Nick Hastie

Personal Details

Name	Nick Hastie
Dates	Born 29/03/1947
Place of Birth	Colwyn Bay
Main work places	Edinburgh
Principal field of work	Human molecular genetics
Short biography	See below

Interview

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Personal Scientific Records

Significant Record set exists
Records catalogued
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Summary of archive

Biography

Professor Nick Hastie is Director of the MRC Human Genetics Unit and the Institute of Genetics and Molecular Medicine in Edinburgh. He has worked in many areas including gene expression, genome organisation and protein evolution. He has had a long-term interest in human developmental genetics, concentrating on the childhood kidney cancer, Wilms' tumour. Recently his group has shown that the Wilms' tumour suppressor gene, *Wt1*, regulates the balance between mesenchymal and epithelial states in a number of tissues through transcriptional regulation of *Snail, E.cadherin* and other EMT genes. Moreover, Wt1 is required for the EMT that produces cardiovascular progenitors. Over the past few years Professor Hastie has also become heavily engaged in a major population genetics project to identify genetic risk factors for common disease. Professor Hastie is Chairperson of a number of Scientific Advisory Boards, including that for the Sanger Institute. He was European Editor of Genes & Development for a decade and currently sits on the Advisory Boards of Genes & Development and PLoS Biology. Professor Hastie is a Fellow of the Royal Society and was awarded a CBE for Services to Science in 2006.

INTERVIEW WITH PROFESSOR NICK HASTIE, 26th MAY, 2004

PSH. I am in Edinburgh at the MRC Human Genetics Unit talking with Professor Nick Hastie, Director of the Unit -26 May 2004. Nick, could I get things going by asking was there anything special in your early life that gave you an interest in science?

NH. No. In fact almost by default I did an undergraduate degree in Liverpool. I scraped into University. I did an undergraduate degree in microbiology and even then I wasn't sure what I wanted to do. My friend said "Why don't we do these courses?" I said "Why not?" I had a very good time at University. A very good social life. Wasn't all that interested in science at all. But at the end of my honours microbiology, working mainly with viruses, somebody said why don't you apply for a PhD, and I thought, well I'm not really interested in science that much. This is all honest. And I wrote for a PhD, as did the same friend, to Cambridge. He was not called for an interview, I was, and out of 12 people they offered me the job, a PhD to work on influenza virus replication.

PSH. Who was that with?

NH. Somebody called Brian Mahy who is now head of virology at the Atlanta Centre for Disease Control.

PSH. Did you write to him because of any special reason?

NH. Sadly, he advertised. But it so happened my project as an undergraduate was on the effect of arginine on influenza virus replication, for reasons I can't quite remember, and I got interested in, I did get somewhat interested in viruses and influenza virus and that is why also I applied to this advert, but I was not pro-active. I responded. I did OK in the interview because I had got through life in a way on having social skills rather than necessarily being particularly bright I would say. So I did this PhD and for the first year or two I floundered around in Cambridge feeling actually somewhat, you know I had a great time socially again, but feeling somewhat disadvantaged intellectually in every other way. But towards the 2nd and 3rd year I suddenly started to make a contribution, and my work was some of the key findings contributing to the idea that influenza is an RNA virus that replicates in the nucleus, and that was very much based on my work. That got me interested in the nucleus and the role of the host cell and I said "Hey I am more interested in the host animal than I am in viruses". So then I did decide to write for a post doc to Edinburgh to John Bishop, who is a world expert looking at RNA in the eukaryotic, particularly mammalian and chick cell, and so I started to get interested. So I really started to get interested in science towards the end of my PhD.

PSH. When was that?

NH. That was 1973 when I finished, just about.

PSH. You would have been in Liverpool in the late 1960s?

NH. Yes that's right.

PSH. Can I just go back a little bit then to Liverpool. You said you weren't terribly interested . .

NH. No.

PSH. But there were some interesting folk around, I mean that was the time when people like Philip Sheppard and Arthur Cain were in Liverpool. Did you come across them at all?

NH. No, not at all. Let me say I have never had a lecture in genetics in my life. Which is really why I am not a geneticist. I am a sort of molecular biologist you- know-what, bit of a biologist and I'm picking up genetics still as I go along. So I am not a card-carrying geneticist.

PSH. Because I was in Liverpool . . .

NH. Yes Sheppard was there

PSH. In 1967 to '69 myself.

NH. Good God.

PSH. Working with Cyril Clarke.

NH. So we overlapped 2 years.

