Gill Bates

Personal Details

Name	Gill Bates
Dates	1956
Place of Birth	UK (Kenilworth)
Main work places	London
Principal field of work	Human molecular genetics
Short biography	See below

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
Date of Interview	21/02/2006
Edited transcript available	See below

Personal Scientific Records

Significant Record sets exists
Records catalogued
Permanent place of archive
Summary of archive

Biography

Gillian Bates studied genetics at University of Sheffield, UK, and did her PhD at St Mary's Hospital, London, under Professor Robert Williamson. She began research into the isolation of the Huntington's disease gene as a post doctoral work with Hans Lehrach and has continued this, in particular the construction of a transgenic mouse model for HD, at Kings College, London, where she has been Professor of Neurogenetics since 1998.

INTERVIEW WITH GILLIAN BATES, 21ST FEBRUARY, 2006

PSH. It's Tuesday 21 February 2006 and I'm talking with Professor Gillian Bates at Guy's Hospital, London Gill, before we get on to Huntington's, can I go back a little bit and ask what was your first degree?

GB. Genetics.

PSH. And where was that?

GB. Sheffield.

PSH. And can you remind me, who was at Sheffield then?

GB. Alan Roper was the Head of Department. It was a department that worked very much on the genetics of Drosophila, Aspergillus, and Saccharomyces. It was a very classical genetics department. It had a great atmosphere. I did a general first year and then second and third year special honours Genetics. The department was set among some prefab huts in the history department's garden. So it was all very quaint and everything smelt of Drosophila agar. Pete Sudbury works on Saccharomyces and I gave a talk at Sheffield this November and he came to my lecture. He is very white-haired now. He is the only one left who is still working there.

PSH. So after you had done your genetics degree, what was your next port of call?

GB. Well, what I wanted to do was human genetics, so in the third year of our degree we did a six month research project and I did that on maple syrup urine disease in what was then the Medical Genetics Department at Langhill, and then, because I didn't know what I wanted to do, I went to work as a cytogeneticist. I didn't want to make a mistake and do a PhD in something that I wasn't sure of. So I started working as a cytogeneticist in London with Les Bulter at the Queen Elizabeth Hospital for Sick Children.

PSH. At which hospital?

GB. It was at the Queen Elizabeth Hospital for Sick Children on the Hackney Road. When it closed, the cytogenetics department went to GOS [Great Ormond Street], . It was a little children's hospital. And while I was working there, I did an MSc at Birkbeck College in Biomolecular Organisation with Tom Blundell. Around that time Kay Davies' paper came out in Nature on X-linkage and Duchenne Muscular Dystrophy with the first markers and then I wrote to Bob Williamson and said I would be very interested in coming and working in that field and did he have any openings. He employed me to do in-situ hybridisation initially, and then I did a PhD with Bob.

PSH. Now was that in 1980?

GB. That was '83 I went to Bob's lab, yes.

PSH. So at that stage really you had no idea of Huntington's or anything about Huntington's?

GB. Huntington's, I first came across when I was a student in Sheffield because two years running or maybe even three times in the end I worked as a cleaner in a psychiatric hospital, one of these big old Victorian hospitals, for my summer vacation job. There were two Huntington's patients, on what was basically an Alzheimer's ward and I remember them distinctly. One of them was a woman called Pat, and they really stuck with me because they were much, much younger than all of the people around them. So that was my first memory of Huntington's.

PSH. Well coming into Bob's lab, which I remember very well from my contacts, what was your first impression of Bob, Kay and the St Mary's set up? What about the lab set-up, which always struck me as being not exactly a model of lab organisation?

GB. No it wasn't. I worked with Kay originally, on Duchenne muscular dystrophy along with Susan John. We were both research assistants and we were supposed to be running blots to search for polymorphisms. Basically you just had to work it out as you went along. If you were determined you would find somebody who knew how best to do each stage of the analysis and then piece it together and make it succeed. There were some great people around, so you always could do that because there were some very, very good people, there but in terms of being taught how to do something, it was a bit hap-hazard.

PSH. Who else was there with you of particular note?

