Alec Jeffreys

Personal Details

Name	Alec Jeffreys
Dates	09/01/1950
Place of Birth	UK (Oxford)
Main work places	Leicester
Principal field of work	Human Molecular Genetics
Short biography	To follow

Interview

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Personal Scientific Records

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Interview with Professor Alec Jeffreys, Tuesday 16th February, 2010

PSH. It's Tuesday 16th February, 2010 and I am talking with Professor Alec Jeffreys at the Genetics Department in Leicester. Alec, can I start at the beginning and ask when you were born and where?

AJ. I was born on the 9th January 1950, in Oxford, in the Radcliffe Infirmary and spent the first six years of my life in a council house in Headington estate in Oxford.

PSH. Were you schooled in Oxford then?

AJ. Up until infant's school and then my father, who worked at the time in the car industry, he got a job at Vauxhall's in Luton so then we moved off to Luton. So that was my true formative years, from 6 to 18, spent in Luton.

PSH. Can I ask in terms of your family and your parents in particular, was there anything in the way of a scientific background, had either of them or any other people in the family been to university before. Or were you the first?

AJ. I was the first to University, so we had no tradition whatsoever of going to University. In terms of scientific background, my father, he was very stimulating, he had a very natural inventive bent, was forever doing experiments and so on and that's going right back to my, four, five years old days, back in my Oxford days, so he would do chemistry experiments and all the kids would come around and marvel at what he was doing, sort of bangs and stinks. So a self-taught scientific enquiring mind and he in turn got that from his father, who was a prolific inventor with a considerable number of patents to his name. He invented one major process that was the Jeffreys three dimensional photosculpture process, whereby you go into a photographic studio, you'd be photographed in a rather cunning way and those photographs would be automatically translated into a three dimensional

bust. It was all the rage in London, he had a studio on The Strand, he had minor royalty, even a Prime Minister, Neville Chamberlain went along to the studio. So there's a sort of inventive streak, I guess running through my father's side of the family.

PSH. When did you first start getting interested in science?

AJ. Right from the outset, I think it was always deep inside me. What really got it moving in a practical sense were two gifts at the age of eight from my father. A wonderful microscope, a Victorian microscope, which I still have, it is now on show at the Wellcome Trust Identity Exhibition, which includes me. So that got me into Biology, and then a fantastic chemistry set, which was most lethal. This is not a standard modern chemistry set, I mean this was the real McCoy! So my father was not an expert chemist so he managed to weed out the obviously dangerous things like white phosphorus, but the rest of it, potassium metal, that was all in there, and I've still got the scars to show it! In terms of chemistry, organic chemistry I was self taught, I think up to first year University level by I guess the age of eleven or twelve, something like that, I just soaked it up. There's a lot one can do at that sort of age.

PSH. So, you moved to Luton for your secondary education. I mean did you get much encouragement, science wise?

AJ. The education was at Luton Grammar School which turned itself in 1967 I think into Luton Sixth Form College, which was the first sixth form college in the country. The Grammar School was very much a traditional school, the Masters there were inspiring, particularly my biology teachers and certainly by the time I moved up to A Level, anything I wanted, for example I decided I really needed to dissect a dogfish, I had never done that, and a starfish as well, the biology master went off and ordered them. Quite extraordinary. I had a lot of encouragement there.

PSH. Did you have what you might call a whole animal interest in biology as well as that more mechanistic interest?

AJ. It went right the way through, so certainly I was a keen dissector, probably the grimmest example of that was, I think, I was about 14/15 years old and I discovered a dead cat while on my newspaper round. I stuck this dead cat, rigid with rigor mortis, it had obviously been knocked down by a car or something, so it went into my newspaper bag with four legs sticking out of the top, took it home, this was on a Sunday morning, dissected it on the living room table, this was a dining table and unfortunately ruptured the gut and so had to evacuate the house. It was ghastly. So we had that, but also about the same time we start to see a lot of beautiful information on protein structure. There was a wonderful write up, either by or about Max Perutz on myoglobin structure and I remember looking at this and thinking, what an absolutely fantastic structure and actually attempting to build a model in my bedroom out of balsa wood from spare bits from making balsa wood planes, trying to create a myoglobin model, which I did completely. And again, that would have been around the age of 15 or so.

