Interview with John Burn 22 September 2014

JB – John Burn

PH – Peter Harper

PH It's Monday September 22nd and I'm interviewing John Burn at the Liverpool Convention Centre and British Society for Genetic Medicine congress.

John, can I start perhaps at the beginning and ask, when were you born and where?

JB I was born on 6th February 1952. I was born, to be precise, in the front bedroom of Number 7 Rugby Terrace, West Auckland, a home delivery, and I discovered many years later that my sisters were not advised of my imminent arrival, which created certain relationship problems with my younger sister – the younger of the two. And I grew up in West Auckland, which is a small former coaching station/pit village in West Durham, and lived there until I was 18 and went to university.

PH Thinking of your family, was there any kind of scientific or medical background from your family?

JB No, quite the contrary actually. I think it was Neil Kinnock who said he was the first member of his entire family to be at university, and that was the case for me. My father was a very bright man. He was a sort of inventor who set various companies up. He grew up the son of a tenant farmer and in those days – the second decade of the twentieth century – the fact that he came from a working class background meant that he had to leave school at 14. Although he passed all the exams, they were interviewed, he remembered, by a lady who asked him questions, and that was how he didn't move on. My mother was the daughter of a butcher, and she was expected to leave school at 14 and help run the shop. So they were both very intelligent but uneducated people, but with a tremendous sense of confidence and identity and my dad set up his first business at 21 making caravans, after having served his time as a joiner. And both my sisters went to grammar school in Bishop Auckland from the 11 plus. I was then sent to the new grammar school at Barnet Castle. And my mother in fact thought that reading might turn my brain and was worried for me that I read too many books.

The other influence of that non-academic background was that being the youngest, but the first boy, and also the youngest generationally – I was the youngest, the baby boy of the extended sort of valley pedigree – I had this tremendous sense of being special and loved and the Dalai Lama of South-West Durham in their eyes. But I was too small to talk to. So I got from a very early age into reading in my science books and telling

them interesting things, like how far it was to the moon. None of them paid any attention, but I think it was the beginning of me being a lecturer because I was seeking their attention, and I was just fascinated, in a very ill-formed way, and I think grammar school was probably the formative experience of realising that there was a bigger world outside. And so I was very much the first in my line, so to speak, from an academic point of view.

PH Was there anything that pointed you in the direction of science and medicine, rather than in a different direction? Any particular teacher, perhaps, and formative influence?

JB Yes, at the grammar school we used to have very good graduate teachers. The grammar school turned into a comprehensive while I was there, but they were all well-qualified. And the science teachers – I gravitated towards science, maths and biology. I was originally planning to be an engineer. I was quite taken with the huge chemical plants at ICI and envisaged building one. But I liked biology and a small grammar school had to force you to choose between maths and biology, so that directed me away from engineering. And we had a Mr and Mrs Mason, who were a married couple who taught biology, and they conveyed tremendous enthusiasm for biology, and in particular took me to a lecture being given by an Oxford geneticist, or Oxford biologist, in 1969. And we sat and had explained to us the genetic code. And what was striking was, I remember, I have two snapshot memories of the event. One was wandering in the garden afterwards, talking to this man about what he did and how he did it and why he did it, and the second was sitting on the bus back to the school and Mr Mason came to sit beside me and asked me to explain it again because he hadn't quite understood. And that was fascinating. I was mesmerised by this wonderful simplicity of this genetic code and how you could turn that complexity into a simple explanation.

PH Who was that?

JB I don't know. You know, it's one of those things I meant to go back and find out. I will find out. But he inspired me. I will find out who he was. But he was obviously just giving a lecture to the large school community. But I mean it just reinforces the benefit of those lectures. I keep meeting now people who said "I saw you talk when I was 15". And I think, you know, it really captures people in that teenage window, when they can be really turned your way, so to speak, or turned towards science. Anyway, so I kind of hung on to that. But by this time I had been persuaded to apply to go and do medicine. And I did very well in my O-levels and I was given easy grades, as they used to then, to get into medical school. I went to Newcastle. And having – I didn't do so well in my A-levels, mainly because I became preoccupied by driving my Mini and – well the Mini car and the mini skirt probably it is fair to say distracted me from my

academic pursuits. So I knew I needed 3 grade Cs at A-level to get past, and I made it, but closer to the fence so that I was a little anxious.

I remember arriving in medical school and deciding that I should try really hard. Because although I was a cocky youth I was feeling a little insecure surrounded by all these sons of doctors, this middle class community who seemed to know where everything was and what they were doing and I knew nothing. I remember arriving at the hall of residence wearing my three-piece suit, because no-one had told me how to dress on arrival. So I worked really hard when I first began, which is unusual for me, and I suddenly found myself top of the class. And then of course you've got a position to maintain. So I ended up being in the top couple of percent from then on. And I got the option of doing a degree, a BMedSci degree, in the second year. And so I thought, you know, that's quite an interesting idea, and so at the end of year 2 I dropped out and genetics was the obvious thing. So I went to talk to Derek Roberts, who was a geographer originally and came and did human genetics and population genetics. And his little department had a biochemistry wing so I did a BMedSci with Derek Roberts and David Gardner-Medwin, who died very recently, who was my paediatric neurology supervisor. And that really was the making of me in the sense that I suddenly went back to medicine with a knowledge of genetics from the early 70s when virtually no-one else in the hospital could spell the words, never mind give any opinion. So I found myself increasingly being call upon to express and explain genetic issues. And then I took my elective period to go to Johns Hopkins, just after you were there, and spent 3 months with Victor McKusick, Tony Murphy and the gang. And that was it then, I was sold on the idea that not only was genetics fun but that I could actually make a living out of it, I could take it up as a sort of professional golfer, that I could actually do this for a living. So I came back to England and the entrepreneur and the showman decided that the best thing to do was to announce the fact that I was going to be a clinical geneticist before they'd actually been invented. So that sort of caught the imagination of my peers and slightly depressed some of my seniors. The head of surgery was very sad that I wasn't going to be a surgeon because he thought I was probably good enough to be a surgeon, but then when I went back as the first clinical geneticist, history had been re-written, and he presented the idea that he'd actually encouraged me to do this, he was so pleased to have me back. So it's interesting how history does get re-written and so everything I've just told you is probably a re-write of what actually happened. But there is absolutely some truth in what I've just said.

PH What year was it that you qualified?

JB I qualified in '76. I went to medical school in '70 and I did my degree in '72 and married the same year and then qualified in '76. And then did general medicine and paediatric rotations over the next 3 years as houseman, SHO and registrar.

PH Was that in Newcastle, or Newcastle area?

JB In the Newcastle hospitals. So I basically worked in all of the 3 hospitals that now make up Newcastle Hospitals NHS Trust. One of the nice things was, partly because of the genetics degree, I had sort of proven myself to the paediatricians and they were very keen that I join them, but they allowed me sort of to leapfrog in and out of medicine and paediatrics so I did a paediatric house job in place of my surgical house job, which we could do then. Then I did an SHO general medical rotation through all of the –ologies with the Professors, and then came back as a registrar in paediatrics, so I was able in a very short space of time, from ’76 to ’79, to actually get up to the point that I could go and visit Cedric Carter and ask to come and train as a geneticist, which is what I did. I actually applied for an MRC Fellowship, but didn’t get it. Not surprisingly, in retrospect. I wanted to work on spina bifida but I hadn’t really thought through the science of it very well.

