Han Brunner

Personal Details

Name	Han Brunner
Dates	Born October 18th 1956
Place of Birth	Rotterdam, Netherlands
Main work places	Nijmegen, Netherlands
Principal field of work	Human clinical and molecular genetics; medical genetics

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
Date of Interview	28/10/2014
Edited transcript available	See Below

HB – Han Brunner

PH – Peter Harper

PH It's Tuesday October 28th and I am talking with Professor Han Brunner at the Academy of Medical Sciences in London.

Han, may I start at the beginning and ask when were you born, and where?

HB I was born October 18th 1956 in Rotterdam. As the first son – the first child, actually - of 4. My father was then a lawyer and my mother, who was very intelligent but never went to university, and afterwards with 4 children became a full-time housewife.

PH So, may I ask, was there any tradition of science or medicine in your family, among relatives around?

HB Most strikingly there is no tradition of business anywhere in my family. They are all either servants or in the trying-to-be-helpful, not-for-profit occupations I think. My father was the first to go to university in his family. His family was in the railway system. So if I can go back all the way to my great-great-grandfather, he came from Switzerland, which explains my name. Brunner is a very Swiss name. Around 18, just after Napoleon, he enlisted as a mercenary in the Dutch army. He had a son who became the first station master at Zevenaar railway station, which is on the Dutch border with Germany. The train to Germany went through Zevenaar. That was around 1865. And then he had many children, including 7 sons, and my grandfather was his youngest son, born 1884. So in 3-4 generations I go all the way back to Napoleon and that. And then all of his children also joined the railway in various places. Some went to Indonesia, a brother of my grandfather went to South Africa at the time of the Boer War, and my grandfather became very involved in the electrification of the tram system in the Netherlands. Only his children really went to university. So that was new in our family. We had no tradition. My father was I think the first scientist and scholar. He was a lawyer for 20 years in Rotterdam, which is why I was born there. He was very involved with ships and shipping. Rotterdam is a big port and so there were a lot of things that went wrong with these ships and then there would be claims and damages and my father would be a lawyer for either party. He was a lawyer for the eastern Germans and for the Russians when things went wrong. I remember him going to a ship that had run aground near Vlissingen and he came back and they'd had lots of Vodka discussing with the Captain what had happened. But he got tired of being a lawyer after about 20 years, when he was 45 years of age, and he felt it was becoming much too – money became too important in the business. It was all about making more money and lawyers were becoming very rich. So he decided he didn't want to do that anymore and he looked around and then was asked to become a Professor of Civil Law at Groningen University so we were all transported to Groningen. I was 16 at the time. I remember not liking the idea very much. I came from this big metropolis of Rotterdam, you know very busy, kind of like this city, like the centre of the world to me. So we went to this out-of-the-way place in the countryside called Groningen. But it turned out to be wonderful. My father was very, very good at analysis. He was very precise and he could really take an argument apart into its constituent pieces. So he would write comments, commentaries really, on the judgements of our Supreme Court. So that's a task that's given to a scholar, someone in the country, and so there is a case for the Supreme Court, they make a judgement, they write an extensive motivation. Then there is someone who writes a commentary, usually both explaining why they came to this conclusion but also quite often pointing out how all that was ridiculous and wrong, which I think is something he enjoyed very much. Now I was personally never in awe of him, or intimidated, but he was quite a large professional figure so when the time came for me to decide what to choose in terms of my

career, well actually my university, I had worked out that it could not be law. I would have loved doing law. I think I would have liked the sort of systematics of it, the rigour, and getting it precisely, the formula precisely right. But I was also very clear that that would have been a very hard battle to fight. I think his shadow would have been over me. So I decided to choose something really very far away from law, and partly because studying medicine meant that you could go in so many different directions, including some quite scientific, I thought at the time that was quite a good choice but I really had no idea of where I was going to end up within medicine. So that's how it went.

PH So when you went to study medicine, which university was this?

HB That was still at Groningen University.

PH Did you, at Groningen, did you take a primary degree first and then medicine, or was it medicine and allied sciences from the beginning?

HB No it was from the beginning. We have that system where you choose at 18, which I think is rather silly because at 18 I don't think you have any – well, I certainly did not have any idea of what I wanted to be or was ever going to be. I don't think I had any idea of where I was going until I was 25. But no, you had to make that choice early on. And I found that a very difficult choice. I can remember thinking "If this is a disaster, I will not feel bound to it. I'm going to allow myself to break free whenever I find this is the wrong direction and want to do something very different." But that never happened. There turned out to be things within medicine that I quite liked and enjoyed.

PH What were the things, as you went through your course that you found particularly enjoyable and worthwhile?

HB I think, oh it was clearly the subjects that presented little puzzles to solve. So internal medicine, endocrinology, feedback loops – things going up because other parts of the system went down – homeostasis. All those things where just by thinking about a problem you can solve it. So I think those were the subjects that interested me. I was completely hopeless at anything that involved manual dexterity. I was assisting an Assistant Professor with experiments in my second year and he kind of looked at me and said, after 2 weeks he said, "I really don't think you should become a surgeon", he said. I took that to heart. I was not planning to do that ever.

PH Would you say on the whole in your medical training that it was the more clinical or more basic science that attracted you, or was it the kind of interface and mixture between the two?

HB I think intellectually I was most drawn to the basic science. As I've said, I was in physiology and this was a very good department at the time. But it was individual scientists in individual rooms thinking about their individual problem, and it seemed a very, very lonely pursuit. So when the Professor, after some time, at the end of my studies, said would I want to do a PhD in his department, I thought about it for a few days and then declined, somewhat to his surprise, I think. Because I did love it, but I just thought it would be too lonely. And also I was unsure then that I was fit to be a full-time scientist. I really didn't think that would work for me. So it was a combination of things. And I've always liked, one thing I do like about medicine, of course, is interacting with patients and talking to them and listening to them. That was always there. But I wasn't going to be... So the way it happened then, at the end of my rotations, that's what they call it in England, I had just done obstetrics, which in those days meant you would do the outpatients in the morning, admit inpatients in the afternoon and then in the evening you would be on call for deliveries with the midwives. That was for about 4 weeks. And that was very lucky because every night I was on call I would be called at midnight and then you would be home by 5 or 6 in the morning. So you didn't sleep and of course at 8 you had to present again because all these things about sleeping in after the night were not even

invented. That just didn't exist. So I did that for about 4 weeks and then found out I was becoming psychologically unstable. I literally would have tears in my eyes when a baby was born. I thought that's really not me. I'm a positive character but I'm not that sentimental and emotional. So it was clearly the lack of sleep that was not doing me very well. So after that I took a break. There was a scheduled break for about 2 weeks and my girlfriend, who is now my wife, we talked about it and I said I really like clinical medicine but I don't think I want to have a specialty that has these long hours. And I also didn't like the way they treated their trainees at the time. It was all very top down and very negative. Always pointing out the mistakes people made and making them insecure. And I said "I want something scientific" and so that kind of – when you cross these things off then the only thing left more or less was clinical genetics. At least it was for me.