PSH. And what year was it that you went to university?

AJ. That was 1968.

PSH. So there was a fair amount of detailed information on the protein structure by then?

AJ. Yes, absolutely. So I remember in my formative years, before ever going to University, being really intrigued with genetics. DNA was becoming an increasingly prominent discipline, so it wasn't just Watson and Crick, it was the genetic code and what have you. That was taught quite remarkably well at school, at A Level standard, and that really hooked me, that I thought was really fascinating. I think it was at that point I started drifting away from the

whole animal or whole organism level and getting rather more molecular and that was really reflected in going up to Oxford to study biochemistry.

PSH. So, you went to Oxford 1968.

AJ. '68 yes, a good year to go to University. Student riots and the rest of it!

PSH. And did you do Biochemistry as a degree or did you do it as part of .....?

AJ. Yes, it was a biochemistry four year degree.

PSH. Who were the main people who influenced you there?

AJ. Gosh, it would be invidious to start picking names. They were all fantastic. Yes, I am not going to pick names out. They were all great.

PSH. Ok, well who were the main people there?

AJ. The main person for me was Dennis Parsons, who was a lipid biochemist and my college tutor. I was also tutored by Alan Malcolm, who was wonderful, I mean they were all brilliant, George Radda, he was one of my first tutors, slightly scary but a superbly impressive person, who I know really well, he is a very good friend and Rex Richards the NMR person, so it was some pretty impressive tutoring that I got there and of course that was one-on-one tutoring as well as standard lectures.

PSH. Was there much then in the way of actual formal genetics?

AJ. Not a great deal, no. There is, as you know, in Oxford, a Genetics Laboratory buried inside the Department of Biochemistry and I don't think I had an enormous amount of contact with them until I got to do my undergraduate project; that was done in that department; that then led onto

going in there as a PhD student, sorry DPhil student, as well. But the genetics was rather scattered, it was there though there was also a good presence in the Department of Botany as well.

PSH. Was Walter Bodmer there at that time?

AJ. He was indeed. Yes.

PSH. Ok, and Darlington had probably left by then.

AJ. He had gone, yes.

PSH. So you did a degree, did you go straight on and do a DPhil?

AJ. Yes, straight on, no gap, straight in.

PSH. You'd avoided, National Service and things had all finished by then.

AJ. That, by the grace of God, it had. I think in 1961. I remember as an 11 year old breathing a sigh of relief. Even at that age I think I knew what I wanted to do, and not spend a couple of years doing national service, thank you very much.

PSH. So, for your DPhil, am I right that you did that with Ian Craig?

AJ. Yes indeed, I was his first PhD student, DPhil student

PSH. And was he, at that point actually in the genetics lab or was he part of the wider biochemistry lab?

AJ. I think anybody in the genetics laboratory was part of the Department of Biochemistry, de facto, but no and he was a fully paid up member of the Genetics Lab, I think initially as a demonstrator and I don't know how old

he was when I started doing my DPhil with him but he was very young, I was ridiculously young, but we got on like a house on fire. It worked out well.

PSH. How did you come in contact with him, to do a DPhil with him?

AJ. I did an undergraduate project with him so it was just a matter of an obvious continuation and we got on extremely well and it was a good place to go.

PSH. So remind me what the actual topic of that was.

AJ. I'll quote it chapter and verse. So the title was 'Studies on the mitochondria of cultured mammalian cells' and this is all pre DNA, so it was basically trying to find out more rather about the nature of proteins within mitochondria and whether one could use a somatic cell hybrid approach to define those proteins that are nuclear coded, rather than those that are mitochondrial coded, and also some work on selection of drug-resistant cell lines where the target was likely to be a mitochondrial target.