PH How did you get in touch with the London and the rest of the country’s genetics set-up. Had you made links already by then?

JB The only formal link I made initially was with David Siggers and because I knew he had set up as a clinical geneticist and obviously you were in Cardiff and he was in Southampton, and for some reason – I can’t remember exactly what triggered it – I remember going to do my final year elective for a month in Southampton. And so I knew David and the team in Southampton. But to be honest I just kind of rather cockily turned up at Cedric’s door and said “I am John Burn from Newcastle. I’ve done a BMedSci in genetics and am now a trained paediatrician and I want to be a clinical geneticist. And I understand you’re the best person to come and talk to”. And he took me at face value and gave me his last clinical officer - clinical scientific officer - position, before he retired. So I got a year and 9 months, having not got the Fellowship. He took me on on the staff, which in parentheses is causing me a few problems now, because it seems to have disappeared from my pension entitlement and I am currently arguing that I was actually employed by Great Ormond Street as one of their staff. And so I went in as a Senior Registrar at Great Ormond Street. So at an exceptionally young age I was a Senior Registrar at Great Ormond Street doing genetics with Cedric and then when he retired I had got my act together. I was working by then under Marcus Pembrey and Michael Baraitser and alongside and with Robin Winter and Gerald Corney, who was a great influence on me, from the MRC unit, because I had become really interested in the twins and twinning heart malformations in twins. I took that with me partly because my last job – almost my last job before I left Newcastle – was in paediatric cardiology. And my father in me - the entrepreneur sees the gaps in the fence, not the wood – you know I could see that there was a gap, that the paediatric cardiologists were dealing with birth defects and malformations and syndromes, but knew nothing about genetics. I mean not a thing. And when I talked to geneticists they

had no idea how the heart worked, what it looked like, what the transposition of the great arteries was, and I thought this is an obvious moment, I can step into that gap and hold hands with both communities. And that worked immensely well. But then I realised that the twin data were completely misleading. It said that heart malformations weren't genetic because only one twin was affected. And it was very obvious to me, knowing a bit about embryology, that the twinning process was obviously causing malformation and that the twin method was completely unreliable. And so I worked with Gerald Corney on that and got some nice work from out there, which became my MD thesis. And so that took me through to '84 and then I applied for, and was made, Consultant Clinical Geneticist back in my alma mater, like what I had said I would. So exactly 10 years after I had announced my plan I came back as Consultant.

PH Staying a little while with your time at Great Ormond Street and Cedric Carter, when you went there, what was the set-up? Several people have told me from different angles, but it's nice to hear, what was your impression and how did you see it and who were the people who you mainly interacted with?

JB So it was a real culture shock, as a front-line clinician, to go and join the department because remember, I had just come from in fact doing neonatology where I was virtually one in one on-call, looking after tiny 23, 24 week babies, cannulating them, catheterising them, you know, surrounded by death and mayhem on all fronts. To then go into this quiet little corridor where everyone just sat and read books and chatted now and again, it was a dramatic change of pace. So we were on the – I think it was the 2nd floor – of the Institute of Child Health and Cedric, his door was always open and he was always facing his desk, you could see it from the side. Michael Baraitser had just arrived. Michael was a neurologist of South African extraction – you have probably spoken to him …… – he was a very, a true intellectual, rather like David Gardner-Medwin, who had a huge influence on me. I had never met people who were so embroiled in academe. They were attracted just to the pure knowledge and joy of learning. And Michael was a tremendous reader and polymath and he knew the literature. And then Marcus Pembrey who I was kind of more like … typically, a rather more bouncy theoriser. And still going strong at whatever age he is and still bouncing around and theorising. And that's just it. Those two – Cedric, very solid, very competent, very opinionated and Michael, slightly other-worldly, academic book-reader and Marcus, the sort of theorist, were a tremendous kind of trio to learn with. But we all just sat in our rooms on that corridor, we used to go down into the Outpatients and Cedric would do genetic clinics and he would allocate, rather like a GP, about 12 minutes to each family and then dismiss them and tell them that he'd write a letter to their doctor. And I mean the idea of actual counselling really hadn't permeated.

Michael was a bit better, but he was an adult neurologist and most of what we were seeing were children. Having trained as a paediatrician I knew how to sort of win a child and examine that child and Michael had never actually mastered that so I kind of taught him how to examine children. Because he would just walk over and look at them and they would cry, I mean there's a way of engaging with a child first so that the child trusts you enough to actually allow you to take their clothes off and look at their arms and legs and so on. The first thing I used to do in the clinic was to go and sit on the other – we used to sit on these long tables like we're sitting at now, with the patient on one side and all the doctors on the other. So the first thing I did was take my chair round and sit on the other side next to the family so that they didn't feel quite like the Spanish Inquisition. And so I think I brought quite a lot to the team because they hadn't been together very long, and they weren't really very functional as clinicians.

And we've talked about this before in the context of the history of clinical genetics, I think it was just at that time – Dian Donnai was in Manchester similarly and what you guys were doing down in Cardiff and at Guys. The clinicians were kind of ticking over in a way that hadn't been the case before. Cedric was a doctor, but he wasn't a clinician. He was an academic, theologian turned eugenic geneticist who was interested in the mathematics of genetic disorders. And so I think that sense of dysmorphology bubbling through and discovering that dysmorphology was the most interesting and profitable aspect of our work and that I, as a trained paediatrician, could really get immersed in that. So very soon after I started I went up the street to the camera shop and bought a camera, because I discovered the only way we could record our dysmorphic children was to send them to photography and they all sat in a line for an hour. So I bought us a camera and we started taking pictures in the clinic. And Di was doing the same with her little Pentax up in Manchester and so we got this little community of dysmorphologists starting to emerge. And so that was really the making of my clinical practice then. I became the dysmorphologist and a sort of quantitative geneticist in its earliest form, looking at malformations in twins and so on.

PH How did Cath Evans fit into the picture?

JB Well, Cath was a rather indomitable character and family tree drawer and academic counsellor. But she was, again she was rather like Cedric, she worked with families in terms of studying malformation patterns and so on. She didn't work with us in terms of seeing families referred with a genetic disorder, you know, she wasn't a clinical counsellor, she was more in the research team. It was a very, I would almost say, subdued atmosphere. It wasn't a sort of raucous place. And I was a rather strange addition to their – as the professor of immunology said, the rough diamond from Newcastle. But I think probably they rubbed off my edges and I livened them up a little! So most of Cedric's practice by that time was

about assembling large series of disorders, you know, cleft palate or whatever, and looking at the recurrence rates in first degree relatives, very meticulously documenting them and, as you know, that data remains incredibly valuable because no-one ever did it after that. And I think we are actually coming back round now to actually understanding the importance of that penetrance and expressivity which we heard today is going to be really, really important. And we are still referring back to the data that he collected. What he didn't have, of course, was any of the tools which we now have to go deeper into the causation. And so he was sort of trapped at the numbers, head-counting sort of process.