GB. Conrad Gilliam was there. He ran the chromosome 4 group, which was being investigated from the point of view of cystic fibrosis and I think a cilary trophic factor had been mapped there. He worked with Pete Scambler who started on the same day as me and Mark Baxter. And then in the Duchenne group there was obviously Kay, Kim Ellis, a postdoc whom you may or may not know, Gill Bell was a senior technician. Kevin Davies started his PhD at around the same time as me and then went on to do a postdoc with Harvey Lodish before becoming the first editor of Nature Genetics. Steve Humphries was head of the heart disease group and Steve Brown had just started as a new lecturer. John Hardy came about a year or so later as a lecturer. Rosemary Ackhurst came as a new blood lecturer..

PSH. It was always incredible to me the amount of talent . . .

GB. Keith Johnson.

PSH. Ah Keith, yes.

GB. As a PhD student with Alan Malcolm at that time. Alan Malcolm was there.

PSH. It is amazing. There's a lot of people who have gone on to do great things, all in a way cut their teeth in that lab, and even though, as you say, there wasn't a huge amount of what you might call direct supervision.

GB. I think it was being thrown in at the deep end. Bob was very inspiring and I think if you had potential then you could show it in Bob's system. So people who might not have necessarily excelled in the same way, found their capabilities. I mean I know that was true to a certain extent for me. I was terribly, terribly shy and terrified of giving talks. Bob would just throw you into things and then you found out you could do them. He also gave quite good advice too. Not necessarily experimental details, but how to give a talk and how to prepare yourself and go about things and build up your confidence. He was always telling us how good we were and that we would be running science. So for people he believed in and thought had potential, he was forever telling them not to under-sell themselves and I think that really was quite good. Rodney Harris came as a visitor for a while. Sue Chamberlain came while I was there of course.

PSH. So how long were you at St Mary's, Gill?

GB. Four years.

PSH. Did you do a PhD there?

GB. Yes. I was there one year as a research assistant and then three years as a PhD student.

PSH. And just remind me, the precise topic of your PhD.

GB. It was cystic fibrosis.

PSH. Yes, because I was thinking it wasn't Duchenne?

GB. No. So after Kay went to Oxford, most of those of us who stayed went on to work on cystic fibrosis. Pete Scambler was already there and then Brandon Wainwright came to replace Kay. Pete and Brandon really ran the project and then Martin Farrell joined us, Nick Lench, Isla Watson and all those other people too. But it was Brandon, Martin and Pete who really were the three key senior people. And Xavier Estivill of course came for two years, he was amazing and the group did fantastic stuff while he was there.

PSH. So the year that you left St Mary's was . . .?

GB. '87. So for my PhD work, I did microdissection with Steve Brown to start off with. At that point we were at still trying to find markers on specific regions chromosomes. The position of the CF gene wasn't known and at that time, there were no dense arrays of markers. I started to do chromosome microdissection as a way of perhaps being able provide a dense map of markers once the position of the gene was known. I made a microdissection library of chromosome 2, the short arm of chromosome 2, I was working on characterising these clones and then the gene was mapped to chromosome 7. The CF gene turned out to be very close to the mec oncogene. Pete

Scambler made somatic cell lines with chromosome fragments containing the CF gene by selecting for the oncogene. So instead of doing the microdisection, I started to apply the other techniques that were emerging at that time: pulse field gel electrophoresis and the preparation of rare cutter linking and jumping libraries. In the summer at the end of my second year (1986) I went to Heidelberg for two weeks to work with Hans Lehrach where I learned how to do pulse field gel electrophoresis and made a Not 1 linking library from one of Pete's cell lines. That was how I got to know the Lehrach lab. Eventually, I asked Hans if he could find a position for me when I finished my PhD.

PSH. So when you finished, had Hans then moved to London at that point or was he still in Heidelberg, or a bit of both?

GB. Well when I asked him if I could have a job, he was going to leave Heidelberg, although at that time he had several offers and a position had not been finalised. Then he accepted the job in London, so he ended up coming to London. He had moved there 2 or 3 months before I joined his lab

PSH. That was in ICRF? [Imperial Cancer Research Fund]

GB. That was at ICRF.

PSH. So then in 1988 you really then moved to ICRF.

GB. Yes, Autumn '87.

PSH. So that was as a post doc initially. By that point had Hans got tied in already with the Hereditary Disease Foundation Collaboration?