PSH. And you got several good papers out of it.

AJ. Well, a few papers, yes

PSH. Right, so, after your PhD, your DPhil rather, what was the next point along the way?

AJ. Well, that was interesting because it was sort of suggested to me that I might consider staying on in Oxford and I felt at that point, having done a four year undergraduate course and three years doing a DPhil, that it really was time to move on.

PSH. I know what you feel like.

AJ. I mean it was a brilliant environment, but enough was enough, it was time to spread my wings a little bit. The DPhil I did was on basically lots and lots of cell culture and protein extractions, purifying cytochrome oxidase and goodness knows what. So there was a lot of biochemistry and a lot of somatic cell genetics but no DNA in there at all. So we are now in 1975, so we had just gone past the first reports of DNA cloning, we'd gone past the Asilomar conference, it was obvious that DNA was going to be the next big thing and that's where I wanted to go. So the question was where to go, and I remember going to a Biochemical Society conference in London and there was a tremendous talk there from Piet Borst from Amsterdam and at the end of his talk he said, anyone interested in doing a postdoc in my department, please contact me and I thought, absolutely great as I wanted to go abroad. I didn't want to go to the States because of the problem, being geographically too remote because I knew eventually I'd want to get back to the UK in some sort of academic position, so it meant Europe. My ability at foreign languages is zilch so then casting around Europe Holland was the obvious place, I mean they all speak perfect English there, pretty well. Anyway I applied for an EMBO Fellowship and was interviewed by Piet Borst who I remember very clearly looking me square in the eye and said 'Alec are you ambitious?' I said , 'No, not particularly', but anyway, everything went ahead and I got the EMBO Fellowship to work on yeast transfer RNA genes, got to Amsterdam, and Piet, and I have to say thank you to Piet for this, he said 'you might want to do this yeast stuff, but you ought to talk to Dick Flavell', who was a staff member within Piet's department and 'Dick has got some plans to attempt to purify a mammalian single copy gene and you may be interested in hooking up with him'. It was an enormously decent thing of Pete to do. So I wound up doing something completely and utterly different from my EMBO proposal and I don't recall even remember telling EMBO about it. I think they forgave me. I hooked up with Dick.

So the original plans to work on yeast transfer RNA genes got lost; instead I moved over with Dick Flavell on a project joint between Amsterdam and Zurich with Charlie Weissmann on a crazy attempt to purify and then clone

the beta globin gene which was the only mammalian gene at the time for which we had messenger RNA and then shortly afterwards a cDNA which could be used as a probe. The idea was to take huge amounts of rabbit DNA , cut it up with a restriction enzyme and then purify separately coding and anticoding strands by using hybridisation enrichment. We were doing the coding strand, Charlie Wiseman was doing the anticoding strand and then the idea would be to hybridise together those two highly purified strands, take the DNA fragment and clone it. The entire project was doomed to failure from the outset for one very good reason and that was an intron inside the gene. It turned out that there was not only an intron but a restriction site for the enzyme that we were using. So the gene that we were trying to purify was in two halves and for technical reasons we were purifying the 3' coding strand and Charlie Wiseman would have been purifying the 5' anti-coding half, and so they would have never have gone together. But during that project, we realised that we had to develop a technology that would enable us to monitor purification, and what we settled upon, which at the time was very new technology, was Ed Southern's Southern Blot hybridisation. And to our astonishment while we were monitoring these fractions by hybridisation with a cDNA probe, we detected the partially purified fragment but we could also detect a genomic fragment back in the starting rabbit DNA. That was one of the very first detections of a single copy gene in a mammalian genome and I think the general feeling up until that point was that the size of a complex genome was going to beat you, you simply wouldn't be able to do this. I do remember Piet Borst being most surprised that we got this going. So that ability to detect single copy genes without cloning then enabled us to fairly quickly build up a restriction map around the rabbit beta globin gene which in turn showed there was something very funny about the gene, there was an intron in there, so at the tender age of 27 we provided one of the first descriptions of the existence of an intron in a mammalian gene. That was quite an exciting moment, very exciting indeed. And then the next stage was to move from Amsterdam to Leicester.