PSH. Yes. So then, when you went to Cambridge you were again with microbiologists, but Cambridge as you say, must have been quite intimidating with all these geniuses around.

NH. It was and so I, by the way, the first year I was in Downing Street but I moved to Addenbrookes; across the road was LMB and when I had, I did go to a few stunning seminars over there, where I would watch Sidney Brenner and Francis Crick tear to shreds a particular seminar speaker of the day and my colleagues at that time in the next building, who I met occasionally, were Gerry Rubin, David Ish-Horowicz, Jonathan Hodgkin, John Sulston and those sorts of people were in the next building at the same time and I got to know some of them socially. I would meet them every now and then and oh, actually there was an evening seminar that we would do every now and then, so I did get to know those guys a bit and that got me more interested. Mike Ashburner doing stuff at the time on ecdysone and genetic clusters and mapping in flies as well.

PSH. Did you realise that those folk who were around with you as colleagues were going to be part of the next generation of really eminent people replacing the first lot.

NH. No. I didn't. Probably if I had had any sense I would. But really I've developed so much as a scientist over the intervening period; I really was very narrow at the time and I hardly knew what was going on. I have learnt. Coming to Edinburgh was an amazing experience. Again I came here, and there was John Bishop doing all his theoretical calculations on RNA complexity and DNA complexity, and I had no idea what he was talking about for the first year. And I would go to the coffee room in genetics and Waddington was sitting there, but I never really had a chat with him. There was Falconer there, next to my lab was Falconer. I had all these people around me but I was focused on learning molecular biology and you asked about papers that one's proud of. Well the paper I got for my post doc there is on Landmarks of Gene Regulation and in Cell in 1976 showing RNA complexities and our different tissues. How many genes are expressed and all that. And I am proud of that paper. But I
haven't given up being proud of papers even to this day I have to say, unlike some of the people. I still think my best papers are ahead of me, or I hope. I'm fooling myself but I wouldn't be satisfied unless it was. So I have to tell you that. I have worked in many different areas in my life, that is the trouble. I am one of those Jack of all trades, master of none, but in Edinburgh after a year of being – am I taking too long with all this?

PSH. No, not at all.

NH. After a year of again being quite frightened I would say, more frightened. John Bishop. Don't know if you know of him do you?

PSH. No. I have never met him.

NH. He was a great intellect and figure and has had a huge influence on a lot of people, but a difficult man in various ways, but he was one of a crowd in Edinburgh at that time. We had just had Max Birnstiel who had just left when I got there. We had Ed Southern just about a few hundred yards away. We had Ann McLaren in the Department, we had Falconer. We had Alan Hill, the wonderful quantitative geneticist. Alan Robertson sorry. Hill is menswear. Alan Robertson. You name it. Oh Ken Murray and Noreen Murray developing all the bacterial genetics to do cloning as well. So we were surrounded by all those people and by the way, another 100 metres away, somebody I had never heard of, didn't know what was going on. You know there was a certain Murdoch Mitchison with his post doc was Paul Nurse and the student, Kim Nasmyth, on that campus. All those people at the same time.

PSH. That's quite amazing.

NH. So you might understand why I knew nothing of genetics. Here I was learning RNA complexity and gene expression and the beginnings of cloning on that site and it was an amazing place. Ed Southern was developing the

Southern blot, which in human genetics terms has to be considered landmark by the way, the Southern blot. Whether it is or not, it has to be considered, it has had so much impact on the whole field of human genetics. Without the Southern Blot, we would be way back still. I don't know if you realise that. You probably do.

PSH. I do actually. So when you talk about being on the campus, most folk outside Edinburgh find it quite confusing

NH. I know, I'm sure they do.

PSH. This was the main centre you were based in was the Department of Animal Genetics? Is that right?

NH. Yes that's right. In a sub-division of epigenetics by the way. Which is still part of it. It is just a separate building where there is more molecular biologists got together in the Department, rather than classical geneticists.

PSH. Then am I right then Ed Southern and his group moved into a specific building?

NH. Yes they were zoology and then they moved to the mammalian genome unit, which is next door. A specific MRC unit for the mammalian genome. Yes.

PSH. And then already by that time this building [the MRC Human Genetics Unit] had been built hadn't it, so did you have much contact with them.

NH. Not at all, I said to you. I had no awareness of this building. I had no awareness even of the seminal work that had gone on here, both in banding chromosomes and in the whole sex chromosome classic work of Pat's [Pat Jacobs] and others. I had no idea about it. For my sins I knew nothing about human genetics and had not even thought about it. Mouse genetics I was starting to get interested in and I did that as soon as I went to America. But I knew nothing about, I was a molecular biologist really and very ignorant.