PH What year was it you qualified?

HB I qualified in '84. In February.

PH So by that time clinical genetics would have existed as a specialty, even though fairly embryonic still.

HB Oh yes. There was an active group at Groningen, led then by Leo ten Kate, who was a very good clinical geneticist, very systematic and interested in dysmorphology. And I did a small, 2 week course with him and that quite took my fancy. And they also had, in that time they had projects in that department trying to clone – unsuccessfully in the end – trying to clone the retinoblastoma gene. So there was this, you could see how genes existed in the real world because they were actually becoming more accessible to the technology. The DNA technology had just started becoming productive. But there were not a lot of people who realised that at that time because when I told my peers, I told my fellow students at Groningen University "I am going to do clinical genetics" they couldn't make any sense of it. They said, you know, why not do something interesting. You know, they thought, partly because genetics was taught at university it was all Bayes and complex pedigrees – that genetics was a completely statistical art, nothing to do with real patients.

PH Before you went into clinical genetics, was there the pattern of training that we have in Britain where you need to do for a few years some paediatrics, internal medicine and other clinical specialties before you go back into clinical genetics as a specialty? Was that the pattern then?

HB Yes, the pattern was there but there was no official training programme. So I believe I was the first in the Netherlands to go straight from medical school into clinical genetics training. Everyone before me had either done paediatrics, or some had done internal medicine or neurology or had worked as general practitioners. So that was a new thing, and I'm not sure why they chose to do it that way. This was in the end I think at Nijmegen.

PH Did you move from Groningen to Nijmegen around this time?

HB Yes I did. So that was June '84. I was trying to find a position in clinical genetics so I wrote – no, I called – every clinical genetics unit in the country. Most universities had one. And I would work out who the chief was and ask to speak to said person, introduce myself and said "I'm finishing my medical studies. Would you have a training position for me?" And that was very unsuccessful and no-one really responded. Except Martinus Niermeijer, who was at Rotterdam, who said "We don't have anything but if you still haven't found a position in 3 months' time please do call me again." Which was very typical of him, very caring. So I called Nijmegen and I got Ben Hamel on the phone and he said "Well, actually, we do have a position but we're rather looking for a neurologist to fill that position because we think we have weaknesses in that area and we don't think we want someone straight out of medical school." I thought that was the wrong answer, I didn't want that answer, so I called again because I knew there were two in Nijmegen and so I asked the secretary "Can I speak to Ben ter Haar?" And I talked to him and he was much more responsive so I decided

there and then that I would try and stay clear of this terrible person Hamel, who has been one of my best friends for the last 25 years! So that was still there. Ben I think would have favoured – and the unit, the clinical genetics unit, was still semi-independent from paediatrics at that time at Nijmegen. So what happened was I got talking to Ben and he said "We may have something in a little while, I'm not sure." This was around the time that Hans-Hilger Ropers was going to succeed as the new Professor and Head of Medical Genetics and he wanted changes and he also wanted to do more science. It was not a very strong scientific department.

PH May I ask who was it then who was head of the academic department before Hilger Ropers?

HB I'll get the name. It's escaped me.

PH Not to worry.

HB It'll come back.

PH So am I right that this was partly an academic unit and partly a sort of clinical, hospital-based unit? Or was it entirely academically-based?

HB It was 3 units which were in different locations in the hospital grounds. There was cytogenetics that was located in dentistry. There was human genetics that was somewhere else in another building. And then there was clinical genetics which was in paediatrics. And that was clearly wrong so the hospital had decided – Geerts was his name, Sjoeke Geerts. He organised one of the gene mapping conferences I think, and then retired. But these 3 were potentially not talking to each other, especially the cytogenetics and the human genetics units were very, very far apart and could not be brought together by persuasion or force. But then Hilger Ropers came in and was given the task of uniting it and he went forward very energetically and did that. But I remember people outside the elevator after a seminar shouting at him – from cytogenetics – "you're destroying this department!" Which was clearly wrong. It was all about change and fear, and he was very vocal. He came in late '83 I think and he said – they were doing the chemistry of nucleic acids in the human genetics department, which was about DNA, and they made some scientific findings I think to do with HPRT deficiency. But that was basically it. And Ropers said "We're going to do recombinant DNA." And it was completely new. So that really transformed the unit and he brought it together with the support, I would say, from Ben ter Haar, who was a wonderful free thinker and a very positive person. And Ben ter Haar was the one who trained me in clinical genetics for the first year. So the plan was I was going to be trained in clinical genetics and I would also do, sort of intermixed, a PhD on myotonic dystrophy which was the subject they had chosen. I don't know how it had been chosen.

PH Can I just ask you: Hilger Ropers, had he come from elsewhere in the Netherlands or had he come in from Germany.

HB No, he came in from Freiburg.

PH From Freiburg. Because the boundaries are all rather close geographically and I can never be quite sure whether Hilger was Dutch or German or whatever.

HB He is everything a little bit. He is German – he was born in northern Germany. His wife is Dutch so he is always connected to the Netherlands. The reason he came to Nijmegen was because – he's told me – at that time, he was in his mid-40s – that he was unlikely to be asked to chair a department in Germany, which in retrospect seems silly because he is one of the best in the business wherever. But he came and – he would drive up from Freiburg on I think the Friday morning and stay until Monday, in this interim period, and it was

like a 6 or 7 hour drive and characteristically he would just race up on the Monday and then race down again. He was really changing everything very, very quickly and putting it together into one coherent unit. So he was the one who built that department much the way it is today.

PH Now before we get on to myotonic dystrophy, I was just looking through your publications and you seem to have started off, and indeed remained quite a lot, with the X chromosome and I saw that your first publication – am I right? – was on Alport's syndrome, but I couldn't read it because it was in Dutch.

HB I had forgotten about that one.