So we are now into the spring of 1977 and the question was, what was I going to do with the rest of my life. There were basically two options. Certainly go back to the UK, but first either do another postdoc, or second, try and get my own independent academic position. For the postdoc, I in fact applied to Ed Southern and spent two great days up in Edinburgh and mapped out possible projects going into the future. But about that time I'd also applied to various Universities in the UK for lectureships and I had a phone call out of the blue from Bob Pritchard who was the founder and head of this department here in Leicester. He phoned me up and said 'we are interested in your application, would you like to come for an interview?' so I said yes certainly, and then I had a panic as I had no idea where Leicester was, but a Dutch colleague found a little map of Europe and by a miracle Leicester was on it and so I knew where I was going and I arrived here for interview and immediately fell in love with the department. It was relaxed, informal, very collegiate, it just had a good atmosphere about the place. So after a bit of soul searching I was offered a lectureship in Leicester and I thought OK, it's time to establish my own laboratory now rather than carry on the postdoc route. And it sort of worked out fairly well.

PSH. So before the DNA fingerprinting what was the initial project that you got going in Leicester?

AJ. Well the initial obvious project was to carry on with the intron work, but it was going to be a non-flyer. Here I was in a lab, the only DNA jockey at Leicester, no grant, no nothing and at the time there were some very big labs moving into the intron field and I felt simply that we couldn't compete with that. So instead I decided to put together this new fangled molecular genomic technology with my past background in human genetics. If you can detect specific restriction fragments in the human genome, then logically you should be able to find human variation in fragments due to single nucleotide polymorphisms creating and destroying restriction sites. That led to our publication in 1979 of one of the first descriptions of RFLPs. In fact it was the second, beaten by Kan and Dozy who did accidentally find an RLFP near the

beta-globin gene, so at least we consoled ourselves that we had done the work quite deliberately. We also provided one of the first estimates of just how many single nucleotide polymorphisms there might be in the human genome; based on this tiniest of surveys we extrapolated like mad and came up with a figure of 30 million. But a good colleague of mine, Peter Little, pointed out that had I screwed up on the calculation and it was in fact 15 million and of course the current tally of SNPs is 11 million, something like that but remarkably close, more by luck than design!

AJ. So we are talking about how we got from late 70's RLFPs to DNA fingerprinting. RLFP's were utterly tedious and genetically pretty uninformative, so we started thinking about extremely variable regions in the human genome and given the size of the human genome such things had to exist. We started thinking intuitively, taking as our model satellite DNA. Satellite DNA was known through cytogenetic analysis to show substantial length variation, or copy number polymorphism using modern jargon, between people. So we started wondering about whether dispersed around the human genome there might be shorter repeat versions. This was all sort of hypothetical until a paper came along in 1980 form Arlene Wyman and Ray White on the accidental discovery of what proved to be the first truly hypervariable locus found in the human genome. But if you read their paper, their interpretation was based on transposition which reflected, I think, Ray White's background in Drosophila genetics where transposition rules the roost. I think their idea was, here is a locus with a transposable element moving in and out with high frequency, taking bits of DNA with it and creating these length variations. I looked at that and thought, I'm not so sure about that, maybe it's tandem repeat DNA instead. So we then started this program of all sorts of crazy ideas, trying to get at short tandem repeat segments in the human genome and basically got almost nowhere. Then out of the blue in 1982/83 was a report of the accidental discoveries of what we now call minisatellites or VNTRs near the insulin gene and in the alpha globin gene cluster; at that point I knew these things were real so we doubled our efforts and still got nowhere. Then the eventual clue for getting at these bits of DNA