PSH. What year was it you went to America?

NH. I went to America '75, so I only did a post doc for about 2 years. Of course I became group leader in America at 28. Unheard of nowadays. It did happen then more. So it is crazy and I got two grants and I worked on development gene expression mouse genetics while I was over there and mouse genome organisation.

PSH. Where were you? Remind me.

NH. This was Roswell Park Memorial Institute, it's a Cancer Institute in Buffalo, New York. And again I sort of drifted into that. I should tell you at the time when I went to Cambridge and just beyond that time or towards the end of my PhD I did a lot of singing at that time and one possibility was I could move to become a singer. Probably I would have been a complete failure no

doubt, but it was one possibility that was going on and people were encouraging me to think that way.

PSH. What kind of music?

NH. Well, I suppose more classical, it would have been or operatic as a baritone bass so, bass baritone and I'm afraid I haven't done any of that for ages now. I did a lot in America.

PSH. Not even at the Christmas party?

NH. No no. They don't know about this side of me at all. I'm shy about that. I did the karaoke in Elvis songs but I haven't done . . . So for me it was a slow development, and now I am as enthusiastic about science as I ever was and I'm much more broadly based as a scientist now. I mean I really am interested and I read quite a lot and hopefully aware. But it took a long time Peter, through many iterations, because then I had gone through many phases and it was only after being in America I came back here. See what happened was, I was in America, I had tenure, after 7 years I had tenure, 2 NIH grants, a group of 10 people, but my wife and I had always wondered about whether we should come home, because the parents got older and of course we had always planned to come home. And Ed Southern phoned me. Now what happened in this unit. There are so many things one can talk about, because one thing I wanted to talk to you about was how important all those developments going on across town as well as here were for the succession and the current generation, because there are links, in all areas there are links and the most important development, Dolly the sheep, came from one of those links, as well, one of the most important developments. So there are many links. There are areas of continuity that are very important.

PSH. So how come then that you came back to this unit rather than to some other part of the Edinburgh set up?

NH. Well, it was entirely because, so what happened, this unit of course which had a fabulous history in chromosome analysis, I think there is no doubt, around about towards the end of the late '70s there wasn't much more you could do with classical chromosome analysis.

PSH. No.

NH. It must have been a golden period when you can have, you know a couple of great techniques and a large amount of biological material and learn so much with these experiments, but you can't do that any more very easily.

PSH. I suppose things start to run out of steam unless they bring on board new ideas and techniques.

NH. That's right, so Ed Southern was given the task, because he headed the unit across town. He was Assistant Director of this unit under John Evans, and Evans tried to bring molecular biology to this unit. So that's why they called me over, to have somebody in-house to do this. So I came as a little group leader at the age of 35. back here. And I remember, the salary they

were about to offer me was half the one when Ed phoned me, that I had in America and John Evans thank God fought for it to be higher because even then we came back, we were rather poor for the first few years I have to say.

PSH. It's difficult when you have been in America for more time a short time to re-adjust isn't it.

NH. And Ed at the time was encouraging me to get more involved in looking for restriction fragment length polymorphisms and things. And actually that didn't really interest me. So what I wanted to do, I had always wanted I suppose to be involved in aspects of developmental genetics, and I'd watched with awe the stuff going on with Drosophila and Ed Lewis' stuff and all that. I had followed that with so much interest. You know antennapedia and all those great mutations, and I thought can we get into the area of interesting developmental genetics, and of course using the human chromosome knowledge. So here we have a syndrome, Wilm's tumour aniridia genito urinary abnormalities, mental retardation which the unit had already contributed to mapping under the microscope, these deletions. So Veronica, [Van Heyningen] who had skills in somatic genetics and myself got together and said why don't we try and map all these deletions, develop technologies to positionally clone genes and it would have been the first tumour suppressor, the Wilm's tumour gene if we hadn't been beaten, first of all by the retinoblastoma people but at one time we were way ahead actually, but then we fell behind, and you know, at that stage I was asked to organise the first tumour suppressor symposium at Cold Spring Harbor and things, because we were very much in the forefront but we fell behind, you know, but it was the right sort of thing I think to get us interested. It brought the chromosome side together with trying to get at the genetic basis of human malformations and I think that was the right sort of thing to try at the time.

PSH. What year was it you came back to here?

NH. '82/'83 round about then, yes.