PH But you are quite right, I mean, it really is impossible to do studies now on how common a genetic disorder is because the line between overt disorder and presence of the gene has got so blurred that most of the time you are not quite sure whether you are counting just symptomatic people or counting a whole lot of healthy people who just happen to carry the gene.

JB Absolutely. And I think we probably – in fact, today's lectures emphasised that – how little we understand about penetrance and expressivity and the degree to which – and I mean, when I explain it to patients, the analogy I use, which I think is quite useful to think about, is if you think about the road traffic system, when a lorry jack-knifes and blocks a motorway, it could cause total mayhem. On the other hand, if it does it at the right point so you can turn off onto the B road which runs alongside the motorway and come back on further down, there's a slight delay but, you know, it doesn't wreck your life. And I think, you know, that's obviously biologically how we've evolved. I mean anything where one gene could stop the system, there has to be evolutionary pressure to find a way round it. And the people who survive are the ones who have a B road and so you will get a proliferation of those back roads, or second motorways even, that will allow you to sidestep these things. So it's perhaps to be expected that everything that can cause a monogenic disease doesn't always cause a monogenic disease. And of course that's going to cause us major problems as we move into the genomics era because you find the deletion, you look it up on OMIM, you announce that this is the diagnosis, and we give people completely misleading information. So I think it's going to be an interesting leveller in the next few years.

PH John, when you first went to Great Ormond Street and the Institute of Child Health, were there close clinical links already between the people – the paediatricians – seeing all this abundance of syndromes and the genetics unit? Or was it something that just came gradually when you were there?

JB I think it's fair to say that we built that over those few years. I mean there were a number of good people like Nick Dennis and so on who had been there before me as the clinical officers and so there was a tradition of us getting referrals from the wards and doing ward referrals and doing

dysmorphology. It just became more and more central to our activity. We used to go to the weekly Grand Round session and present cases. That was a major interaction, and we used to call them “24 hour papers” because I always tried to write a paper about every case we presented on Wednesday. We didn’t do it every Wednesday but we turned out a paper every month on a new syndrome or something in those days. So the links were semi-detached because Great Ormond Street was the epicentre of paediatric training and the people going through there were essentially paediatricians who were going to go back out to their home towns to be the specialist paediatricians in their area. Genetics was in the building next door, attached to Great Ormond Street, accepted within it but seen as a slightly oddball group. A little bit like immunology and Jim Tanner’s growth unit, we were clearly relevant but we weren’t paediatricians. But then as more of us became trained, or people like me – paediatrician-trained – came through genetics, that gave a much stronger bond. And of course the other person who had a huge influence, who I haven’t mentioned, was Robin Winter. Now Robin in fact wasn’t initially a consultant but ended up with visiting rights. I never worked out whether he was ever formally made a consultant in Great Ormond Street, but he was certainly – he was just a little older than me – immensely talented, hardworking – too hardworking I think – and he developed the database and was really at the front edge of the mouse models and of the dysmorphology database with Michael. And so, again, he had an encyclopaedic knowledge. A rather quiet-spoken, thoughtful chap but with a great sense of humour as well. I mean we got on extremely well and his loss was devastating to the community. But I’m not that surprised, in the sense that his lifestyle became very monk-like. You know, it was almost as if he was writing the Lindisfarne Bible when he was doing his databases. He would just get up early in the morning and sit and plough through photocopies of papers and get them onto the database. He was completely obsessed with getting that database comprehensive. And he did become completely encyclopaedic in his knowledge because of that, in the same way that Victor did with his Mendelian Inheritance of Man. There’s no doubt that writing a comprehensive textbook gives you that desire and ability to get your head round the topic. And I used to work hard, but I always used to feel inadequate compared to Robin and Michael, who always seemed just to never stop, you know, I mean they were just at it all the time, you know, ploughing through these piles of paper. Marcus and I were much more prone to have a cup of coffee and rock on a chair and debate exactly how can Fragile X work. I remember some wonderful discussions and Marcus never really got the credit for discovering the premutation concept, which we worked out on a blackboard as we chewed around different ways it could possibly work. So it was a wonderful experience, and it was an otherworldly experience, detached from the sort of day-to-day grind of thousands of referrals. We got a steady flow of referrals, we saw a lot of patients, but I don’t remember it being quite the overwhelming burden that it became.

PH Did you have much in the way of links with the other London genetics groups, or were they fairly separate?

JB They were fairly separate. I used to go across to see the people at the Galton Institute, and became quite well known to them. By pure coincidence, my work when I was a medical student had come to their attention because I had discovered a previously unknown fetal version of one of the esterases in the human brain, which got me one of my first papers. And so I knew Professor Hopkinson – Hoppy – and various other people there, I'd been to see them, and Gerald [Corney] took me under his wing, a wonderful guy. And so I spent quite a bit of time there and that was very much as an academic MRC department - old-style MRC department – where there wasn't this drive to publish or perish, you know, they would actually sit and have a chat with you about something interesting. So that was a great learning experience. I didn't see – I mean, I knew Caroline Berry and Paul Polani and the team over at Guys', but they were just another genetics department. We didn't really have any formal links. Lindsey Allan was a cardiologist there and we did professional work together for my research. She was an ultrasonographer still living in London. And Michael of course and Robin ran to Northwick Park and did the Kennedy Galton Centre, and visited the Centre with all the kids with learning disabilities and so on. I think that was about it actually. I don't think there was very much, so I don't think there was a great deal of cross-talk. We were all sort of like islands in the Pacific, weren't we, I mean each of the centres – there were only a scattering of them – and we came together for our little Clinical Genetics Society meetings, but we didn't really have very much interaction beyond that.

PH Thinking of the Clinical Genetics Society, you must have gone to London not that long after it started up.

JB I should have been a founder member, except Derek Roberts forgot to send the form in. Because I think it actually moved from being a club to being a society around 73-4, something like that, so I actually did, I am probably now one of the longest-serving members of the Society, but I wasn't quite there at the start. You were there and there was …

PH No, I wasn't, because I was in America.

JB OK, fine, well in that case I may well be one of the longest-surviving members. But, yes, I already was aware of it and I joined as soon as I could, and I remember attending meetings. One in Surrey I drove down to as a houseman and I actually gave my first stand up plenary talk as a paediatric registrar, based on my time with David Siggers, and I'd developed a theory on trying to explain the weird sex ratios and so on in spina bifida. Which actually got published, I think, when you were editor of the Journal of Medical Genetics and I think it's one of my pointless answers, if you think of that thing on the television, I don't think anyone ever referred to that hypothesis again. Nevertheless it was a good

exercise to do a plenary presentation and I actually liked the idea of it being polyallelic in the sense that there were a small number of genes but in fact that since one of the most obvious things was, well the lateral thought was that maybe what we're missing was that this isn't the genes that cause it but the genes that cause it to be lost. That in fact there is a natural spontaneous abortion rate in vast numbers of malformed babies. And what if we had a genetic defect in the ability to do that? That they therefore came through. And if that was the case then the zone of expression would be the placenta and its capacity to separate and that that would be a maternal-fetal interaction, that genes from both sides might be added together. It was an interesting mind game and it probably got me my training position in retrospect , because the fact that I'd stood up and given a talk and got it past the selectors and stood up to this audience as a boy was a good test.