came from our gene evolution programme that we were working on. It actually came through a study of the myoglobin gene, initially in the grey seal, which provides an abundant source of messenger RNA needed to identify and clone the gene. In the human gene that we sequenced we found a minisatellite inside an intron and took one look at the sequence of the minisatellite repeat and it looked familiar and it sort of showed a similarity to the repeat sequence of the insulin minisatellite and the alpha-globin minisatellite as if there were some sequence motive associated with these tandem repeat DNAs. So we took the human myoglobin minisatellite and went into a genomic library at very low hybridisation stringency and showed that you could indeed pull other minisatellites. We then used the sequence of those minisatellites to define a little sequence motif shared across all these different minisatellite loci. Then we thought, ok we now have a generic way of getting at minisatellites. Of course the reason for getting at these was to provide much better and more informative genetic markers for linkage mapping and other applications in medical genetics. So just to check this idea before taking this little shared core motif and using that to go into a genomic library, the obvious experiment was simply to take a repeated core probe and hybridize it to total genomic DNA to check whether it picked up multiple variable minisatellites. That was the key, almost accidental, experiment that triggered the entire field of human DNA identification. On the autoradiograph that we got was a set of fuzzy bar-code-like patterns coming out from the three individuals that we had on that Southern Blot. They happened to be my technician, still working in this laboratory, who in the New Year's honours list got an MBE, which is very, very good, for services to science, and also her mother and father. We could tell those three people apart, and you could see how the child's fingerprint was a composite of mum and dad's, so we could immediately see biological identification using DNA and we could see establishing family relationships. All of this was gained purely by accident on this first Southern blot. We had a whole lot of non-human species on the blot too. So there was a mouse, a rat, a cow, a seal, a lemur, a baboon, tobacco DNA, and just about everything came up with what looked like a DNA fingerprint. It was an extraordinary moment and I think the penny dropped

within seconds from that first autoradiograph coming out of the developing tank. I think my first reaction was what the hell is going on here, what a mess, and then the penny dropped. Here was DNA-based biological identification, family relationships and then all of the non-human applications, from dog paternity disputes to conservation biology, biodiversity monitoring, it was all there. It was a very exciting moment. I'd never ever planned to come up with a technology for identification; we just found it.

PSH. How did you decide which of these multiple avenues to take up first? Was it forced on you?

AJ. It was not really forced on us, but the following sequence of events meant that I was now embarking on what I call the great detour of my academic life, which was to go charging off into the world, of forensic and legal medicine. So the sequence of events was that we published this in Nature, and in the paper we speculated on biological identification, though for patenting reasons we said little about the animal identification. That article was picked up by Andrew Veitch, a science correspondent with The Guardian, he wrote a lovely little piece on it that was read by a lawyer in London who represented a family involved in a very tricky immigration dispute. They'd been through all the blood group testing that basically failed to convince anybody of anything so she then wrote to me and said look I've heard about this new fangled DNA stuff, could you possibly help with this family? And I thought ok, right this is, we'd done a lot more work; fuzzy blobby bands had turned into something quite pretty and highly informative, so we thought ok this is crunch time now, you cannot possibly say no to this woman. So that was our first case, which had a successful resolution, a young lad facing deportation reunited permanently with his family. It was a good news story, a great story. So that was the trigger and as soon as publicity came out on this case there was an avalanche of enquiries – I'd no idea of how many people were trapped in immigration disputes, they all wanted DNA testing. So that case was done in April 1985, and I think it was in June that the immigration tribunal dropped this case against this boy. By the summer of '85 we'd taken on the first