PSH. So I can understand why Ed Southern, he was involved in all the Duchenne and related work . . .

NH. Yes he was. He was yes.

PSH. Around that time wasn't he?

NH. Yes. And I did not want to develop, you know, yes, the other project with the chromosomes, I wanted to develop approaches. I do not want always to use other people's approaches. I do like to be involved in trying to develop approaches to do things; that is why we are involved in chromosome mediated gene transfer and sorting hybrids with different chromosome complements with Veronica. I mean it was enjoyable to actually apply cloning genes that mapped in the region. I mean that was something that gave me some satisfaction at the time to try to do that. It was very competitive and frustrating, but it was satisfying and it had links with the chromosome side of the unit. I wanted to talk about the continuity in the chromosome side as well.

PSH. Go ahead and do that now.

NH. OK. So I actually, whether it is known or not, the unit continued, I think, to make important contributions to chromosomes and that might not be appreciated because, you know, after the cytogenetics there is the whole aspect of molecular cytogenetics and so I think it's several areas where we continued for a time to make contributions and Wendy Bickmore particularly in this unit has made the biggest contributions I think. I don't know if you know what she has done or anything.

PSH. Yes I do.

NH. Yes. Sorry. I don't mean to sound insulting Peter.

PSH. You don't. It will be good to tell it in detail because, I only know in very general terms.

NH. So this again shows the links. Wendy, who did a post doc with me, part of that was mapping CPG islands in the Wilm's tumour/aniridia region and she noticed that CPG islands in the dark band, the dark G band you know, were a much lower density than the light G band and she mapped that. Now she was influenced by having Adrian Bird across town, who is a wonderful star in the whole area, and epigenetics is an issue we should touch on perhaps because Edinburgh has been very important in that area.

PSH. From the beginning.

NH. From the beginning, and continued under Adrian and people to be world leaders, so I think that's continuity there. So what Wendy did then, she combined chromosome analysis, fluorescence in-situ hybridisation and showed that CPG islands, and now we know genes, are not randomly distributed in the genome, they are enriched in R bands and its T bands and that has been all supported by the genome sequence, but she was in a way, the first to do that. Then she went on to show that human chromosomes are non randomly positioned in the nucleus. If you have 18 and 19, two chromosomes you know very well are about the same size, 19 has a far higher density of genes and it is much more likely to be internal in the nucleus rather than peripheral for example. And she has gone on to do some beautiful stuff. She has recently has actually been able to show that particular regions of chromosomes are extended far outside chromosome territories and recently been able to show beautifully for the HOX cluster shown that's regulated during early development in a temporal way, this chromosome shedding outside. You know this is really beautiful work and she has also been able to put reporters into chromosomes to watch the mobility of different chromosome regions as well. But it goes on and on what she has been doing recently. And it's getting better and better.

She has also now been able to look at the condensation of regions of human chromosomes by combining fractionation with screening human genomic arrays. So now she can actually relate chromosome condensation to different segments of the human genome. All this is very beautiful and it is innovative

and it is different than many of the other things people have been doing. It's looking at the holistic aspects of the genome instead of individual gene by gene as well.

PSH. And it wouldn't really have been possible if she hadn't been based in somewhere that had a long tradition of microscopy and chromosome research.

NH. Absolutely. Quite. The chromosome research. That is one thing. The other part that we continue to work on and what I am proud about. This is the continuity. She did her, now this is the cupid thing here. She did her PhD with Howard Cooke in the mammalian genome unit across town, where she was exposed to Ed Southern and Adrian Bird and all those guys and Howard Cooke about chromosomes and CPG
islands. My post doc was her boyfriend then, Robin Allshire, who had also done his PhD with Chris Bostock in the mammalian genome unit. Robin came to work with me and he is brilliant, and he continued to make fundamental contributions to chromosomes over here. With me, when he was a post doc in my lab, first of all, he did the audacious thing of putting fission yeast chromosomes into human cells and showing they can replicate properly. But that led us to getting access to human telomeres through that route, which we did, and Robin with me showed that, one of the papers I am most proud of, a Nature paper, we showed that human telomeres become shorter and shorter every year of our life and shorter in cancer, and that's probably my most cited paper and I think there's a nice figure just showing as we get older our chromosomes get shorter. One figure in a Nature paper but actually that's loaded with implications.