PH But how did you get onto the X chromosome and Alport's and then X-linked deafness?

HB Two reasons. One is that Hilger had worked on the X-chromosome and he had created a panel of X-chromosome hybrids and Hilger Roper's entry into the field was unique because he had an X-chromosome mapping panel so whenever someone found a polymorphism he could map the location of it from his panel and that's what he did. And that got Hilger very interested on the X and there were very few markers on autosomes as I remember. And mapping on autosomes was daunting because it was such a big place. I remember – and you do too, of course – the people mapping Huntington's disease on chromosome 4, I believe after 10 markers or so; it was incredibly lucky and you could easily – a project to actually map something could take years. Because you would do one marker and then would have to, with all the hybridisations and the autoradiography you would have to wait for 4 weeks or 5 weeks and then the bands were not good and you had to repeat the experiment and it just took forever. So the X chromosome at least was kind of tangible. These were projects one could do. These were projects you could actually, with a bit of creativity, almost do on the side. So the Alport's came about because I was in a room and my next door neighbour was a paediatric nephrologist who had Alport's families. And he had two clearly excellent families. And that was – we did not have enough meioses, of course not enough informative meioses to confidently map it, so I had to find another family and I found one in the literature and it was from Essen which is not very far away, but is in Germany, and the senior, the last author on that was Eberhard Passarge.

PH Ah.

HB So I went and visited Passarge and said "We are mapping Alport's syndrome to the X chromosome". And Passarge said "But it's not on the X chromosome". Because there was an influential paper that – I forget what the term for it was – was it pseudo x-linked or inherited? Someone had, because at the end of the day we now know that there are autosomal dominant and X-linked semi-dominant families and these had been mixed together and then someone tried to create a unifying theory of that, which was very complex because the gene was on an autosome but it was somehow influenced, I believe, by the X chromosome in its segregation. It was a very creative but crazy theory. And Passarge had read that and I said "No, no, no, I know, it's clearly on the X and we've more or less mapped it. Can we have your family?" Luckily for us he decided he would go along with that. Which gave us in the end a lod score over 3. And a publication. It did turn out to be where we had mapped it. So that was my first really successful mapping. I had been trying to map myotonic dystrophy for some time. At that stage we just never had something that was worth publishing.

PH In that case, tell me how you got into myotonic dystrophy in the first place because it's I suppose not the most obvious disease, unless perhaps you are a neurologist. So how did that begin for you?

HB I don't know because Hilger, I think, chose it. I honestly don't know how he chose it. I think the arguments at the time were this was relatively frequent, it was at least not exceedingly rare among late onset neurological disease and there was linkage to begin with, of course, as you know, because you were one of the people that mapped it, contributed to the mapping. So I think it was that combination. And then Hilger

got in touch with the neuromuscular society, the patients' society in the Netherlands called VSN and the families were all very, very enthusiastic about this and really, in their perhaps characteristic way, the president of the Myotonic Dystrophy Society wrote to the Queen and the Prime Minister, saying they had to support this research.

PH I don't imagine that happening in this country quite, but …

HB The patient organisation had located families so I was assigned to drive around the country – to rent a car, I didn't have a car, rent a car for the day and drive up to some village where an entire family would have gathered.

PH Yes

HB And I would explain the project and I would take their blood, which as I mentioned I'm not very dextrous. I always found that quite exacting, to get blood samples from everyone, and the children who would scream. Sometimes these houses were quite dark and it was really logistically quite difficult. But that was a fantastic experience and of course seeing the families in their own homes, listening to their stories, I think is very good, very revealing, and I was very impressed by the psychological aspects of myotonic dystrophy, what it does to the way these people think and express themselves. And I have never been able to quite catch it. I don't think anyone's ever, for me, quite captured it, what the core of it is. It's quite distinctive.

PH It's distinctive and very complex, I think, too. And I am interested that you were impressed by the fact that you were visiting families at home. It gives one tremendous insight and I think it's a great privilege to be able to do this. And if one hasn't, I think one misses out on a huge area of impact of genetic disease.

HB Oh yes. And even the downward social mobility that is associated with myotonic dystrophy, these early adult onset people who are not quite destitute. We don't have that in the Netherlands so much although there is a previous thesis, I think by de Jong, going back to the 1920s, where he does describe that kind of family. But certainly not in the 80s when I visited. They were living in rather poor circumstances and you could see very large differences in social success, I even think in happiness, between the affected and the unaffected, even within a sibship, so all these things did indeed have a big impact on me.

PH Were you doing both the clinical and the lab work in this project or were you just doing the clinical work or how was that?

HB I was doing the clinical and I was assigned the task of doing the linkage which I very much enjoyed. Running the linkage programs and trying to work out the pedigrees. Both were fun. The linkage programs were very unsophisticated and you would have to type in zeros and ones in the first versions and then if you made one single error in the spacing then the program would crash and you would have to redo the entire file and it was all terrific. I spent long nights doing that.

PH Were you using LIPED by that stage?

HB LIPED, yes.

PH I remember in the equivalent situation I used to carry around Newton Morton's lod score tables but then LIPED was very good. I was impressed with it.

HB Yes, Liped was invented by Jurg Ott. But it was not very easy to handle. It didn't have an input format. So I remember I would do this at night usually, I would go back to the lab as I've always done, maybe around 10, and I was very, very tired and I had access to the one university computer. I could run my – I had a very clever student at that time, Eric Lambermon, he was a multi-talented person who actually did understand - I

did not understand –computers but he did. And he somehow managed to get us our linkage programs run on the one available server at the time and we had one computer in the department that could be connected to this university computer, but only if we did it at night. We were not allowed to do that during the daytime so we would go back and do it at night. But it was also, I think, and we were very unsuccessful because we were mapping, as was everybody else, from 1985 onwards. We knew there was linkage with APOC2, which I think you described.

PH Jointly with the St Mary's group. Bob Williamson was there at that time and I think that that's probably how Helger Ropers got interested because he was working with Bob, or collaborating, at the time of the first Duchenne x markers with Bob and Kay Davies. And then we went on to something autosomal. And the choice for us – and there weren't very many other choices – was myotonic dystrophy, which is how I especially got involved. And I guess Hilger would have known all about that through the links with Bob.