GB. Yes he was already tied in. I think it was '84, when he first became involved with HDF. Allan Tobin had become stranded in Frankfurt on his way back to the States from - you probably know the story - from Israel, and rang up Hans because they'd known each other at Harvard and went to stay with Hans. Hans told him about pulse field gels that were published that year and about the jumping and linking libraries that he was developing. So Alan invited him to an HDF workshop and got him tied in at that point. So by the time I joined there were the Gusella, Housman, Cantor, Wasmuth and Lehrach groups.

PSH. So was that the first thing you started off on?

GB. Hans had one post doc on that project, who was Maja Bucan. She'd been making the pulse field map of the HD region and she was due to leave. So I overlapped with her in order to replace her on that project.

PSH. She is someone I often wonder what happened to, because she went off to Belgrade didn't she?

GB. No, she went to Penn, Philadelphia. She initially worked with Davor Solter who was a mouse geneticist there, and then became an assistant

professor. She's still there as far as I know. I think she is still there. I saw her in '93. She got married and had a little boy.

PSH. So with your Huntington's work, what was your remit when you first started off?

GB. We worked within the collaboration, so Hans's lab took care of the large scale cloning and physical mapping. YAC libraries had just been published, so I started off trying to make YAC libraries. I was also, characterising some of the Not 1 linking clones that Anne-Marie Frischauf had made and at the same time starting to make YAC libraries, so I spent a lot of time just getting the transformation protocols and things like that sorted out.

PSH. Which was the first Hereditary Disease Foundation meeting you went to yourself?

GB. New Orleans in 1988 and that was very memorable. I met everybody there of course, Allan and Nancy and all the other members of the collaboration. I hadn't known John Wasmuth. I hadn't met Charles or Cassandra before then, and I also met Dennis Shea. At that time my partner was a chap called Robin. He was coming over at the end of the meeting for us to have a two week holiday and we hadn't decided what we were going to do. We were just going to hire a car and either drive toward Texas or toward Florida. Dennis said to me, you should come to Florida. I've got this little place on the beach. You wouldn't even have to stay in our house. I would be offended if you don't come down and stay with us. So we spent a couple of days in New Orleans and then drove down to Florida, having no idea what we were going to and ended up spending more than a week with Dennis.

PSH. And you thought you were going to be camping or something and then you were in luxury.

GB. It was just amazing, yes, and then we were in luxury. He spent a lot of time with us as well. It was really, really nice.

PSH. One of the things, when I was talking with Allan Tobin, we were going over how very skilled Nancy was in somehow joining up all these scientists, who Allan had suggested, with famous people and giving the scientists a real feeling that they were important themselves. I mean Dennis Shea is a very good example of that.

GB. Yes.

[Break]

PSH. So Gill, we got as far as your first HDF meeting. What about Hans now as a person to work with. You had 4 years working with Bob at St Mary's, now you were working with Hans, was that a transition that came easily?

GB. It was a transition that came easily. They were similar in some ways in that they were both very inspiring but completely different people, obviously, in terms of their approach. Hans was just an amazing person to work for, I

found. I learned how to do science with Hans. I learned what the scientific method was: how to plan an experiment, how to try and develop a technique, how to break things down into steps, how to find easy ways of controlling things with cheap reagents. Hans was amazing because even though he had a huge lab he would come and tell you that the magnesium concentration in your buffer was wrong. He could still do science at that kind of level. So I found him really, really inspiring. And he was always so enthusiastic about experiments.

PSH. That's interesting because in terms of how an outsider might see them, Bob was always you might call, demonstratively enthusiastic, whereas Hans was always very quiet, so how did his enthusiasm transmit itself?

GB. On the way out in the evening, he would go round the lab and ask people how their experiment was doing. He always had an interest, a very close interest in your day-to-day lab work, he was very enthusiastic at the bench level about what you were doing. He always had so many ideas. That was his downside, if anything because you never had to have an idea in the whole time you worked with Hans, because he had so many for you that you couldn't possibly bring them all to fruition. So people either did very well with Hans or they didn't do so well, and that was often because they were unable to prioritise. You had to be able to prioritise. Because if you couldn't, Hans would drown you and you wouldn't know what to do first.