So that's one area. Another area where we continued with chromosomes, but Robin Allshire has gone on really to do the most beautiful and best work. He has left the unit now and has gone across town back to Adrian Bird's domain as a Wellcome Principal Fellow. He has done the most beautiful work on understanding what a centromere is and how it functions, and how that relates to silencing of genes. Again that is continuity. And then the other continuity of course was Howard Cooke making some of the first artificial chromosomes. Ming Hong is here doing that but also just recently Howard by studying human infertility and these Dazl genes, has just
managed to identify, God help us, using micro arrays and things by analysing germ cell development, two of the key components of the synaptonemal complex we think during meiosis. Again it's a chromosome link that's continued in this unit and I think we are going to continue contributing hopefully to chromosomes. The other chromosome link though, is a thing I thought was vital when I became director. Do you know we have never had a clinical geneticist in this unit. Now we have David Fitzpatrick. We have Alan Wright who is trained clinically, but we are going to get more in here because I think clinical geneticists are wonderful scholarly people who,
already David Fitzpatrick is bringing an enormous amount to this unit. So for example what David is doing and it again relates to chromosomes, he is taking the route, he is interested in dysmorphologies as you probably know, and in a way he is doing an obvious job but it is beautiful. He is just saying, OK we all know balanced translocations could disrupt interesting genes. Of course very often they might not be doing anything. They might be co-

incidental. So David is taking particular dysmorphologies. He looks at the human chromosome haplo-insufficiency map. He asks if particular conditions like cleft palate for example and blindness. Things we work on here. Do those pick up in particular regions of the genome? If so, through haplo-insufficiency mapping can you find translocations in that region, can you find more than one. And doing that together with very efficient fluorescent in-situ hybridisation with Judy Fantes, they are cloning human translocation breaks at quite a fast rate, in the last year or so they have got some wonderful genes that way, involved SOX2 they have showed that's a Nature Genetics paper that's causing blindness when it's haplo-sufficient, but they have got several more in the last year and some of the inversions they have got look as though they are going to be very important in telling us about chromosome regulation because they are having spreading effects. So he then will link with Wendy Bickmore and others to try and analyse the chromosome consequences of these translocations that involve dysmorphologies, and so the links go on bringing dysmorphology to chromosome biology, which people have known about for ages and are using but now I think Dave is doing it in a much more systematic way and together with Di Donnai in Manchester they have a grant where they are characterising at least 50 different translocation breaks and they are going to get the molecular basis of those break points and they are going through it very quickly and that is very interesting as well.

PSH. I think that's fascinating, really fascinating. There is one area also, I could be wrong, but I identify as being a new development based on an old strength, is the work on three dimensional modelling . . .

NH. Sorry, I was going to come that.

PSH. You are going to come to that. But am I right. I remember there was Denis Rutowitz, the physical and mechanical developments, which were all down in the basement and then the cytoscan and things and I have always supposed that this in some way then gave the foundations for the more molecular approaches in this direction later on. Would I be right?

NH. Yes that's right. This is again two things coming together. This is the importance of bringing sciences from very different directions together, very different fields. So what happened, Denis Rutowitz had this brilliant pattern recognition section, as you were saying, and one of the scientists that they recruited was a physicist Richard Baldock, who is very brilliant and on the other side, my section got
involved much more in developmental biology and developmental genetics, so I was working on this Wilm's tumour gene, which is clearly vital for development of the kidney and the gonad and things and then Bob Hill had been a post doc, I'm afraid there's an awful lot of incestuousness here, Bob Hill who had been a post doc with me working on another paper I am very proud of in Nature, we had the first evidence I think for showing Darwinian evolution in particular proteins. That was a paper Bob had with me in Nature in 1987. Bob Hill started to work on developmental biology in HOX genes.

Now Duncan Davidson who'd worked here for years with Tom Elsdale working on, of all things, somite development started to do molecular biology development with Bob Hill and then Duncan who is a very clever man, talked

to Richard Baldock so the developmental biologist working on molecular development in the unit talked to the physicist and they said, let's start to think about what we need for the future. If we are going to be looking at huge numbers of gene expression patterns, you know, it's no good just to keep looking at individual genes and compare them. You want a framework for that and it should be a 3 dimensional framework, so that is why they started to put together this 3 dimensional computer atlas of the mouse which is probably I think the leading one in the world just about now and many people in other organisms are talking to them about doing it for their organisms. Even invertebrate people are following this. And this is really going well. It is a big international programme and it's starting to work very well and thousands of gene expression patterns are being put into the framework of this computer atlas, and also the computer atlas which is on CD roms and various things, one thing we are trying to promote and there is interest as a teaching, an anatomy tool for schools and medical schools and that's starting to happen as well, so this goes far beyond the immediate science. I think its an educational tool it's important and I think one day when we want to understand how genes interact in development and understand human developmental anomalies and all this sort of stuff, this atlas is going to be extremely important.