HB That's probably true, yeah. So we were very unsuccessful at mapping myotonic because first of all while we had quite a good set of families, we did not in the end have many informative meioses to take us beyond. We basically had no recombinants with APOC2 that we could use to then further map it. So we never progressed much beyond APOC2. The other reason, which I had forgotten about but I have spent some time re-reading my PhD thesis as a preparation for this interview, it turns out that we were all using a somatic cell hybrid that had a piece of chromosome 19 in it. And everyone assumed that the myotonic dystrophy gene would be on that particular piece of chromosome and in the end that turned out to be wrong. It was beyond this somatic cell hybrid, on another piece of piece of chromosome 19 that nobody was studying until much later. That was, I think, was Keith Johnson who then changed everything by looking at another piece of chromosome 19. So I think for about 4 years we had not many informative meioses that we could use to progress, and we had no markers that were better. They were all – whenever we found something without linkage but it was always further away and on the same side as APOC2. So we couldn't bridge myotonic dystrophy. That was all done by other people. So I spent 4 years not getting anywhere. I had a lot of fun. The mapping itself was really interesting because the DNA markers, certainly in our lab, were not entirely reliable and therefore you had to not just do the linkage but you had to look at your data and think "What if one or two of these genotypes are wrong? And if I changed them would they, would the whole thing then make more sense?" So this was all conditional thinking and you could spend – I did that too, I think everybody did that – we would create haplotypes by hand and then work out which went where. I would make 20 versions of a pedigree with the marker information, saying "what if this is on that haplotype and that is on the other haplotype, and how would it all work out and then which of the marker genotypes that I've been given by the lab (so I never did any lab work) could be wrong?" And then it took a bit of courage to go back to the lab and say "I think that genotype is wrong. Would you run it again?" Because even a single genotype was a significant investment and people never like – do not enjoy – repeating previous work. So they would try and avoid me, from having to do that. That's the one thing I got really good at and it helped me a lot. I helped other people map things because they were confused by their results and I would say "everything would fit if this genotype is different from what you are telling me it is, so go back to the lab". And I had the same thing later with myotonic dystrophy, where I had a complete pedigree and it all made sense except one person who was – this was later, this was not a family I had seen, this was referred by a neurologist so it was not in the initial 20 or 25 families and the neurologist had indicated that person was affected but the pedigree only made sense with my marker data if that person was unaffected. So I called the neurologist on the phone and said "You've sent us this family, thank you very much, and we've done some genotyping and is there any possibility that this person might be unaffected?" And he went very quiet. And then he said "Are you a neurologist?" I said "No". And he said "Then do not try and diagnose my patients". But I still thought he was probably unaffected.

PH Well, I mean, having done the clinical studies yourself on many families, you know how very difficult it is sometimes to be sure about whether a person is mildly affected or free from it. Yes.

HB We did a small study later on when we had the myotonic mutation and looked at what the French Canadians had called the partial syndrome, which was minimal little bursts that might or might not be myotonic, on the EMG and non-specific opacities in the lens and so on. And we could see – even though we had small numbers – it was very clear that these had no predictive value at all. I think it was over-interpretation. So the, especially the milder forms I think, must have been occasionally over-diagnosed by people.

PH So your thesis – and I can say without hesitation it's a very nice thesis, and one which I used a lot – was on myotonic dystrophy and you did really some quite detailed clinical studies as well. What made you leave myotonic dystrophy? I ask that, again perhaps personally, having been somebody who never meant to spend most of their life studying it but found it very difficult to get away from. Did other things come along about that time? Or what happened?

HB Yes all these things happened. Other things did come along. There were all these – I got very interested in intellectual disability and studying the syndromes. The other thing is that Be Wieringa, who'd been running the lab, very successfully and also was a participant in the eventual cloning, although not I would say the main driver of the leap, he left human genetics. He started his own department – Cell Biology – and he moved across the road to another building, took the myotonic dystrophy project, and that also made it seem like a good – and they were also going into the cell biology of it. So it seemed that that was the time to move on I think. But I was ready to move on. I'd done almost 8 years of it.

PH And by that time you must have completed your training in clinical genetics.

HB Yes

PH So what post did you move to next? Or was there a post, or did it just kind of get created around you?

HB No it was created at the time, but I think it was always intended when I started that if I was found to be of use that I would stay. They really took me and trained me with the objective of having another clinical genetics staff member. Clinical genetics was growing. There were two. I was to be the number 3. And the only thing is they did not just train me, they said I would do 50:50 between clinical training and this scientific project. That all worked out differently because Ben ter Haar was my clinical chief and the person training me. He developed lung cancer after one year. So I had been there for a year and then he had lung cancer and then he battled with lung cancer for another year, and then in '86 he died. So that meant that Ben Hamel now had to see all the patients alone. There were about 500, at that time, per year. So I more or less dropped – I didn't quite drop myotonic – but I certainly could not spend any more time in the lab. Which was not a great loss. I was never any use in the lab actually. And I could go back to doing my bits of linkage in the evenings and I would see patients and do regular clinical genetics in the afternoons, which I found a very good combination. It was not particularly good for being a real scientist. It was good for being a hobby scientist, which I think is what I am honestly. And it's what I chose, you see. When the professor of physiology said would I want his PhD, had I done that I would have tried to have a real career in science but what I have done in reality, and I think what I chose, was to see patients for a living and then, whenever time and other pressures allowed, to look at them in a scientific way and see if we could develop little projects. So that's what I've done and that, I think, turned out to be my – I think I was always going to end there. That is my destination, I think that is what I can do well.

If I am allowed another anecdote, I saw another family with precocious puberty, again around 1990 or so. Or maybe it was earlier – late 80s. So this is the autosomal dominant male limited precocious puberty where the boys develop clear precocious puberty by age 4. And there is actually a tale in this family that the women,