PSH. Were his ideas mainly on the methods side, or were they on particular biological problems?

GB. I think he wanted to be able to describe a living cell / organism, and it's almost starting to come to fruition now with systems biology. What Hans wanted to be able to do was to develop the computational powers in parallel to the biological experiments, and be able to put them all together and to be able to understand how a living thing worked. I think that was his aim. Back in the early eighties he was building the first robots, and developing the programmes or the databases that might even be able to begin to do these sorts of things, which of course are now still being developed. Or he would say when he was thinking about doing embryo in-situ, wouldn't it just be fantastic if you could put all these in-situs together and you could just walk into an image, walk into an embryo. So he was always thinking on a very big scale of being able to describe a living process by breaking it down. When he was a PhD student he told me that he could still take a computer apart, he understood everything about the computers he was using. So even when he was running a huge lab he would just tear his hair out in exasperation because he would have an IT team who did not understand what he wanted them to do. And he would spend his Christmas vacation trying to write the programmes because he couldn't get anybody to do what he wanted to do. He was still doing that when I worked with him. .

PSH. I'm trying to think where he got that from or whether it was just his own character. Because had he been in Heidelberg for a long time?

GB. Well he did his PhD in Göttingen and I can't remember who that was with, and his postdoc was with Paul Doty at Harvard. He was at Heidelberg

about nine years. I think the two parallel interests had come together when he was younger and that he had the fascination with computers and being able to understand them. He was very good at developing technology. It was Hans who published how to do a Northern, the techniques for running gels for Northerns were developed by Lehrach. He was really in at the beginning though cloning collagen.

PSH. Again, thinking of diseases, Hans stuck with Huntington's for the whole of the collaboration didn't he, even though I never look on him as being a kind of disease orientated person.

GB. No mostly he wasn't. Mostly he was interested in analysing genomes and building up the technology to do that. In the early eighties he was trying to bridge that gap between linkage and gene. The long range cloning techniques were needed to get from a linkage to a gene. He developed the techniques and wanted to have diseases to apply them to, so at that point he worked on cystic fibrosis, Fragile X syndrome and Huntington's disease. He would have one or two people working on each disease, but he did get very drawn into the Huntington's disease question. He worked on HD for a long time after the gene was cloned with Erich Wanker and he still has an interest in CAG repeat diseases as Sylvia Krobitch is a group leader in his Institute.

PSH. Over that period I sensed that towards the latter part, in some ways you had taken over the main initiative on that side.

GB. In terms of the HD, I ran the day-to-day small HD group as it was. We actually had four of us at the end working on HD, two post docs: myself and Holger Hummerich; a student, Sarah Baxendale and a technician, Michelle Kirby, which was quite a big group by Hans's lab's standards. So yes, I was recognised as the group leader and had senior authorship as well on some of the papers. Hans would say that I was running it and I would give most of the HD talks and all the teaching lectures on HD. But he was very much involved in it and in driving the direction. I wouldn't pretend to have been driving the direction of the research.

PSH. During that time, what do you think were the main contributions that your group provided to that collaboration, thinking in terms of before the cloning of the gene.

GB. Before the cloning of the gene? Well obviously the physical maps were very important and it's hard to imagine now, but closing one of those gaps was a really big deal. That foundation was very important to setting up the clone base that covered the four million base pairs of DNA between G8 and the telomere. I cloned the telomere of chromosome 4p which defined the limit of the physical map. To clone the whole region, we first made the YAC contigs, so that most of the DNA was available to search, and then Hans's techniques for creating cosmids meant that it was easy to convert the YAC contig into cosmid coverage. The cosmids were exon trapped by Alan Buckler in David Housman's group and he sent the exons to Marcy at MGH for cDNA isolation. The cosmids that the exons for the HD gene came from were from cosmids isolated earlier-on. But together we would have all had the entire region covered, cloned all the genes in the entire region. So the one thing

about the way the collaboration worked was, because we weren't all racing to win, we together took a systematic approach - in case it was necessary. Do you understand what I mean?

PSH. I do.

GB. We didn't just pull out one gene and look to see if it had the HD mutation. That of course was happening as well, but we had the luxury of saying, we will cover everything, that way we will definitely find the gene. We might find it as we go along, but we will definitely find it in the long run.