And so, yes, I was in CGS from a very young age. I was its first representative of geneticists in training, back in about 82 or 81, and then I was prevailed upon by Alan Johnston et al to become its Secretary in the later 80s. In about 86 I guess. And you will recall – in fact we talked about this in another setting – that we had an early conversation that it seemed to me that merging it with the ACC, as was then, would make sense to try and build a kind of, and the newly emerging molecular community, and that was what led to the BSHG. We then changed the name to the BSGM where we are today. So I guess one of my useful contributions was to be an integrator and to bring together the different groups, which I still think there's a natural centrifugal tendency of tribal gatherings, and that works in the professions like everywhere else. I think almost it requires a very conscious effort to keep pulling them together and they always appreciate it but they'll still drift back into their separate oil and water separation, given half a chance.

PH You're absolutely right there. I think there are always only going to be a few and I reckon I probably, like you, was in that place, at sort of interfaces, and people would always say "Oh, he's all these things, never really good at any of them" but you need, you actually do need people ….

JB The generalist, yeah.

PH …. to keep things together, like you say. The other grouping, which must have started when you were there, was of course the Dysmorphology Group. Because that very much was based for years and years, and still is, at …

JB … the Institute, and I became the Secretary, and was the office and the library, that's right. And I became the sort of organiser. I think others will remember him for that Wellcome history book but I think the Dysmorphology Club had started when I joined. I think it started just a year or two earlier and there just began to be the first gatherings for discussion. But certainly it was in its infancy when I arrived. And I

became fairly central to that because throughout those four years, because Great Ormond Street was the epicentre, and I was the boy, it was my job to organise it. And I remember introducing the first radical idea that people might all put 50 pence into a container for us to buy coffee and things. I mean it was very, very basic. And it started off sitting around a table in the library and then we moved into the lecture theatre and then we just gradually accumulated and gathered more and more of our kind together and it became more and more formalised. It always was fairly informal. It would just be a list of – I introduced the people introduced like bringing a list of the patients they were going to present, partly because my attention span wasn't sufficient to remember what was going on. So I had to have an aide-memoire. And I always remember, yes, Michael and Robin were incredibly effective as diagnosticians, and I became pretty good. I wasn't as good as them but I was world-class, given that I was actually with some Olympic stars! I remember Robin and I doing an entertaining session a few years later in Montreal at the David Smith meeting and we had a Dysmorphology syndrome spotting competition and it was me and Robin against the rest of the world.

PH I won't ask who won.

JB We held our own. Well, with Robin behind me and me doing the fast chat we were a pretty formidable team. But it was at that time when you could know it all, you know, if you really devoted your energy to it, there was a totality to the literature. There were a limited number of paper journals, nothing was online to speak of then, and if you just read those journals and you interacted and did that for a living, which we did, you could genuinely be in command of the literature. And if you could, I mean as you know, some people can look at a face and recognise, and others say "I don't know, I can't see what you're seeing". So that pattern recognition ability I had and still have, I mean I can still float past and give an idea in the clinical meeting. It's like old knowledge becomes so burnished into your brain that you never quite lose that trick and so any of the syndromes that were extant prior to 1995, I guess, I can still recognise. But there have been such huge new additions since then, especially with all the exome sequencing and various deletions and so on, I don't pretend to know them all.

But I kind of moved away from dysmorphology very consciously in the early 90s because it seemed to me that cancer genetics was just the bigger challenge and that we were …. dysmorphology is the most entertaining aspect of clinical genetics but not, I thought, that which needed the greatest attention in terms of our academic expansion and clinical responsibilities. So I very consciously decided to start downsizing my dysmorphology, although I gave plenary talks at the Birth Defects Conference probably for another decade, I was increasingly not a dysmorphologist , and it became harder and harder to think of something entertaining to say that was relevant to the dysmorphology audience. I

remember my last talk was actually on next generation sequencing, when I actually ventured to suggest – I showed a picture of Indiana Jones, the classic scene where the Egyptian comes out with two big swords and threatens him and he pulls his gun out and shoots him, and under that picture I suggested that rather than, as we had just done, go through agonising debates about differentiating Costellos from CFCs or from Noonans to decide which gene to test first, why didn't we just shoot the lot? And just do a panel. And of course now we do that, we offer a panel for all genes. And I think we've probably now been through the golden age of dysmorphology, in the sense that that reliance on your capacity to have an encyclopaedic knowledge and pattern recognition – because that is the definitive test – is now secondary to the fact that you will have the molecular story and maybe RNA evidence and maybe a whole bunch of echocardiography and so on. So you still need the dysmorphology but it's going to be driven by knowledge of the underlying mechanisms and so on in the same as cardiologists are still great cardiologists but they aren't the auscultatory geniuses of the last generation, who could diagnose the most exquisite, subtle sounds. They don't need to any more, they just take an ultrasound picture and the echocardiography tells them everything they need to know. So they move their expertise into other areas. And I think that's what's happening in dysmorphology now, you know, we're struggling a little bit to retain that clinical skill in the face of the deluge of molecular data.

PH So, John, coming on to Newcastle. What year was it you went to Newcastle, then, as a Consultant?

JB I remained in touch throughout my time in London, and I did some of my research in Newcastle. But I actually moved back – I was offered a Consultant paediatric job, and declined. I said I wanted to be a full-time clinical geneticist. And so they created a job which I applied for and, not that surprisingly, got. I remember doing a deal with Peter Farndon that he could do Birmingham and I'd do Newcastle and there were only about 4 or 5 of us in training at the time so we could more or less divvy it up between us. And I was interviewed, and got the job, and started in July of 84. And basically I inherited a clinical team which comprised a part-time clinical assistant, Rosemary Boon, two part-time health visitors, who did family trees – Dorothy and Margaret – and Val Davies who was there with the cytogenetics team of about half a dozen, I guess. There was a disproportionate number of NHS funded staff doing things like blood grouping and HLA typing which I subsequently shut down, because they weren't really of any value clinically, but they were very valuable for Derek's population studies. And then there was the academic team, which was about a dozen strong. So it was a small backstreet department next to the hospital. There was a certain degree of consternation in London that I left to return to Newcastle, to this strange little department, when there were clearly places I could have stayed in London, but it was always my game plan to return to Newcastle, partly because, as a doctor, I

was completely clued in to the North East, and I knew that I could introduce the specialty across the North East without having to prove myself. I had already proved myself to the physicians and surgeons and paediatricians. And so it proved to be and I was welcomed with open arms and never had any access problems and was always supported across the region. And we still are. When – just last month – when the Genome Medicine Centres were called for, the head of the neighbouring Trust, who is the Chair of the Chief Executives of all the Trusts in the region, contacted me personally because there's always been a bit of tension between our Trust and its rather combative Chief Executive and all the other hospitals. And he was worried that this call might be jeopardised because we weren't representing the whole region. And they were just saying how highly they regarded the Northern Genetics Service and how they wanted us to know that if they needed a letter of support for the bid, they were happy to send one, even though they didn't necessarily get on with our Chief Executive. So that was quite nice, you know, that there was that sort of community support for genetics that I was able to build on and develop, and still persists, and that was a great asset. And I think I probably told you I did draw strength from your experience, because I knew that what you'd done in Wales was very comparable, that it gave you a home base to operate from. And it was a very similar sort of population – 3 million or so – large rural hinterland with a strip on the coast, just rotated through 90^{0}.

