is to go and maybe look at text book photographs of these and that is so important. I can remember, because one of the other areas that I got involved in was the European scene and you may remember that after the thalidomide issue in 1961, that it was realised how important it was to have registers and one of the positive things that Alan Stevenson did for Belfast was that he established a congenital register on all births. Again it flowed from his work with WHO and the work he had been doing with the burden of genetic disease in the community, but he established a record system at that time where every baby that was born, it was recorded what abnormality that baby had if it had an abnormality. So there was in '61 the beginning of a register. When I came in '67 the European scene was interested in establishing records. I remember Jo Wetherall, who led that EUROCAT register, coming to Belfast and indeed took on board the format that we used, so that now that system is practically in every European community and that was valuable because it showed the decline in neural tube defects, but also it is there that you have got a baseline to go back on to look at if you've got a query environmental problem that crops up, that might be causing abnormalities. So Belfast was leading that in terms of registers and now it has become accepted fact.

PSH. Can I ask about one person who you may have had contact with. Nina Carson, inborn errors work. She was a remarkable person.

NN. Nina Carson was attached in Belfast to the Department of Child Health and the clinical biochemist at that time was a man called Desmond Neale. Nina was interested in the amino acids and one of the projects she was involved in was looking at the amino acid profile from those who were mentally handicapped. We had at that time a very large hospital called Muckamore Abbey for the mentally handicapped and she was screening

many of the patients there and it was as a result of that she recognised the first case of homocystinuria. She published that with Desmond Neale and some of the paediatricians at that time, but she was very interested in the screening for inborn errors of metabolism. In addition, Belfast established in the '60s not only the register for congenital abnormalities, but every newborn baby had a heel prick done and it got three tests and Nina was interested in screening for phenylketonuria, methionine and homocystinuria at that time. Again at that time you didn't have to get the consent. I know they are going to introduce screening in the UK and there's a lot of heart-searching about how you get consent and what happens if people refuse, but in Northern Ireland in those days, you know we just went ahead. It's done and it's still happening, no consent but yet we have every baby that's born has its heel prick done and Nina was interested in things like the frequency of phenylketonuria. By the way, we have again in the UK, well, apart from the gypsies I gather in Cardiff, we have one of the highest incidences, one in every three and a half thousand newborns are going have phenylketonuria, and one in every three and a half thousand have hypothyroid disease, all coming from the screening, which means you can have effective intervention in terms of treatment of those patients and again screening for phenylketonuria. One would have liked to have develop that further, but we are just limited to the three diseases at the moment; PKU, hypothyroid disease and the third one is cystic fibrosis. So that's been going for well over 30 years, screening.

PSH. Another colleague that you had of course for many years, was John Dodge in terms of the cystic fibrosis work.

NN. Yes. John came as a lecturer in the Department of Child Health and then when his predecessor Ivor Carré retired John was appointed Professor of Child Health, and John's interest has been cystic fibrosis and we have a very high incidence of cystic fibrosis. I can remember with my brother, who is a Reader in Biological Sciences at the University of Ulster and Aileen Redmond who ran a clinic for cystic fibrosis, doing a population study, and we indeed found that something like one in sixteen hundred babies that were born in Northern Ireland had cystic fibrosis. Now I think the higher incidence that we have compared with the mainland is just simply because we have probably got a better ascertainment, having neonatal screening plus a very good central clinic, but John's very much interested in the whole field of management and treatment of cystic fibrosis and I think he has made a major contribution as far as the UK has been concerned in that area.

PSH. Norman, the last area, because I am wearing you out, taking up too much time.

NN. No no no, you're not taking up too much time at all. We're fine.

PSH. Well the area I would like to finish up with is your involvement with the forming and development of the Clinical Genetics Society in Britain. Can I ask, were you involved in the very first discussions about forming this?

NN. Yes. I'm not quite sure who the initiative came from, but I think it probably was Cedric Carter, and it was in '68/'69 the preliminary discussions really began. It was the whole question of having a group, in fact the word

group was used very much in the beginning, a group that would be interested in clinical genetics. There was the Genetical Society. There was the Royal Society of Medicine, but there wasn't any forum really for clinical geneticists. So Cedric did his homework very well and he was certainly very ably assisted by Sarah Bundey, who was also a driving force in developing the Clinical Genetics Society, and they wrote around to find out about expressions of interest and there was really a good response from that from all of the regions, and indeed Peter, the papers I have given you actually document some of the respondees and also the responses and where they have come from so it was quite clear that there was a desire there to form a group who would be interested and the aim at that time was to share experience in diagnosing of genetic diseases, share experience of how you advise the families and so forth, and he then wrote, I think he first wrote to the Genetical Society, David Hopwood was the President at that time and it was to see in fact if there was a possibility of linking up with the professional society, and the response obviously from the Genetical Society was very positive, but it was clear that we would have a problem in terms of being able to hold joint meetings and so forth, so I think that was set aside. The decision was then made to call a meeting and the first meeting was held in the Institute of Child Health Lecture Theatre on Friday 1 May 1970. It was a good turn out, in fact there were 87 people turned up. From that we had a few presentations and I saw this morning that you actually showed that programme.