when a boy is born, the older women go and look at him and they look in his diapers and they say they can see at birth whether he is going to get it. I am not sure that is – that's not been really confirmed, but that's what they tell me. So it's very very early. And this is autosomal dominant. I had this family. I went to the lab and said "Would anybody want to do linkage?" And they all went "Nah". Because linkage was like a 4 – 6 month project and they were all "Eurgh" and they all said "Yeah, we have our own projects" and "Go away". So that was frustrating and one evening suddenly I thought "I know what this is" because, you see, these boys have, their testicles, their Leydig cells start making testosterone, but there's no signal from the pituitary, there's no luteinising hormone released, so there's got to be something else. And the dominant theory – there was a paper in New England Journal of Medicine a few years earlier from NIH, which worked on the hypothesis that it was a circulating something, perhaps an antibody, akin to what happens in thyrotoxicosis. And they called this testotoxicosis. They said there's something in the blood that stimulates the Leydig cells. So they took blood of these kinds of boys, injected it into Rhesus macaques, and fiddled with the data, I thought, and got a testosterone response so they said ''there's something in there circulating in their blood". I did not believe that paper. That was prior to me seeing that family. I thought "That's wrong". That looked too artificial and - it was just - I didn't think the analysis was right. And it just ended up, it was a NIH group and they were very well known, and it ended up in the New England Journal of Medicine, and people believed it. So I had this family and I thought "It's not that. It's not in the blood." And then all of a sudden – I do this when I teach first and second year biology students – I present the data and say "Where do you think this is?" And they need 30 seconds and they say "It's probably an activating mutation of the luteinising hormone receptor gene". So I went back to the lab and said, to the same person who denied me linkage, "Would you sequence luteinising hormone receptor gene?" And she said "I'll look at it. And she looked at it and she came back and said "Do you know that's 12 exons? I'm not going to sequence 12 exons." That was still a lot of work in 1990. I was so sure I was right. This is a G protein receptor, so I went to the library and tried to find any precedent for an activating mutation in any protein; I found two, one in an acetylcholine receptor and one in a muscarinic receptor, I think. And they were both in the third intracellular loop. So I went back to the lab and said "Would you sequence the third intracellular loop?" That was 100 amino acids and they said "Ah oh … alright". Two weeks later she called me out of the blue and says "Do you know what? I've found it!" And that was really good. So that's been my kind of thing and of course, having found this one and then another one, after that it got a lot easier. I would go to the lab and they would say "Would you have another interesting family?" So it all worked beautifully. I'd try and select the patients I think are most interesting and most likely to give us interesting results and I find a friend. In the beginning I would go and find someone who I knew to be on a project that was not very productive, and they would be more accessible. So that's how I've done it.

PH Can you take me back to the X-linked mental handicap, which has proved to be such a fascinating area? Again, how did you get involved particularly in that, and how did the work evolve?

HB I wasn't. I was really not involved in the X-linked mental handicap for many years, because that was Hilger's thing. I mean he ran it with Ben Hamel, who was by then my colleague and friend, and Ben was collecting these families so the X-linked mental retardation really was between Hilger and Ben and a few other people.

PH But am I not right – I probably didn't phrase it well – what I was thinking of perhaps was not quite so much the X-linked mental handicap as the monoamine oxidase, which you have done a lot.

HB Yes, I will not deny that. Oh that was a fascinating story in many ways. So this is a family that came, basically it did not start as a scientific project, it was just a family that came, they were referred for genetic counselling. And the first time they were seen was in 1978. So well before I went into genetics. And they were seen by Ben ter Haar. And this family were referred because, there was, the lady who was referred had a son who was affected and he was being seen and evaluated quite thoroughly by our paediatric neurologists. Our paediatric neurologists at the time were very thorough. They would do lots of investigations – metabolic things and

muscular biopsies and spinal fluid tests. Everything they could think of. Which was unsuccessful. But the lady had her own, a written account of the family history. And this was written by a grand-uncle. I think her grandmother's brother wrote this. Or maybe her mother's brother. No, I think it was her grandmother's brother. And so, and the entire family has Xeroxed copies of this great grand-uncle's, account which has a title. And so these are handwritten. They're in a, you know, schoolboy's notebook. Handwritten account and the title, he gave it a title, and the title reads "A curious case". Or in Dutch "Een merkwaardig geval". So "a strange case", "a curious case". And he just, he doesn't, there's no extensive description, he just says "from 19.." – I'm making this up now because I forget the years – " from 1937 to 1956 I was a teacher in special education and I often wondered about the cause of" - and he calls this "debilitas mentis" (mental disability). And then he says "I encountered this family, which taught me that it could be inherited, but then I noticed it ran along strange lines" is what he says. And then he basically describes the family tree, so this person married that person and they had so many children, and so on. And clearly he must have travelled all around the country to visit all its living relatives because they're quite dispersed. It's a small country but they're in quite different places and he indicates who has the condition, the "debilitas mentis". And then he says "so from this I concluded that mental disability could be inherited but I noticed it was only transmitted by females and it was only the males that were affected." And he does not then go on to interpret that, so he's probably not a biology teacher. Clearly that was, it all looked very X-linked.

So when they came in '78, Ben ter Haar did fragile X testing, which was the only really known thing at the time. And that was negative. And then it stopped. And then she came back in '88 and then I saw them. Ben ter Haar was dead, had since died in '86, so I saw her again. And now she said it wasn't about her son, she said "I have two daughters and I'm worried they might", she said – they were now about 16 – "this is the time I need to know whether they are carriers, because if they are they should know about it." And the reason she was very concerned with this is not just her son, who was quite difficult, but because she was from a large sibship of maybe 8 or so sibs, among whom were 4 affected brothers. She had 4 affected brothers. And there was, I think, maybe 1 unaffected brother and 4 sisters. And these girls had all left home early. I only found out about that particular thing later. Actually it wasn't very clear what the condition was. I thought it was X-linked intellectual disability. I hadn't really, really studied her son that intensely. I mean I'd done the, I'd looked at him from the dysmorphology point of view and I couldn't see anything particularly interesting about him so I just left it there. So she said "Can you do something?" and I said "Well, we can do linkage. If you are interested we'll do a scientific pursuit and try and find if we can map it and if we can link it perhaps we can work out whether your daughters are carriers." Because this was a large family with 14 affected over several generations. I think about 8 were still around at the time. 8 affected, and several unaffected males as well. So I said "You will need to mobilise the entire family, otherwise we'll not be able to say anything with sufficient confidence". So she did. And it turned out that, except one or two small branches, everyone in the family really wanted this done. They were very enthusiastic about it. So I went around, I organised things such that I would go to a regional hospital in another part of the country and I would have a list of people who would come at 15 minute intervals and they would come in and I would say "Are you this person?", "Yes", and take their blood and that was basically it. And then I got a surprise because these men, these affected uncles and distant cousins, they seemed to come in by themselves, walk into my little office and say "Is this where I give blood?" And I'd say "Yes" and I took their blood and I'd say "Do you have this condition?" and they would say "Oh, yes" and they would leave. So I was really puzzled. I called the woman and I said "I can't work this out. They are not severely handicapped. Why is this such a big problem?" And she didn't even tell me then, when I asked her. I had to sort of continue the conversation a bit. She gave me evasive answers for a little bit. And only then did she start telling about what the real problem was which was not, obviously was not severe intellectual disability at all. They do have a bit of a handicap. They're slow learners essentially, low normal intelligence, different from their unaffected brothers and sisters but not very abnormal. But the problem, the family problem, was about the behaviour. So it turned out the grand uncle who had written this account of