So I knew the model worked and basically Derek had evolved into a clinical geneticist of sorts, in the sense that he had done it because no-one else would or could. His problem was he wasn't a doctor and he was too cautious about making any definitive statements. And I used to sit in with him and I realised I had to kind of move him out of that role, because he really wasn't equipped to handle a clinical consultation. He had no clinical training. And so I gradually persuaded him to leave the clinics to me. And he did, and then gradually over the next few years I took over the clinical operation completely, shortly before he retired. And then when he retired, his job became Tom Strachan's position, and I got a clinical Chair from the Faculty, sorry from the region, funded by Liam Donaldson, who was then Regional Manager. And so they created an NHS-sponsored Chair of Clinical Genetics in the university for me in 1991. And that was the making of the next phase with me as overall Director and Head of the Clinical Service and Tom Strachan as the University Chair, although I was Head of the university department as well until we got through the Research Assessment in 96, and then we were merged with the Genetics and Biochemistry department and during that phase I became involved with the creation of the Centre for Life, which then moved us into our own Institute and we were separated again. And after the usual little bit of pushing and shoving about who ran the world, we came to the conclusion that Professor Strachan should be the Scientific Director and I would be the Medical Director. And that was a good outcome. I mean basically Tom

wanted to be in charge, understandably, he had been Deputy. I didn't want him to be in charge of the clinical service because I didn't think he'd cope with that, I didn't think they could cope with him, and I still think that would have been the case.

So splitting it into a clinical service and an academic service was appropriate, and having a leader for each, but Tom was the recognised head of the institute. And he remained so until 2004-5. And at that point I was stepping down from being head of the service in favour of Michael Wright and I was actually planning giving up being head of anything and concentrate on my research but then Tom's wife became ill so I was then asked to step in as head of institute, so I returned as a full-time university head and stayed in that job until 2009 and then I was – in fact I gave it up in 2010 I think, but in the meantime I'd been headhunted to become lead clinician for the strategic health authority working under Stephen Singleton, implementing the Darzi reforms, which was an interesting challenge. And I had also been asked, and had taken over as the genetics lead for the National Institute of Health Research genetics specialty group and alongside that been given a programme grant by Sally Davies to develop genetics, which they felt was sliding a little in terms of its research performance.

So between being lead clinician and being head of NIHR in its range bits, it became obvious I wasn't able to devote the energy to running the university department and so I was very happy when Chris Day suggested that maybe I should step down in favour of another person. I was happy to do so, and the person that we had in mind and who got the job was Patrick Chinnery, because Patrick was ready to take over the institute, and was being headhunted by others. And I had always, in fact I had tried really hard to get Patrick to come and join our institute as a mitochondrial genetics neurologist, and he had always felt unable to separate from Derek Turnbull in neurology because he is also a mitochondrial doctor and so he had never really joined us but had always aspired to, so bringing him in as head of institute was a perfect way of getting his expertise into the institute and that bolstered our numbers. So when I stepped down there were 36 academic teams and I've just learned that we've now become 42 academic teams and we've gone from 18 to 20 tenured full-time professors among that group and so the institute – and I think we've discussed before, getting an exit from positions, I always think, is the most important thing. If I can do something well but then get out of it, and hand it to someone else who then does even better, then I feel I've done the job well. Whereas getting out and leaving it to flounder is not, doesn't make you happy. So I was very keen that Patrick took that over. And I think one of the, I think probably looking back, being enthusiastic about not carrying on in a leadership role has given me ever more leadership roles because people know I'll give them away as fast as I can. And I think that's quite a useful lesson in life, you know, give it away, you'll get more. And so I kind of gave up being head of the clinical service and Michael

Wright took over and then Paul Brennan, both of whom trained under me, and Patrick in fact was a medical student in Newcastle, so I still feel very connected but I studiously avoid ever expressing an opinion on what they're doing, as a result of which they ask my opinion quite a lot. But they know that I will not go out and say they did something stupid. So at the moment it's really a very comfortable relationship in the sense that we have a northern service in the NHS, we have a very successful academic institute. I am a member of both, and accepted by the leadership of both, without rancour and without the sense that I am a sort of presence to be avoided.

I remember being very influenced by a little article in the BMJ where a man in Edinburgh said how he used to dread the sound of the footfall of his former head of department coming for another chat. Because he said he suffered from a serious case of detached retinue syndrome. So I try studiously to avoid having detached retinue. As it turns out, I just acquired another retinue so I have kind of, the NIHR job has flowered and in fact I am probably going to give that up now, if I can, in the not too distant future, but we have become very established because the programme grant Sally gave me to help develop genetic services and genomic research nicely dovetailed in to running the specialty group of the NIHR so that gave me an extremely good team, including Jill Borthwick who was a former, actually she was a brilliant academic who could have had an academic group but was a woman and had children and fell off the system and we were really bad about getting women back into practice as academics after they had had their families. In fact one senior colleague, who I won't name, actually suggested to her that academic medicine, academic research clearly wasn't for women. And it was just amazing. So she ended up becoming an administrator, she sort of fell off the top of her re-entry funding and ended up becoming a university administrator. And I got her back as my manager to run the genetics research team, which she loves because she's so well-suited to it, as a former academic, but she's got that application and knowledge, so she is my right-hand woman now and I fund her through the NIHR resource. And now we've set up a new clinical trial, which we're just launching in fact tomorrow, for a dose-finding study for aspirin in Lynch syndrome. So she's going to be the head of that and I'll put her funding onto that grant, which runs for another 7 years. So that secures her position. And I'm now trying to evolve away from the NIHR, having done quite a lot to secure its work.

The thing we're most proud of is in regards what's called the Musketeers' Memorandum because I had the idea that we could get every Trust that has a genetic service to sign an agreement for rare disease research that if one of them approved a project, all the others would automatically approve it, so that the research team didn't need to get 20 or 30 or 50 or 100 contracts in order to collect a few samples. And it just takes us back to the way we used to be when we would phone each other up and say "Have you got any of these? Let's do a project on them." And

I would say it's about two and a half years but we've got that into play now. So if someone wants to do a non-interventional project on Rubinstein Taybi, once it's approved by IRAS and their hospital, the other hospitals have three days to approve it. And that so-called Musketeers' Memorandum I think is going to be a useful contribution to rare disease research. So having got that into flight, I am planning to back away from NIHR because my new job is being Board member of NHS England, which is a very intriguing challenge and I am going to be very much at the forefront of working out how NHS England reacts to the genomic revolution, which I think is quite an important job, and having a knowledge of the whole system I am well suited to really.

PH It's very important, it really is important, because I think we have seen already, just in the last year or so, how the people involved in the genome applications centrally have gone from a state of I would have said almost complete ignorance to one where, well at least realise they don't know everything and they need to talk to people, which I think is encouraging.

JB Mmm

PH Tell me John a bit now about how your interest in cancer genetics started and evolved.