PSH. And it wasn't at all clear which lab the actual relevant clone might turn up in.

GB. Well no, and you couldn't predict where that would happen, because we had divided up the region for analysing cDNAs. Your lab, our lab and Marcy's lab were looking in different regions because it was silly to look in the same place. No, I think from that point of view we potentially buried our egos as much as any scientists can.

PSH. What was your reaction Gill, at the time when, before the paper came out, at the time when you learnt that the gene had been found? How did it come to you first by the way?

GB. I think Marcy and Jim must have called Hans. Hans told me, so I didn't hear first hand. They were sure that they had the gene before they let any of us know, as you know. So I think that they pretty much had the paper written before they let any of us know.

PSH. Yes, that's my understanding.

GB. They wanted to make sure, but I think it went extremely quickly at the end because the 10.3 kb cDNA had already been sequenced. It was composed of cDNAs that had been cloned from some of the first exons that had been trapped (IT15 and IT16) and it was only the very 5 prime end, where the mutation is, that was missing. The sequence of the gene was already all in place. Once they had found the CAG repeat, it was a case of running PCRs through patient samples, it all came together very, very quickly at the end. So I just felt immense relief actually. I just was so happy. This was partly because we were all worn out by it by that stage. We were completely worn out. It had just gone on too long. We were all bracing ourselves for the fact that it might require sequencing the entire region. Of course we had already started working on that with John Sulston - on sequencing the entire two million base pairs. He had all the cosmids and was starting to do that. I was just so happy, the relief was just unbelievable. And then I don't know how we kept the secret either., Jim and Marcy didn't want us to tell anybody, and so we just locked ourselves up and didn't communicate very much for the next month. I had never thought I could keep a secret like that. I don't know how it worked for you, but even in the lab we didn't tell anyone because, there had been this really clear directive that this was too dangerous and it was potentially too easy to find this mutation and we mustn't let it out. If you knew what you were looking for it was very easy to find.

PSH. Yes, I put one potential foot in it myself during that time, because I had assumed that Nancy already knew.

GB. You were starting to tell me that in Manchester and then they dragged me off, Anne came and dragged me off.

PSH. I had assumed, I think probably quite reasonably, that Nancy already knew and phoned up to congratulate her only to be told she was in Venezuela, so I left a sort of brief message saying I want to add my congratulations Nancy. And then of course somebody who'd got that message, 'what's going on, what's going on?' Anyway it wasn't until Nancy got back from Venezuela, I don't think they could get hold of her there anyway and they didn't know what the congratulations were about. It was an amazing time.

GB. For you as well. For you it was different, you had that huge amount of work. I mean the excitement of then following the mutation, because of course for us we never had the patient samples so we all started planning how to make mice and all this sort of stuff. We weren't in the crazy . . .

PSH. I have vivid memories of Russell going to ground with about 500 samples and I was always worried about the amount of radiation he got exposed to during that time. But he worked solidly for about one week, more or less 24 hours a day. Then of course the thing that was fascinating was after the gene had been found, really everybody was sent back to the drawing board again, weren't they, nobody knowing what the function was and it has always interested me that different people started off again in different areas. What made you take the transgenic route, because it has proved hugely productive? Was it a conscious decision?

GB. I suppose I stayed in Hans's lab for about nine or ten months after the paper came out and we started lots and lots of different things. We were making constructs for expressing proteins, starting to make constructs for various mouse projects and Sarah (Baxendale) was looking at the Fugu gene, so there was the evolutionary project, the protein and the mouse work. Hans basically said to me I could do whatever I wanted when I left and we sort of decided I would carry on making the mouse. So we divided up the projects roughly that his lab would carry on with the protein work and I would take the mouse work, but he always said there were no constraints. You could do whatever you want because there was so much to do. We would never be in a position where our efforts were overlapping. We could always help each other. So that was just the way it happened really. I had started making constructs when I was there and brought them with me to UMDS. I wrote an MRC grant before I left and managed to get that funded, so I was only here a couple of months when I knew I had an MRC grant.

PSH. Remind me again. The gene came out in '93 and you moved '94?