the family, who'd studied the family and described the pedigree, this grand uncle, his brother was convicted in I think the late 1940s for attempted rape of their sister. And he was, and I did see, and then he was sentenced by the judge, not to jail but to what you might say was a forensic psychiatric institution of the day. So it was with the monks somewhere in the southern Netherlands. And that institute still had his charts, so I have reports of what happened there when he was with the monks. He was in this closed institution, and he would do manual labour, and he would live in a pavilion, and he was frequently transferred from one pavilion to another pavilion, because problems would ensue with other patients, or inmates if you will. And the most serious thing was one day he was working, he was shovelling hay with a pitchfork. Not quite a pitchfork, the three …

PH Yes, a pitchfork.

HB It is still a pitchfork? OK.

PH I would say so.

HB So he was shovelling hay and then somebody comes and says "That's not the way you should do it" and he turns around and stabs that person in the chest. Didn't kill him, by the way, but he was never then released after that. So that clearly was why the grand-uncle went after this. The women and her brothers had not been born by the time he wrote this account, or they were very young, so they're not even in the pedigree. But again, similar stories were there for almost all these men. And it turned out that that was an even bigger secret. That actually wasn't what worried, wasn't the main worry of the family, and certainly not of the women. The main reason these women left home early was that these men had very unpredictable sexual behaviours, so rape is very unusual but there was a lot of inappropriate holding and hugging and it was sort of boundless, and there was exhibitionism and voyeurism and things of that sort which made it to the women quite, they felt very unsafe to stay at home. So they all left home by age 16. They would go and live independently because of that. So I was very impressed with that. I was also very impressed that even though they would know that a cousin in another branch had it, but they wouldn't know about the behaviours. These were all family secrets and if I would go and visit them and say "What actually happens?" I would get, you know, a similar story. There was one male who had one sister, and they lived in an upstairs apartment. And she had, they had on the mantelpiece a glass of water and they had a broomstick, so that if she was alone with him and something happened, she could throw the water in his face and bang the floor with the broomstick so the neighbours would come up to rescue her. So she had created this system. And again, in that particular family, I don't think anything actually happened beyond the threat of it and the unpredictability of it. Very, very impulsive. Two of the men, two of the brothers of the woman that I say, after their parents died in a car crash, very suddenly, so in a period of great stress, became arsonists together and put houses on fire. So by talking to this family about their secrets, I found out that they had a behavioural mutation.

BREAK IN RECORDING. HAN, COULD YOU SUPPLY A BRIDGING SECTION?

Han Brunner part 2

So we are resuming the recording with Han Brunner. Han, you were telling me about the identification of the monoamine oxidase gene and your finding of mutations. Might I ask, did that have practical applications then in that family?

HB Oh yes, yes. So really that was the purpose of it. I was aware of course that it might have scientific implications but the purpose was always to just answer the family's query which, as you recall, was the woman asking about her daughters, whether they might be carriers. Two daughters. So that was the immediate reason for doing the project and it was very gratifying to go back and then test the daughters for carriership. And other unaffected women in the family who had the same, wanted testing done. That has

been done. And we could potentially provide pre-natal diagnosis in the family. I have always avoided saying whether pre-natal diagnosis was actually done because there is really only one family and it would be identifiable I think whether or not that was done. But there were certainly many people in the family thought this was a severe condition and they would certainly have contemplated it. The other thing that was good was that I went round the family again to explain the results and I talked to an older lady, in her seventies I believe, so this is around 1991 or 2, when we'd found it. 1992 I think. And the older woman, her son – it was the son who was affected, and he had one sister. He was born in 1941. And this was her first pregnancy. And after 3 months into that pregnancy – or maybe it was, no 1941 – so after 3 months pregnancy World War II came to the Netherlands. Her husband was in the military, he went east, and the Netherlands was overrun, I think in 10 days, but it took 6 weeks for him to resurface. So she knew nothing about him for 6 weeks. And she was worried sick, as you will imagine. And when she had this son who grew up as a real problem child in many ways, it was an immense relief to hear from me something which was scientific evidence that it was not her worrying that had damaged her child. In her heart of hearts she had always felt that she had somehow, that her worrying had damaged his brain and his personality into the very problematic and torn person that he became. And I think that was a big lesson and we've seen that later, we've seen that providing a biological explanation for a disturbing handicap provides great relief because mothers tend to blame themselves for anything affecting their children.

BREAK IN RECORDING; CAN YOU PROVIDE A BRIDGING SECTION PLEASE?

Han Brunner part 3

PH Well, where had we got to? We had more or less finished monoamine oxidase, I think.

HB Finding the gene. Talking to the family. Finding that it was useful information because it relieved the family of a lot of – it was practical because they now knew who the carriers were and they could, these carriers could now take appropriate measures and could either not have more children or could have prenatal diagnosis or some other solution. And it was a relief to them. It was a relief that their condition was not, it was not a social thing, it was not about them educating their children badly, which of course their neighbourhood would say, you know, there were lots of people who said "people have always pointed at us for raising our sons the wrong way and this is a vindication. And it was also very practical. I thought about publishing this. I actually wasn't completely sure whether I should, although I had by then published by then several papers on a variety of topics, and this was good science. I was a little worried because I was very aware of the possible implications of finding, of publishing on a biological explanation for behaviour. The biology of behaviour was very contentious, certainly in the 70s with E O Wilson at Harvard writing sociobiology and being very, very heavily attacked over this by his students, and also by his colleagues in the department at Harvard, I believe – Steven Jay Gould and Lewontin. But also in the Netherlands we had had examples of this. There was the first real professor of biological psychiatry, von Praag, was very, very heavily attacked in the 70s over even proposing the topic of biological psychiatry, to the point that this was then one of the reasons why he went to New York, where he set up a fantastic system for schizophrenia care, and later came back. But there was this other professor in the Netherlands by the name of ……., um, OK, it will come back to me [Wouter Buikhuisen]. This other professor, he was a professor of criminology, and he proposed in the late 70s to study a cohort of boys and then follow them up to see whether he could find any early indicators for anti-social behaviour in adolescence and early adulthood. And as part of that proposal he proposed to take blood samples and test them for serotonin. And this really got people very, very upset because people felt he was marking young children of kindergarten age for their lives. He was going to put a mark on them.