JB OK, again we've talked about this in our Wellcome Trust history book and in essence it began probably, primarily it began when being approached by Alistair Gunn, who was a surgeon at Ashington, who had worked at St Marks with familial adenomatous polyposis. And it's the sort of thing, I mean I am sure throughout your life you've had the steady flow of enthusiasts who wanted to enthuse you with their particular enthusiasm. But I was kind of taken by FAP because it struck me that it was something that as a phenotype it was an interesting phenotype. There were some dysmorphic features to it, with osteomas and jaw cysts and so on, but the important thing was that we could cure them by removing their colon and stop them dying. And as a dysmorphologist I spend a lot of time making diagnoses but I rarely could claim to have saved the patient in the process. And so I became more and more involved and immersed in it and we'd got a very good research nurse, Pam Chapman, from some money that Alistair had raised, and we started collecting these families together and I discovered that St Marks had told the world that they ran the national register and of course it was based in London, and I thought it was a pretty good guess that their register didn't cover our patch. So I asked them how many families they thought there were in the north east, and they said there were three. So I came back with 70 and suggested that maybe they didn't have the coverage they thought they did.

But also it became a very fruitful interaction because they were very receptive, in a sort of London-centric way, but I gradually turned their heads to sort of realising genetics was actually what they were doing, they were practising a sort of form of surgical genetics, and that they needed

geneticists, because we understood about tracking down genes and about phenotypes and about family trees and all the rest of it. So I got drawn into that and we were doing rather nicely, and got a nice paper on the congenital hypertrophy of the retinal pigment epithelium as a phenotypic marker of the syndrome, and I wrote a paper in the Journal of Medical Genetics about how people needed to use Bayesian rules to incorporate pedigree data and age and endoscopy results and so on into a single predictor. And then it struck me – I remember the actual time, it was very specifically when I went to see a family with Pam who had FAP. The mother had had a panproctocolectomy. I can't quite remember why we went to visit them. I think we were trying to involve them in one of the sort of observational research projects and they were down in Monkwearmouth. But what struck me was that the mother had osteomas as an extra-colonic feature of the syndrome and her 12 year old son had the same forehead osteomas but he had just had his endoscope and it was clear. And I thought "he's going to get polyps" and it really preyed on my mind. I thought "wouldn't it be nice to actually intervene in some way?" And I started thinking about what one might do medically. And at just about the same time I was asked to speak at a meeting by John Mathers in the Nutrition unit. And I spoke alongside people from the Dunn Nutrition Unit and they were telling us all about how resistant starches were fermented in the gut to butyrate and short chain fatty acids which had an anti-neoplastic effect. And the Dunn Nutrition Unit was founded off from the work of Dennis Burkitt, who was actually in the audience and I met on that one occasion, and he was the man who came back from Africa in '69 and said "Africans don't get bowel cancer". And he thought it was because they had a high fibre diet but it was because they had a high carbohydrate diet, almost certainly because population-wise there's a very strong correlation with high carbohydrate diet populations have less cancer than low. And so I got together with John Mathers and Tim Bishop – I slightly forget the order of how we met each other but Tim Bishop was working for ICRF and he was working in genetic epidemiology in Leeds and we set up a project to give resistant starch to our FAP patients in a very naïve way I just thought "we'll do a trial", you know, and we talked to the Dunn people and they told us about different starches. We could use ordinary corn starch, comparing it to Hylon 7 and potato starch and then along the way Malcolm Dunlop said "what about this paper from Melbourne about aspirin?". So Gabriel Kune had written an observational study saying that people taking aspirin and aspirin-like drugs were under-represented in colon cancer cohorts – or their cohort compared to their case controls – and speculated that maybe anti-inflammatories were cutting the cancer risk. And so I immediately thought "that's great, we'll give them aspirin as well". And so we started CAP1 with an aspirin-starch combo as a factorial design.

And I actually learned about trialling from Nick Wald because throughout the 1980s my interest in spina bifida had taken me into the folic acid story

from Cardiff and Michael Laurence and the guys and so they were speculating on folic acid being valuable. I had recruited to the original pregnavite 40F study, run out of Leeds and Guy's, which sadly had no randomisation. So it crippled it and Nick Wald argued that we needed to do it again but with a properly controlled population. And he was being vehemently criticised by John Edwards and others who said that the stats were perfectly adequate. And he was right, they were right of course. The evidence was already strong enough to say that there was something in the multi vitamins that was good, and it was probably the folic acid. But Nick was also right that if you are going to supplement a population you have to nail it to the ground. You can't just give a smart mathematical answer. And so he set up the MRC study and I was just about going back to Newcastle so I became wing man on that. I was his enforcer when all the people came– because he was a very bookish sort of mathematical guy, Nick – and I contributed as an enthusiastic recruiter, but also giving a sort of street cred to his project against some of my former colleagues on the previous study. And so I led the biggest recruiting team in England and Marietta van Mourik up in Glasgow beat me because they had such a huge population of affected people. And then Czeisel in Hungary, of course, who had this, and he sort of fell out of favour later, but he had a really big series of patients. So between us we recruited over a thousand women and gave them folic acid and multi vitamins and showed the folic acid had prevented neural tube defects.

So I learned from that about factorial design and about having two interventions crossing each other. And so we set it up in exactly the same way with aspirin and starch. CAP 1 was a learning curve. It proved really hard because we had to recruit all over Europe, we didn't have enough money, adolescents are hard to monitor. It's very hard to count polyps when there are thousands of them, you know, how do you know it worked? We got some results out of that but meanwhile, and because of that, I was interested now in hereditary bowel cancer and one particular family in Northumberland where a young man had developed FAP but got cancer three times in the space of a few months. And it turned out that he had inherited the deleted chromosome 5 from his father. I should say we were sort of peripherally involved in the hunt for the ABC gene because like Herrera we had a deletion case on chromosome 5. And then we found another deletion case – this chap – who'd had multiple cancers. And his mother's side of the family had lots and lots of colon cancers and other cancers. And we discovered the deletion subsequently was of paternal origin, but we found through maternal origin he had an inherited something on chromosome 2. And it was just about that time that the people in Baltimore, using the samples from Newfoundland, had tracked the Lynch syndrome, as we now call it, to chromosome 2 so we sent samples to Kolodner from our family and his team found an MSH2 mutation. And so we suddenly were sitting on this goldmine of first one then two very large families with hereditary non polyposis colon cancer.

And I immediately started drawing up CAPP2, in the month of that paper in ’93, I thought “this has got to be where we go next”, you know, “God has sent us this”. I mean we had been given non-polyposis cancer in adults, we don’t have the counting problem, it looks like it might be more common. Even if it’s not more common, it’s just easier to work with. So we designed CAPP2 and I spent the next two years selling it to my community and trying to raise some funding, and then another two years battling to get it into play. And we started recruiting in ’99. And we finished recruiting in 2005 – by that time, in 16 countries and 43 centres. All of it run out of two offices in the Centre for Life, including the dispensing. That has now been transformed, because of the Clinical Trials Directive and so on, but we produced a result which showed that giving aspirin prevented cancer. And what was exciting was we then deliberately set it up to be followed long-term because it was very obvious from the epidemiology that there was some kind of delayed effect. So we published a paper – which took me two years to get through the refereeing process in the New England Journal - saying that it hadn’t worked at the end of the clinical trial, but then we ran out of money but we got a bit more money given to us by Bayer, who had been very supportive because they love aspirin as their first big blockbuster. So we carried on following as we had planned and in 2011 we were able to publish the 50% reduction in cancer.