But within that then has developed a whole new, a wonderful post doc with Duncan Davies and James Sharp developed a whole new type of microscopy called an optical projection tomography which is on the front page of 'Science' here, where I have it, you see it as you walk in the unit. That was two years ago and it was a whole new, we are using that on human embryos as well now. The microscope allows you to encapsulate in three dimensions, the whole anatomy of an embryo early on in development and we are hoping to apply that to pathology as well so, that's developed through this mouse atlas programme as well so yes, interesting.

And again that brings, you see the way this unit is now, we have some you know we are called The Human Genetics Unit. I am trying to strengthen that component because ironically perhaps a third of us work on human genetics problems, a third, because I wanted to do biology. I wanted to do real mechanisms. I wanted to understand what was going on and I thought you had to have good cell biologists and good developmental biologists, so you have mainly a human genetics component. We have a very good cell biology, chromosome and RNA biology section and then we have my section, which is mainly developmental genetics and developmental biology, and the hope is they will all sort of link with each other. And I must give you one example of that recently. Bob Hill again, who was a post doc in my lab, was working on a limb mutation in mice. Bob wasn't necessarily looking at human genetics at all. He wasn't necessarily, dare I say, that fascinated. He was interested in the basic biology of limb abnormalities in mice. They identified an insertion of a transgene over a megabase away from the sonic hedgehog gene, and to cut a long story short, using beautiful genetics in mice, they showed, using a cis-trans test, they showed that this insertion is actually causing activation of sonic hedgehog at a megabase away. So then, using comparative genome sequencing, they identified a conserved sequence in this area and that conserved sequence not only has point mutations in mouse polydactylies but also in a whole range of common human polydactylies as well. So it goes from the mouse genetics of one megabase regulatory element away from the

gene to that. Now that's another story. Again it's bringing chromosome effects together with human anomalies and everything else. So that was a recent story we just had. It was highlighted in many editorials from the unit again recently. So you are always hoping that the development together with the chromosome people, that all these links come together and they are starting to you know. The different segments of the unit are getting together more and more through all this and that's what I wanted you know. Still a long way to go I think.

PSH. Nick . . .

NH. I am rambling on here. It's terrible.

PSH. No. Don't worry about that. But there are two things that I have already said to you that I try to ask everybody I have been talking to and one is, is there a particular person who you would put down as having influenced your scientific development, or has it more come gradually through a whole series of people?

NH. Yes . It has been a whole series. I think John Bishop in Edinburgh had a big influence on me. Mouse geneticists next had a big influence such as Vernon Chapman who sadly died who was a mouse geneticist in Buffalo, he had an influence as well. He introduced me to the idea of genetics I think really. And then since I came back here, no it's been a host of people. I'm always being influenced by all my colleagues every day. My post docs, everybody. Its difficult. Veronica's been an important influence I think as well.

PSH. Veronica was here in the unit before you came back wasn't she?

NH. Yes she was. Yes.

PSH. So I guess there has also been an important link between the older parts of the unit and the newer one.

NH. She has yes. No no. She and I formed an alliance immediately, which I think is very important for the continuity of this unit, the fact we have even survived so far. I mean she was very important. She taught me a lot. Influenced me a lot. So she would be an influence, yes. Hope she would like to think that, but I am saying that.

PSH. You touched earlier on what piece of work you might be most proud of and I don't think one should feel that one has to limit oneself to one. But is there a particular, well what do you think, at least until now, you'd pick out, or is it not easy.

NH. Well it's not easy and it wasn't easy when they gave me the Fellow of the Royal Society as well. I got an FRS for whatever reasons and you look through my career and I have had quite a large number of papers, quite a large number of Nature and Cell papers in about five different areas, and I am not one where anybody can put their finger on it and say well this is and I'm sure that has been gossiped about – "This person, what did he particularly do?" Well I think I have made quite important contributions in several areas