PSH. Of course I was in America at the time, so I missed out on

NN. You missed out on being a founder member.

PSH. I did.

NN. But I have actually, and I'm going to give this to you. I have actually got an account of the, because what happened is the first part of the meeting was clinical presentations. Joan Slack for example presented her work on ischaemic heart disease and the hyperlipidaemias, then we broke for a cup of tea in the mid afternoon and then we had a business meeting and I've got an account of that business meeting. I don't know whether you've got that or not?

PSH. No. I haven't.

NN. Well I think this will be very valuable for you to have, and it states that Cedric chaired that meeting. There were 87 people present.

PSH. That's a good number.

NN. That was excellent. It was first class and it was proposed that a new group concerned with medical genetics be formed, and it was agreed. Now, there were a number of issues that arose even from that statement and the first one was 'should it be a medical genetic society or should it be a clinical genetic society' and I remember the proponents of each view. One was Alan Stevenson and Alan was very adamant that it should be 'medical genetic society' and the other one was a another Alan, Alan Emery and Alan Emery was very adamant that it should be a clinical society and then what happened

in fact after that discussion, Alan Emery proposed the title of Clinical Genetics Society and that was accepted. I think this was a very good decision, and it is interesting to see that this is, well, to some extent was followed, but in recent years they have gone back to one venue. Cedric was adamant that indeed it should not be confined to London, but that it should visit all of the other genetic centres at that time. I think the reason for that was that it would give moral encouragement to units that were developing at that time.

PSH. I think that was hugely beneficial, certainly I remember when it came to Cardiff, you know the next year in early '72 it was a great stimulus for Mike Laurence and myself to involve anybody interested in genetics.

NN. Well, I think not only did it encourage the unit, but the unit had the opportunity then of involving those in whom genetics was of interest to their specialty, and I think that was a very, very good decision to make, and indeed it came down to the bit that two meetings a year was actually proposed. And the question of being affiliated to another organisation arose. There had been discussion about the Genetical Society. There had been some discussion with the Royal Society of Medicine to have a separate section and I think at the end of the day, following that discussion, we decided to move down and have a Clinical Genetics Society which was independent and you will be interested to know that that was proposed by Professor Alan Emery, who formally proposed the formation of an independent group concerned with clinical genetics and it was seconded by Mike Laurence and Dr Raine at that time and
people accepted that. Then obviously, what sort of structure to manage this, and I think it was decided at that meeting that there should be a sort of triumvirate in London, Cedric Carter, Paul Polani and Sarah Bundey, who would do the management initially. I may be wrong in this but you know I think the bulk of it was carried by Sarah and Cedric, but it was great to have Paul there, and the other decision that was made was to have from each of the regions, Wales, Northern Ireland and so forth, to have representatives on the Council. The other issue that was raised at that meeting, and that was the question of demonstrating patients, because in those early days I can remember going to Edinburgh, to Alan Emery's unit and actually patients being demonstrated. The question if we were going to have a clinical genetics society was we could well have technicians involved in that society and would it be right to demonstrate patients? Now that was interesting that Alan Stevenson and Paul Polani raised the issue, and they asked that the committee should consider the ethical and legal aspects of holding clinical demonstrations of patients before audiences who are partly non medical. I know Alan Stevenson for example, and I have given you some letters there in the documentation, wrote to the BMA ethics committee at that time, got a feedback from this and there were other issues that were discussed as well. Minor issues, the questions of access of the public and the press and so forth, and fortunately that got thrown out, but that was the beginning. At that time again, I don't know whether it happened until later, but the question of if we were holding a meeting about the publication of that in those early days, you were very much involved as editor of the Journal of Medical Genetics.

PSH. That was later.

NN. That was later, but indeed in those early days Cedric was saying that it might be possible to get abstracts published of the presentation.

PSH. Yes, that did happen under Cyril Clarke's editorship of Journal of Medical Genetics. The abstracts of meetings, and of course there weren't very many abstracts in those days, so it didn't take up much space, but at that point, the reports of the society, you know the original ones, were all published through the Eugenics Society, which we were rather uncomfortable about, most of us anyway.

NN. I think most of us were uncomfortable and I remember, yes I can remember at that time we had a working party on the training of clinical geneticists. We had a working party on pre-natal diagnosis, those were two of the early ones. Those were eventually published in Eugenics and we felt very uncomfortable with that, but I think the reason for that was because Derek Roberts

PSH. It was financial, because . . .

NN. It was financial, that's right, yes. They didn't charge the Society any money for the publication of this at all.

PSH. Because I remember then there came a point where we said, this isn't really suitable and then we realised, I think by that time I was treasurer and you were secretary, and I think we realised we actually had enough money to produce these things ourselves.

NN. No, I think it was a good move to actually get into the sort of publishing ourselves.

PSH. How long were you secretary for?

NN. Six years. Oh it was a long time. But I know that during that, I didn't have the facilities of computers or anything like that, but we began to publish on Roneo form programmes and it was just lovely to see what the Society is doing now in terms of even their programme.

PSH. Those were interesting days. Norman, I am very grateful for you sparing so much time talking, and I think I am going to turn the machine off here and thank you very much indeed.

End.