Meanwhile in 2009 I had started trying to set up the next clinical trial, CaPP3, and that’s taken another five years to set up. Now, with the aid of the European Clinical Trials Directive, it’s nigh on impossible to do trials in more than one country. We have to have staff in every centre in Britain to do the recruiting, we have to involve the Pharmacy of every teaching hospital in Britain top dispense the aspirin. I have had to spend £835,000 packaging the aspirin to European standards to give to those pharmacists. So logistically it’s become a massive task. But that’s as life is. So we’re recruiting 3,000 gene carriers into what will be technically called a dose non inferiority study, in order to see whether 600 mg two aspirins a day is actually superior to one aspirin a day or to a quarter aspirin, mini aspirin or cardio aspirin. Because clearly the side-effect profile drives you south. It’s actually not that big a difference between the three but psychologically doctors find it hard to give people two aspirins a day, but they will give them a quarter aspirin, even though it actually doesn’t make much difference. The problem is that there’s a real possibility – and I’ve got a poster at this conference with my crew, showing for example that obesity is associated with cancer but the aspirin obliterates the obesity-related risk. Now obesity causes chronic inflammation so it may well be that the aspirin is eradicating the chronic inflammatory process. We have another poster here on the immune system where aspirin is up-regulating the colonic mucosa and its immune effect. That could easily be an any-dose effect, because that could just be a sort of signalling effect. So I think what we are going to see is that there’s a little bit of a low-level

effect from low dose aspirin, which probably relates to the fact that salicylate has been lost from the modern diet through farming methods, and so giving that back is good for you. But then if you give a bit more then you start to get that anti-inflammatory effect that you see with obesity and in other settings. So it may be that in fact they all work but if you take a bit more you get a bit more benefit for a few more side effects.

So ironically, at the end of this seven year project, I think I am going to end up saying "you decide". But in the process we'll hopefully get past the innate conservatism of the medical profession, who still will send people for a colonoscopy without a blink, but won't give them an aspirin because it's so dangerous. And in fact objectively colonoscopy is more dangerous. Because these patients are getting it all their lives so they are going dozens of colonoscopies, and perforation and death is by no means unknown. So that's my new mission. It's not my only mission but it is one that I want to kind of see through to completion because, rather like Nick with the folic acid, I think pushing through to getting at least the familial cases of cancer taking aspirin as routine in the same way as no-one would bat an eyelid in saying "I've got a family history and I have a bit of angina so I am taking low dose aspirin". That's normal, sensible thing to do. And I think we can achieve that and use the genetically targeted trial model as a proof of the principle that, if we can prove that it works in the highest risk category people, then that's a pretty good guide to giving it to everyone else. So that's become something of an enthusiasm, as you can guess, but I've also, of course, in the process I ended up being listed in the Sunday Times once as one of the country's leading cancer geneticists at a time when I thought, well actually I'm not. But I got drawn into Cancer Genetics Group through that work and then I became its Chair and then merged it into the BSHG. So I spent 6 years as Chair of Cancer Genetics Group and that got me into the more general – and worked with you, of course, on the designing of cancer genetics as a part of clinical genetics for the Harper report. So I became embedded in the politics of Cancer Genetics. I never really was a terribly good one. I have never been totally absorbed in the minutiae of the probabilities of every type of cancer but I'm good enough to do it, and I focus now on the Hereditary Colon Cancer Group obviously.

And then more recently I've come back to it in a big way because I got really involved with the Human Variome Project when Dick Cotton launched it as it seemed to me that the next big challenge was going to be the traffic jam of data and that was obvious back in the mid-2000s and before. And we've been pushing, and I represented the Human Variome Project this year at the launch of the new Global Alliance for Genomics and Health, which is very much a big genomics-type exercise. And rather like the learning curve of the hundred thousand genomes, the other genomicists think we don't need databases of variants anymore because they'll just do whole genome analysis. And they don't appreciate that you still need someone to curate the variants and decide which ones are worth

reporting on and which ones aren't, and what their penetrance is in different settings and so on. So I am trying to marry the old-style databases of variants together with the new-style genomic APIs and bands and VCFs and so on and get them together and I had the idea in March at their first meeting - everyone agreed they needed to do something to prove that they meant business – and so I proposed that we created the BRCA Challenge. And I based that on my experience with Insight because I'd, again as an integrator, I'd brought the FAP HNPCC communities together to create the International Society for Gastroinstestinal Hereditary Tumours, which is a bit of mouthful but it stands for INSIGHT, or INSIGHT stands for it. And the INSIGHT society had its first meeting in 2005 and it's still going strong. Next one is in Sao Paulo. But also out of that we merged all of the databases of people's homemade mismatched repair gene collections into a single, curated, legally enforced ISIGHT database that gets about 20,000 hits a month now. And so diagnosticians refer to it as an advisory base for whether to report a pathogenic variant or not. So it seemed to me that doing that for BRCA, now that Angelina Jolie has made such a major feature of it globally, was an obvious high-profile thing for the Global Alliance to do, to prove that it could. And it was a bit of an each-way bet because I thought, if they fail, it will stop them telling us that we don't need our databases from the human variome project. If they succeed, we'll bring the human variome project in and try and get the two to operate as a joined-up entity. And so I'm having tonight the second of the teleconferences with the international steering committee at 9 pm. And in 2-3 weeks' time I'm going to San Diego for the first face-to-face meeting of the great and the good of breast cancer to try and create a community approach to having a single database of variants. But also to study the epidemiology and penetrance and the broader picture of BRCA1 and BRCA2 as an exemplar for what the future will look like in the sense of that we'll have global databases for all the genes, understanding their pathogenic variants, having a single reference source, rather like OMIM but rebuilt around a clear understanding of the variants and their pathogenic significance. So at a pragmatic level, when you're seen by your geneticist in the future and they find a variant, it's a click on an app on their phone to take them to the, to tell you about that variant. So that's another major enthusiasm of the moment, trying to get them to all work together.

PH John, there are a lot more things we could go over, but we could be here a very long time. One thing I've been asking everyone I've seen – two things, to be precise. The first is, is there any particular person who you feel has been especially formative in terms of shaping and helping develop your career? Does anybody stand out or has it rather more even, and a number of people in different areas?

JB I think we're all influenced by people we meet, to a greater or lesser extent, probably everyone influences us. Some of them stick out above the plot of the rest. I mean it sounds rather clichéd but obviously I've

been married to my wife, Linda, now for 40 years or more. 41 years. In fact, no, 42 years. So that's a huge influence. And she's been a stabilising influence. I mentioned Gerald Corney and David Gardner-Medwin, and the guys at Great Ormond Street who had a huge influence on my emergence. Clinically, Alistair Brewis who recently died. I'm just organising his memorial service. Particularly as just a first-class doctor. So there are a number of people like that who I look back on as guides in my professional life. When you retired I actually said that I thought that I'd looked on you very much as being a sort of reference point for being a clinical geneticist, or academic clinical geneticist. Although I never worked in your department I always saw you as a major influence like Rodney and Di Donnai and the guys in Manchester, and Paul Polani and others so a lot of people influence you from afar but you don't necessarily work up close with. And then there are you know people in Newcastle that I have worked with and still work with. Judith Goodship, I think, has had a huge impact on my career. I worked very closely with her for many years. And Kate Bushby, both of whom are very eminent professors in their own right. And this is a bit like when you receive rewards and you think "oh, I'm going to forget to mention someone". So I spoke about Alistair and Pam Chapman in particular who was tremendously influential in terms of developing the research genetic counsellor model and in really driving us forward and being sort of my wing person for the early stages of the CAPP studies in the way that Jill Borthwick has now become.