and so I wouldn't give one, but I would give the first one in 'Cell' on RNA abundance and complexity in mammalian tissues. I would certainly quote the one with Bob Hill on the evidence for Darwinian evolution working in mammals and this is in protease inhibitors. Certainly the telomere shortening, which was in Nature I think, I am very proud of. It is a very important paper I think and more recently you know with Veronica the demonstration that PAX 6 is vital for eye development, and we did that in mice and humans before it was shown in flies to be so important as a major, that we are part of an important passage of history there, and then the other one was a Cell, the paper this Wilms tumour gene I worked on, we actually showed that here you could have a gene encodes two proteins that differ by three amino acids by alternative splicing through alternate splicing and these proteins have such profoundly different properties and I think implicating one in transcriptional regulation and the other in splicing and I still think that is quite an important contribution. It was a beautiful paper we had Cell in 1995. I just had one recently where we developed RNAi in organ culture and we can start to see gene function in kidney development and organ culture using RNA interference and be able to build up pathways. That was in Human Molecular Genetics this year and I was as proud of that paper as any others I had, I have to say. I'm not necessarily going to get papers anybody notices all that much in the future, but I was as proud of that paper which I think was an exquisite piece of work that I had as I was of any of the others. It is difficult for me to say you know and who knows what anybody will say. They might not remember anything I have done historically, but I have been an influence. I think that is important.

PSH. That's true and maybe this reflects the way science has changed whereas many of the people I have been talking to started their careers when they were doing something alone at the bench. It was just them.

NH. Yes

PSH. This doesn't happen in the same way now and people are kind of part of a team.

NH. It's is true.

PSH. And you can't basically pinpoint one paper and say that was all my work because it almost . . .

NH. The Cell paper on RNA abundance, the landmark paper, that was all my work. I wrote it, did it and everything and I think, that is a landmark paper. There are only two authors on it and some of the others around here had 2 authors that I have mentioned as well. You are right. You are more proud of the ones you had more to do with. The ones where I am one of 20, I wouldn't even mention to you and I remember a number of those. I am on a number of those I am sure. So . . .

PSH. So do you think, I mean I am trying to imagine how you would see yourself in the future, but would it be reasonable to say that you feel proud of the different elements that you have brought together . . .

NH. Yes sure.

PSH. And helped to make them bigger than each would have been separate?

NH. I think that's very fair, Peter, and a number of the new directions in the Unit I think I have somewhat been behind a number of them. I think I have been, I have sometimes seen the links. Often they come bottom up. They come from people like Duncan Richard got talking about developing the mouse atlas. Nothing to do with me. We just help to create the environment as John Evans did. But there are some where I have definitely encouraged directions and they are happening I think. Because one of the big, you said earlier how important human genetics, for us human genetics is so important of course to help us understand the diseases and lead to new treatments but as a way of understanding biology it is unbelievably important and if human genetics has contributed novel things such as you know, what you have been involved in, you know trinucleotide repeats, who knows, mis-match repair systems, there are areas where human genetics has contributed novel ideas to biology I think. There's no doubt and you have been involved seminally in one of those. It's interesting to think where its going as well as doing all this genetic networks and all this, that and the other and I think one thing we have not been involved in but now we are, is we have worked on the genetics of Mendelian, so called single gene disorders mainly and a big issue for me was whether, in my job interviews, whether we should
move into the area of complex disease. I resisted that. I thought it was too complex and I thought so much money was being thrown at it and not getting very far, but you know, the whole idea of how subtle genetic variation influences the variety of physiologies and behaviours and disease susceptibility has got to be one of the biggest things to tackle. And so we now have, and it's something I have pushed very hard, Alan Wright really leads it but with me backing it very much is to do some quantitative genetics and this gets back to the old days of Edinburgh genetics. We are
all working together with Croatian scientists in isolated populations in Croatia and starting in Orkney and places in Scotland, to take large numbers of human traits, a number of them risk factors for disease, we're looking at those, in a few thousand people, we are completely genetically mapping those and we are trying to get genetic factors in stature, cholesterol levels, bone mineral density, cognitive tests. We are doing a whole range of tests in these people to try to tease out the genetic factors and how they interact to influence these traits. And that to me is one of the big new challenges. It's a thing we thought we wouldn't do. But now we collaborate with the quantitative geneticists who came from the classic school across town to start to do this sort of stuff.

PSH. Perhaps you were wise not to get involved at the beginning, because there was quite a lot of naivity involved at the beginning wasn't there?

NH. Incredible naivity. Yes. I give a lecture by the way which I just, I gave to the public in Edinburgh and I have just given to senior civil servants at a Cambridge meeting, a closed meeting, to the head of the Treasury people and all these Office of Science and Technology, David King, Science Advisor, and it's all about "Genetics, The New Fortune Telling" which is what they chose for me here for the lecture in Edinburgh, and what I do really is to try to put some reality into genetics instead of all the hype that there will be a CD one day and

they will be able to sequence your genome and predict what diseases you are going to get and how you are going to look and whether you will be musical and I just try to say, look too many people have extrapolated from the most deterministic situations, such as Huntington's and muscular dystrophy and this is what it is really like in terms of how genes interact and with the environment and I go through cardiovascular disease and cancers and various other things and talk about how genetics is so powerful to help us understand mechanisms, come to new drugs, but what are we really likely to be able to predict and how important public health is in all this as well.