PH And of course there was a precedent of XYY.

HB Well I don't think that played a big role in the Netherlands. I knew - that of course was Pat Jacobs in Edinburgh, I think, at the time. Pat Jacobs never apologised for that, I think. She was always very clear that she thought that this was good science. She just thought it was over-interpreted, which I think is essentially correct. Now this gentleman in the Netherlands, he proposed this. He was not a biologist, a medical man. He was a criminologist. And he put this in as a proposal for a grant, grant funding, which was denied, but then there was an immense explosion of emotions about this. His teaching was disturbed. Students would walk away and ignore him, or shout things at him, and one of our most vitriolic columnists in the Netherlands – Piet Grijs, or Pete Grey. The man is actually – or was, he has just died – a professor of Dutch at the University of Amsterdam. But a very good vitriolic writer when he wanted to, he really did that. He wrote about this, in a weekly journal, he wrote about this man for I think 8 or 10 weeks, every week, about this one man, saying how finally Mengele had found a successor, and so on.

PH This was a serotonin study?

HB This was the serotonin study, which was never performed. And this professor in the end resigned from his Chair in the university and then went into antiques. Sold antiques and made good money selling antiques. I've met him a couple of times and he obviously feels very, very wronged. And he feels very strongly that the university at that time did nothing to protect him. So there was this one very, very clear example – two examples – of how touching the subject of biological basis for behaviour, certainly for abnormal behaviour, would get you in trouble. So I thought about this for a while, sat on it and mused about it, and in the end I asked the family. And they said "Well, we've been looking for a diagnosis for 35 years and maybe there are other families out there. You should go and tell them." So then I thought about it again and I realised that, even though this might blow up in my face, I was not actually going to be destitute if this happened. I would not lose my job because I could still go on and see patients, perhaps not have a scientific career but I reckoned I could survive without a scientific career, and it wasn't that – I still had to finish my PhD, it was around about the same time – so I thought I would survive. But I did try and phrase the….. eventually I divided the subject matter over two separate papers. In one paper I described the behaviour and the linkage and in the second paper I described the mutation and the biochemistry, or part of the biochemistry. And I only very briefly referred to the behaviour, thinking that that was a way of kind of not making it too explosive. I also tried to use a neutral title, so I think the title was "Abnormal behaviour associated with a point mutation in the structural gene (I don't know where I got that – it was from other papers) from monoamine oxidase A". And I tried to be very matter of fact about it in the article, not to say anything that could be, that would be over-interpreted. And that failed completely, of course, because it was very rapidly picked up by Science which of course does not just have published articles but also has a sort of newspaper section which is mainly written by freelancers and they just behave like regular newspapers, so they immediately dubbed this the "aggression gene". And then I was on the phone for two weeks and they would call me. I was still in the telephone directory so the Los Angeles Times would call me at 11 in the evening and the Melbourne newspaper would call at 6 in the morning. It was a fantastic experience and I kept saying "This is, you know, it's rare. The behaviour is not written in the gene". And so on and so forth. And it's true because in this family the affected males do differ in how bad their problems are. And this seems related to whether they are in a stable environment. So the ones that lived with their sister or lived with their mothers do a lot better than the ones who try and survive on their own, who do relatively poorly. So that was OK. And I think I found out that the tide had turned on biological psychiatry, that everybody was ready for this to come, everybody needed, everybody felt there was a biological basis to behaviour and for a while the discussions had gone where the nay-sayers had said "but there's no evidence". And now of course there was evidence, or at least there was a pointer, proof of principle type of evidence, that this kind of biological basis could exist. So that was good. It did away with the environment-only, the nurture-only paradigm that

was so dominant in the 70s and 80s. It did get my then boss, Hans-Hilger Ropers, into trouble, partly I think because he was a little less careful in describing the family in a talk he gave in Germany

PH And in Germany, I can imagine, it would be even more inflammatory than in the Netherlands.

HB Yes, I think he should have realised that. Not only was it in Germany but it was in the department, or at least it was in Cologne, and in the audience was one Professor Benno Müller-Hill, who had written a book on murderous science, which was all about the Nazi atrocities, and the atrocities of the Nazi geneticists especially. He's a geneticist. He's a Drosophila geneticist I believe. So he had very strong feelings, he was in the audience, he very strongly disagreed with the way – perhaps with the subject matter, actually I think with the subject matter but also with the way it was presented. And this collided with Hans-Hilger Ropers being the preferred candidate for the Directorship of the Max Planck Institute for Human Genetics in Berlin, which was a contentious subject of itself because it was, the Max Planck Gesellschaft is I think the successor to some other Stiftung which had a department of human genetics in Berlin which was where the worst Nazi geneticists were employed. So people were wondering whether it was right, or even wrong, to do any human genetics in Berlin. It was felt by a number of people – good people – in Germany that perhaps it should not be in that place and not with Max Planck. And then they selected a director and then this director goes and starts talking about behavioural genetics, and it was all very unfortunate. And I think he – there was a moment of panic and there was then a concerted action, led I believe by Peter Propping, to find people who would vouch for Hilger. And I would vouch for him – I was not asked, of course – because he is the opposite to what you might think of in terms of Nazi science. He is a truly, truly a good person who thinks very deeply and very strongly about this. So he was misframed, you might say. But it needed, I think, evidence provided by, I think it was Aubrey Milunsky and Arnold Motulsky – American, not incidentally Jewish, influential geneticists so say that one should not misjudge Hilger Ropers so all of that shows how powerful that stuff was and I've always been very careful to downplay it a little bit. It needs downplaying because it will then self-inflate to the point where it becomes an important story again, which I do believe it is, but you have to sort of take that into account. And I've done it regularly, I've done it just not that long ago when I was flown to London to be interviewed for a day, at the Institute of Psychiatry, for someone who was doing a documentary for National Geographic Channel. And I never made that, I was cut from that documentary. And I think that was very obvious, that they would keep asking me certain questions, I was refusing to give them simple answers, I don't think, that's not very helpful but then, you know, you don't fit the story and then you're kind of edited and taken out. So a very, very …

PH An interesting experience, yes.

HB …. transforming experience, yes.