GB. I moved January '94 yes.

PSH. So really the whole of the transgenic work was done at Guy's rather than at ICRF.

GB. Yes, I had just started making constructs at ICRF.

PSH. Now did you get help? I mean were there other people either at ICRF or at Guy's involved very much with transgenic work?

GB. No. Well there was a facility at the Rayne Institute at St Thomas's where the constructs could be injected, so I had to make the DNA and send it over there for injection. Other than that there were no transgenic mice at Guy's. I went and looked around the animal facility, which of course is much, much more swish now than it was then. I was shown a room that they were going to use for transgenic mice if they ever got any. Paul Sharpe was hired around that time by the Dental School and we were the first two groups to have transgenic lines. I had never touched a mouse when I wrote the grant. So it was all a little bit scary, and I went on a Cold Spring Harbour course in the summer of '94 where I spent 3 weeks learning mouse embryology and how to do mouse transgenics. Ann McLaren tried to teach me how to kill a mouse, which took about a week. I was hopeless. But I learnt so much, even now that course stands me in good stead. It was fantastic. So what drove me was really a determination to be able to carry on working in some form on Huntington's disease.

PSH. And did putting in the repeat, did that cause practical problems, in the construction of the mouse?

GB. Well yes. The mouse we have now, as you probably know, was an accident in a sense. So the R6/2 mouse was not designed to be a model of Huntington's disease. I was trying to make YAC transgenics and I wanted to use very long repeats, reasoning that we would be modelling a childhood disease rather than an adult onset disease. I had made a lambda phage library from a cell line we got from Coriel years ago. It's a fibroblast cell line from a patient with three-year disease onset. We finally found out that this cell line had a repeat of about 175 CAGs, a huge repeat. Of course we didn't know that in 1994 and we couldn't measure a repeat of that size until I'd been here a couple of years. And so I was making YAC constructs using this DNA. When preparing phage DNA, in order to keep the repeat stable, we used to do 8 phage maxipreps at a time, and about 4 out of the 8 would have maintained a long repeat. The constructs for recombining into the YACs were made by ligating DNA fragments – so that the DNA did not have to be propagated in bacteria which would lead to contraction of the long repeat. After about a year I had successfully recombined a repeat of at least 150 CAGs into a YAC, only to find that it recombined out again and contracted to a very short repeat. I must have hit a size whereby it could recombine out. And so Laura Mangiarini – the postdoc who was working with me on this project and I thought that we should just see what happens to very long CAG repeats if you use them to make a transgenic mouse, before we spent another year generating YAC constructs. Mice don't have very long repeats as far as we know, and so maybe they would be unstable in mice. So we just took a piece of the genomic DNA that we had been using to make the YAC constructs and used it to make transgenic mice, in order to see what would happen to the repeats. No one

was more surprised than us when some of these mice started to develop a phenotype.

And so there was an extremely exciting day when they rang up from the Rayne to say that a couple of mice were showing a phenotype. So Laura went over there and said that there was a mouse that didn't look very well at all. So I rang up Steve Davies because we thought this mouse might have to be perfused and fixed if we wanted to look at its brain. He brought all of his solutions over to the Rayne on his bike, and I hired a video camera, because we didn't have one then. We found Mary Seller, who knew more about mice than anybody I knew, and the four of us went over there. It was really exciting.

Alan Buckler was also here that week as he was teaching on a course at Guy's. And then of course it took us about a year to establish the R6/2 line. They don't breed that easily, well once you know what you are doing it's fine, but when you don't know what you are doing it is not so straight forward. We didn't talk about the lines as we had no idea what we had. I mean the phenotype could have been caused by the disruption of another gene. I was very happy at the time. I didn't care what it was because I had a mouse with a phenotype and if I'd knocked out a gene that was important, then I had an interesting project. I was very happy irrespective of what it was. And I was very worried about saying it was anything to do with Huntington's because I had no idea whether it was. So it was only after we'd really managed to characterise it and were close to publishing that I presented the work. At that point, we were pretty sure that the repeat was causing the phenotype.

PSH. What about the inclusions. At what point were you able to find that there were these inclusions, because they weren't really known about before were they?