So that is what my lecture is and it has made me think more and more about this but you know, how to tease out those genetic factors with small effects and how they interact with each other is becoming very interesting and the most interesting thing that has come from the study in Croatia, mainly Alan and people, but with Brian Charlesworth across town who is a wonderful quantitative geneticist, an evolutionary geneticist working in flies, is that one of the major factors in adult onset disease in a number they have looked at is inbreeding. This is going to be quite a big contribution I think from the unit, that inbreeding is, the more inbred, the higher the frequency of

higher blood pressure and the higher frequency of a number of adult onset conditions.
That was thought to be mainly at the level of perinatal things but this makes sense and has big implications for understanding genetic risk factors and identifying them. Now we are talking about the science going on, this is one of the things we are thinking about for the future I suppose in the unit as well, so.

PSH. Nick, anything else you would like to down for posterity.

NH. Yes. No. I would like to put down the business of Edinburgh, if that's alright if we have a couple of minutes.

PSH. We do.

NH. When I came to Edinburgh as I say, I had no idea how amazing Edinburgh was as a scientific centre. In fact it could have matched anywhere. Of course LMB at Cambridge, who knows, that was stunning, but Edinburgh. So on the one hand as we said, we had this wonderful human genetics going on here in chromosome analysis, which is world leading, and then across town where I was you know, we had the epigenetics people from the Waddington school. We had the quantitative geneticists, We had Henry Kacser doing very important work on flux. We had Charlotte Auerbach, we had Ann McLaren, we had Waddington, Falconer all in the same building. People like Graeme Bulfield and myself coming through from that school, Graeme more a classical geneticist in his training. Then we had people like Alan Robertson, who influenced the whole of the agricultural genetics revolution and have had a huge impact on real agriculture and selective traits

and all that stuff. Oh and then as I said we had the school of Hayes and all those molecular biologists which then had the wonderful people like Ken and Noreen Murray. We had Ed Southern, we had Murdoch Mitchison and Paul Nurse and people all within, I mean I had no idea that I was so privileged and if only I could go back now at that time, I would be talking to people more, I would be asking a lot more questions. So some people now say, "Oh God. Edinburgh will never, ever reach those heights again" and it's a big challenge to us, so what we have got, funnily enough, a number of us who were schooled at that time, went away and came back to take on important positions. I was lucky enough to become director of this unit. Adrian Bird, who's a stunning scientist and I hope gets a Nobel prize one day, heads the Swan Building with all the cell biologists across town, Graeme Bulfield went to head Roslyn and is now head of the College of Science. But you have seen in all these, the next generation, I don't think, will we ever be able to live the wonders of that previous generation? I don't think that's possible, but it's pretty good. Edinburgh's pretty strong and we are talking more and more about how we can strengthen it. You know, look at what happens. You get Graeme Bulfield going over there. You have John Bishop trained John Clarke, John Clarke went over to work at Roslyn. He developed transgenic sheep expressing human proteins in the milk but Ian Wilmut then started to work with John Clarke and then Ian Wilmutt doing reproductive biology ended up cloning the first
animal, and that then again stems from that original tradition I think and if anything, Edinburgh does have a chance to make major contributions in the future and we are all trying to work together at some level to do this and it is very important for us to all talk to each other. But one of the strongest things in Edinburgh still is quantitative genetics. All these people who work on flies and mice and farm animals. These people represent a lot of the continuity as well and they are influencing many areas of science, including us. In human genetics; we have to interact with them and learn from them. Anyhow I have rambled on.

PSH. It's quite a challenge isn't it?

NH. It really is and I am aware of history. Mind you, the only thing that is fortunate in my case is I never expected to be anything and I have already gone far beyond that but you know I'm painfully aware that I have only got a few years probably and I am painfully aware that I want to leave this place in a really strong shape and we are always looking to recruit and bring young people in and develop links across the unit and across town and internationally. And one great thing is we are already part of five big framework – six programmes in this unit internationally in Europe and so we are having an interaction and hopefully will be valuable in the international scene. But it's difficult.

PSH. Nick thanks very much for talking. I'll turn it off now

End of tape.