PH Can I just ask you – jumping ahead now – I've noticed a lot of your publications were finding mutations in a variety of clinical syndromes, a number of dysmorphic syndromes, but then there's a change when, which shifts with the technology, and I'm thinking particularly in terms of the coming in of first arrays and then sequencing techniques. How has that impinged on your career at the interface between the clinical and the lab side?

HB Oh arrays were just so wonderful. You know, I had been seeing – well, all of us - but I personally had been seeing patients with intellectual disability for maybe 20 years and I once calculated my hit rate – you know, making a diagnosis – and it was, I don't know, it was less than 10% I think. I would go weeks without making any diagnosis. And then this came, and someone talked about it and there were arrays, and there was one paper, I think it was from Cancer Genetics during a journal club, where someone in my department talked about a possible application to do copy number variants, which were not called copy number variants then, in cancer. And I just felt this is it. So we had just, though my colleague Ad Geurts van Kessel, worked really

hard to get an array machine and he wanted to do RNA expression and so on and I said "No, no, no, we're going to do molecular karyotyping. This is going to be it." And we got a fantastic post-doc, Joris Veltman from San Francisco, who had worked for a year with Dan Pinkel and Donna Albertson, who were then the foremost array people in San Francisco, so Joris came back to the Netherlands, and he took two years to get the machine to run and I said to him "We're going to do 100 patients and then we'll see." And we did 100 patients and I think it took them a year, it was really hard work. And I think maybe 15 we could make a diagnosis. It was unheard of. 15% was about equal to what you could do with every other test combined, including CT scans and MRI scans and invasive procedures and biopsies and looking at the phenotype and discussing it with your colleagues and doing metabolic studies. All of that was not as good as doing this single test. And that was just, it was mind-blowing, it was unbelievable. And again a lot of interesting things happened. One was we were doing whole genome arrays. I think at that time we were the only ones doing them regularly and then in the US they had started doing arrays but they were doing targeted arrays, targeted at specific loci for known syndromes. This was driven very much from Houston, by Baylor and also later by Lisa Schaffer who was in Houston but then went to found Signature Genomics in Washington. And they would have all these presentations to the American Society of Human Genetics saying whole genome arrays are wrong because they will give you uninterpretable information and you will not be able to, you will misdiagnose, over-diagnose, and it will be a mess. But if you do targeted arrays you are going to find things that you do know and can interpret. And they would have 7 or 8 presentations to the American Society. We would have 1. And we said "Well, actually, you know, it seems to work". And it was Joris really who, coming to us, that gave us the momentum and the possibility for trying something new at the interface of diagnostics and research. And we've always been deliberately vague about where diagnostics, diagnosis and diagnostics ends and science begins. I think there is a bit of a grey zone. Of course now it's all getting increasingly protocolised and we have to make very clear distinctions and we're not, we're trailing a little, we're lagging a little behind the UK and the US who have made much more strict protocols in that regard. We are following that trend. But I still believe, you know, it is fair, if you're not treating, if it's not experimental treatment, I think you are there to make a diagnosis using your creativity to some extent. So that's what we've done. We did the same with exome sequencing and because of the arrays we'd realised, I realised actually, we'd always seen that the most clearly pathogenic copy number variants were de novo. Not all of them. There are some inherited ones that have variable expressivity, but the common ones and the most frequent ones are de novo changes. And then I was on the thesis committee for someone in Copenhagen – a man from Iceland – who was, his thesis was copy number variants in schizophrenia and he described in his thesis the schizophrenia paradox, which is something I was not aware of, which basically says how can schizophrenia be so frequent if it is highly heritable but then it has such negative impact on fertility, or at least fecundity? And the obvious answer I thought to that would have to be de novo mutations and I reckoned that it was there in schizophrenia, but not that clearly. But if it were going to be anywhere it would have to be true for intellectual disability. So I talked to Joris and Lisenka, who was this really fantastic post-doc who really gets his work done in the lab now, and said "We are going to do 10 trios" and it was kind of as much – we could not have done 20 trios then. It was like new technology, it was still experimental. It was hard work. And I said "We are going to find 6 out of 10" which was a pretty crass prediction. But in the end I think we did get 6 or 7 clear de novo mutations. And that was, that's been, very rewarding. I think both things. We are now up to 60% diagnosis, up from maybe 10 or 15% just 15 years ago. Very confident diagnoses, most of these. There is a risk of misdiagnosis but it's small. All the indications are that we don't get it wrong a lot of the time. Similar to what happened with Arrays. We didn't, even in retrospect I don't think we made many false positive diagnoses and certainly not more than we used to make with other – with clinical diagnoses. So all in all I think it's been, I think that's where it comes to. It is, it's been such a journey from being completely in the dark as to what a chromosome looks like when you try and do linkage and there are no maps and there are no markers and you don't know where

anything is, to seeing all the changes and interpreting, and actually being able to diagnose your patients is fantastic, yeah, it's fantastically rewarding.

PH Han, I've been asking everybody I see two questions, and the first is: In terms of your mentors, teachers, people who've influenced your career, is there anybody particularly that stands out?

HB Yeah, many people. I think my first ….. There are many. My first big influence clearly was Ben ter Haar who was a good dysmorphologist, who was a very good clinical geneticist, but he could connect with patients like in seconds and this was particularly impressive when I was starting in clinical genetics. I would really struggle, I would have all this information that I wanted to share with these patients and of course I hadn't yet found out that it's not about giving information, it's about listening to patients. I took many years to learn that lesson. And I could see – for me it seemed magic, magical, because he would do very little and they would come to him and they would connect. I could see that. I became very determined to somehow copy that. I could see how powerful that was. I still do that today. I think Hilger has been a big influence on me. We do things very differently but he gave us the confidence, you know, in a very small university with no standing in the Netherlands at all, or in science, that we could go out and maybe not compete with the big boys but at least be in the game. And that kind of confidence I've tried to emulate and pass on to the next generation.

PH The other question I've been asking everybody is, if you had to choose just one of the pieces of work that you've done or been involved with, which would you choose as being not necessarily the most important, but the most important to you, where you feel you've perhaps made a special contribution?

HB Yeah, I've had two moments of revelation. I think the de novo mutation certainly has the most impact, so I probably would choose that. I think the other thing is what I mentioned, the precocious puberty, because that fulfilled my dream at the beginning of being in a clinical situation and then, just by thinking about your problem, working out what the solution might be and that was immensely gratifying that I could do that.

PH Well thank you Han very much. I'm going to finish there and I'm most grateful to you for taking part and so I'll turn the machine off now