I think I'm sort of an external person. I need someone to play off, you know, I need a partner to bounce ideas off or to enhance. Ideally someone who's a fairly steady-as-you-go, reliable, get to the end of the road sort of person. And then I can kind of bounce off them and come up with the slightly zany but probably quite bright ways of getting there quicker, and spot the shortcuts or spot the ways we can enhance what would otherwise be a slightly pedestrian process. And that works quite nicely and so I am still remarkably able to be very active in my research because I'm now at a point in my career where I can attract resources and I can attract bright young people and I provide them with an umbrella for them to then do the creative things alongside me. But then the other thing, at this conference for the first time we have a stand for our new company, QuantuMDx Ltd, and that's another example where I took under my umbrella a young man called Jonathan O' Halloran who has had a profound influence on me in fact because along with Elaine Warburton, the Chief Executive, they've partnered up to form a crazy idea of a company that could do DNA testing in a handheld device. And I thought, when I read what they said they could do and they thought they might do, I thought "that's worth a punt". And so I've supported them over the last few years and we now have 40 staff. We have a turnover of in the millions. I mean, we are still spending other people's money, but this week in fact we're hoping to see the first live run of our machine in its pre-alpha prototype form. We have a stand here demonstrating it. And that, I think, and I'm very excited about that

because if we can actually develop the possibility to do a point-of-care genotype and give a GP the ability to check your warfarin sensitivity before giving you warfarin, or a pharmacist or a receptionist, or giving a public health doctor the ability to diagnose bird flu on the spot. Those are going to have a profound influence on, not only on medicine generally but on how people perceive genetics and genomics as a part of everyday life. And I don't think this is in any sense in competition with the whole genome approach, because the whole genome approach is giving us the totality of the picture. But if you can distil out a quick easy question that answers your immediate need then why not do that? And so instead of having tall Serbian basketball players I've got little short guys who are under their feet and can be just as effective. So I think if we can get that to fly that's going to be a major driver for the rest of my career because I'm already spending a day a week working with the company and that's going to expand. And we're about to start piloting in warfarin testing in primary care in the north east. The next thing we're going to try and look at is drug-resistant malaria in an African clinic and I suspect, rather like joining the Board of the NHS, that's going to be a kind of new departure in my life, so I hope I remain healthy enough to carry it through.

PH The other question, John, I've been asking everyone is: are you able to choose out one of your contributions which you feel "oh, this one particularly is something I'm proud of"? If you just had to take one with you, so to speak, rather like Desert Island Discs.

JB Yes, I know. I mean, I think there are a number of rather obscure things but I think the one I would have to take with me is the CAPP2 aspirin story. A close follower is the extreme opposite which was the neuroferritinopathy story because that was a sort of end-to-end story because I spotted it in a peripheral clinic, a family that didn't fit Huntington's. We were then able to find the gene. I didn't do the lab work but it was my crew that found the ferritin mutation. We got a Nature Genetics paper. Then with Patrick Chinnery we documented the phenotype and are now at the cusp of starting intervention studies using chelating agents to try and treat their iron accumulation which we've shown starts from childhood. So over a 20 year period we might go from discovering a brand new disease all the way through to treating it and learning a little bit about how iron deposition could affect more common disorders like Parkinson's disease. So it might be that that's the sweetest clinical genetics story. And at this conference a very rare syndrome I discovered in my own home town, which is now called Burn McKeown Syndrome, which is as rare as rocking horse manure, but Bill Newman and the team in Germany – in Essen – have now found the gene. And that mechanistically is really interesting because it's a deletion of one allele and a deletion in the promoter of the other allele, and if you lose both alleles it will probably kill you. So it's actually a compound heterozygote model like TAR Syndrome, which is the only other time it's been described. So it looks like you have to be a compound heterozygote to get that. It's a good example of where exomes don't give you all the

answers. So that's a nice story as well, but I think the one I started with, you know, actually establishing you could give aspirin, something as cheap and simple as aspirin, to people with hereditary cancer and halve their cancer rate, is I think going to save a lot of lives, so that's definitely the one I'd take under my arm.

PH I've got one last question, a little bit tongue-in-cheek. What was your reaction when they offered you a knighthood?

JB Well it was slightly different to yours, in the sense that I know you weren't sure whether to take it or not. I had no great hesitation in accepting it. The story is actually quite entertaining in the sense that I was at a meeting in London and I took a call from the Audi garage. I'd bought a second-hand Audi two years earlier and it had got an oil light on so I took it into the garage before I went to London. And the man from the garage phoned me that the engine was completely wrecked because the oil pump had stopped working and I'd driven 50 miles or more with no oil in the engine, so I'd need to spend several thousand pounds putting a new engine in. So I phoned my wife to tell her this terrible news and she famously said "Never mind that, you've had a letter marked 'Strictly Confidential'. You'll never guess what it says!" To this day I don't think she quite appreciates the irony of that statement. So she gave me the letter and I was just overwhelmed. I felt slightly embarrassed, slightly undeserving, a strange sense of "I'm not quite sure I'm up to this" or whatever. But I was very honoured and even more so when it was awarded. The interesting back story was that in the 1990s it was announced in the local newspapers that I'd been given the MBE and I'd got a letter from the Mayor and everything. And it turned out to be Dr John Burn in Cumbria who'd got it. And I was away camping with my son at the time and so everyone thought I'd gone off to camp just to hide but in fact it was just complete coincidence. So there was this sense that maybe some friends were playing a scam on us. And on New Year's Eve I was forced to get up in the middle of the night by my wife to go and check that it was actually on the website, that it really was true. Because we'd told the immediate family, although you're not supposed to, but there was this terrible anxiety that it was all going to turn out to have been made up. I guess that sums up that I didn't entirely believe that I deserved it. But it was a – and it's interesting that it is, you're not quite sure what to do with it. People say "well, what do you get for that?" My grandson thought I'd get a sword and a horse and things. And you don't seem to get upgraded any more. But it is nevertheless quite an influential award in terms of your recognition within your community and perhaps more importantly the recognition of our community in the bigger world of medicine and beyond. Because there is a clinical geneticist who's got a knighthood who's actually on the Board of the NHS, it actually has a kind of knock-on benefit for clinical geneticists. I think. I hope.

PH You're absolutely right. And I think you can certainly feel that everyone else was very happy indeed about it and that you put it to very good use.

JB Yeah. Well, I try to.

PH Well John, I'm going to close things there. Thank you very much for sparing the time. Lots of other things we could go on chatting about, and perhaps we should, but I'll turn the machine off and then we can …

JB Before you do, could I just say that the other influence, huge influence in recent years, has been our son and daughter and 4 grandchildren. I think in terms of my third age the influence of having grandchildren has been – you cannot overestimate the value of that.

PH I would completely agree with that.

JB It changes your view of the world. Anyway, thank you.