GB. No, not at all. Well, we gave Steve Davies sections of brain because Steve worked in neurodegenerative disease, I mean his interests were Huntington's, Alzheimer's and Parkinson's so although he had not been working with transgenic mice, he was familiar with the structures of the brain. He performed immunohistochemistry with an anti-ubiquitin antibody, we also had an anti-huntingtin antibody (Ab1) from Marion DiFiglia. You can't miss the nuclear inclusions in the R6/2 mouse brain. You see these dots everywhere. We didn't know what they were, Steve thought it might be the nucleolus at first. They have a very good EM Unit at UCL. Steve worked with Mark Turmaine, the head of the EM Unit and uncovered the ultrastructure of the nuclear inclusion. Again you can't miss them in the R62 mouse. Steve started doing some literature searches to see whether he could find anything that had a structure similar to these in other EM photographs. He turned up at my flat one Saturday morning with a book in his hand. 'I'm really excited. I've found something' and he held this book up. I said "Oh I've got that book" because Nancy had given it to me just a couple of months beforehand. It was a neurology book from 1979 that had a chapter showing the ultrastrucure of brain biopsies from people with HD. There was a micrograph in that chapter that looked identical to the ones from the mice and so we thought . . .

PSH. And nobody had really paid any attention to that.

GB. No one had paid any attention to it. At that time it must have been around spring or early summer - something like April or May 1997. Jack Penny and Anne Young were in London as Anne was giving the first Anita Harding memorial lecture at the Institute of Neurology. We had published the R6/2 mouse paper in '96 and Steve started to see these structures in the brain beginning of 1997. Steve rang Marion DiFiglia and told her what he had seen, I guess because she had given us her antibody. And she started to go back and look at her sections and rang him up to say that with that N-terminal antibody she saw a similar thing in human brain, but she hadn't known what it meant because she was also using other antibodies against the huntingtin protein and was only seeing it with the N-terminal antibody. So then she started getting her Science paper together very quickly. We were also communicating with Chris Ross as we also had an antibody from him. And then Chris also saw the same structures in the brain of a DRPLA patient. But they didn't get their paper published quite so quickly and it came out the next year. So it was incredibly exciting actually. And then we read an abstract of Hank Paulson's. I can't remember, I think it must have been a similar time to when Steve rang Marion. His abstract was in Neurology, just an abstract where he said something about a nuclear structure in the brain of an SCA3 patient. So we thought Wow. It sounded like he was probably seeing something similar and his paper came out at around the same time.

PSH. Tell me finally Gill, Max Perutz. How did you first come in contact with him?

GB. The first time I really spoke to him was at that European Society of Human Genetics Meeting. Do you remember it was in London that must have been in 1996? I had been to a seminar of his before that and introduced myself, but had not really had a conversation with him. I found him a bit daunting really. At the Human Genetics Meeting, he was saying, well, what are you going to do with this mouse if you get it? And I didn't really know all of the things that we would do, to be quite honest. We were still too preoccupied with trying to work out how to do a western blot. But he was just fabulous. And then he got so excited when he first saw Steve's electron micrograph pictures and then of course at the same time Erich was seeing the fusion protein starting to aggregate. It all happened at the same time. Because we had generated the exon 1 mice, Erich made fusion proteins with an exon 1 protein. He started to see fibrils and we were telling Max everything as it happened. So there was a lovely time in Cambridge, I guess it must've been around the end of '97. Was that when Halley Bop comet was?

PSH. Yes.

GB. I remember there was Steve, Erich and me in Cambridge, walking through the colleges with Max to Peterhouse, where Erich was staying. We were all intensely studying these electron micrographs, looking at electron micrographs in a little room. Max was incredibly enthusiastic and very, very supportive always. And when you said today, a lot of these people were young, I remember him saying 'science is a young person's game'. And I was thinking, why are you saying that? It's ridiculous. You have just made all these discoveries and you are in your late seventies or your eighties and still

working in science and making seminal discoveries. He was so encouraging wasn't he?

PSH. He was a wonderful person.

GB. He didn't ever make you feel as though he was in any way superior to you.

PSH. He was wonderful. Well Gill I am going to draw it to a close there. We could go on talking right up to the present, but I think I'll stop there. Many thanks.

GB. It's a pleasure.

End of recording