paternity dispute anywhere, to my knowledge, and that then opened another flood gate, and then life went completely mad. So I desperately struggled to keep the science going, but in parallel with that, there was a huge demand from the public for DNA testing. We had unwittingly created this whopping great market, just this huge demand out there which I had no idea existed. So the thing was ripe for commercialisation. For two years we were the only lab that could do this DNA testing; so I recruited a technician to take on case work but we could only satisfy the tiniest proportion of all demands placed on us. It was '87 that eventually there was an agreement with ICI to establish Cellmark Diagnostics. At that point, there was a sigh of relief to get all these applications off my back, because put bluntly, having done your second or third murder case, or your fiftieth immigration dispute, there's no scientific novelty left in it, it then becomes a major distraction. So, 1985 to 1987 was an absolute rollercoaster, fantastically exciting, totally exhausting. And then the pressure was off once it went commercial.

PSH. But before that pressure was off you'd had the local Leicester murder case. How did you get involved in that? Was it because you were local?

AJ. No it was just the publicity. I think that it could have been any constabulary. The fact that it was the Leicester constabulary was a happy coincidence I guess. The work we'd been doing had been given a lot of press so the word was out, you know here was DNA as this amazing new tool, so we were just phoned up out the blue about the Enderby murder case, with a request that we do DNA typing on the forensic samples recovered. They already had the guilty party, he'd already confessed to one of the murders, so the key thing was to simply confirm his guilt, matching DNA between him and semen recovered from one of the victims. However, this person denied any involvement in a second very similar murder, so we were asked to see if we could tie him into that murder as well. So I took this on in the full expectation that we'd get nothing back. Up to that point I'd set up a collaboration with people, particularly Peter Gill, we'd done a lot of work showing that mock forensic specimens could yield typeable DNA because not even that was

obvious. I mean if you take an old blood stain, can you get DNA from it? Can you analyse it? So we'd shown during '85 that that was possible. In '86 the forensic samples arrived here and we went through, not multi-locus DNA fingerprinting, but the single locus minisatellite profiling that we'd developed and that to my astonishment that we got a reading out of that; I expected to get nothing at all, and what the results showed apparently very, very clearly was that the semen from the same man was present on both victims and the DNA didn't match the profile of the person who confessed to one of the murders. My first report back to the police when we got information on the first victim showed there was a mismatch. So I remember phoning them up and saying you know we've got what appears to be a clear exclusion of the involvement of this person in respect of the first murder. Then we had to wait a long time with very small amounts of DNA, very faint profiles, and then the same profile came up with the second victim, completely mismatching the person who confessed to her murder. So I remember phoning the police and saying I think you've got the wrong guy, or that the science is completely shot, take your choice. I won't describe the sort of Anglo Saxon response to that! At that point I really started worrying very very profoundly about whether there was some fundamental flaw in the entire science. The police were so convinced that they'd got the right guy, but anyway, there was then a meeting here, with Home Office forensic scientists, the police, myself and the final conclusion was, yes the science was fine, they'd got the wrong guy. And that saw the release of this young man in custody and so the first time DNA was used in criminal investigation was to establish innocence not guilt. This then led to the police launching what proved to be the world's first DNA-based manhunt, having got the DNA profile of the assailant. They used that to flush him out, and that did work eventually.

PSH. Before we get back around from the detour, can I just ask now, you've had concerns about how this is being used in recent years, in terms of things like the DNA database. What are your feelings about that at present?

AJ. Well they were expressed fairly forcefully to the Home Affairs Select Committee when was it, last week, week before, when I went down to give evidence. They were considering the use of the National DNA Database and I attempted to stay fairly focussed on the fact that, of the five and a half million people now resident on the database, one million of them, roughly, are entirely innocent people who have been arrested but have never even been charged with anything, never mind convicted. I have always taken the view that that's basically out of order, and that view was very much reflected in a European Court of Human Rights verdict a little over a year ago that this retention is illegal and that the UK is in breach of Article 8 of the Human Rights Act which guarantees an individual to the right of a private and family life. I absolutely went along with that verdict, in fact I was involved in working with Liberty in taking that case to the European Court. So I've been despondent, I have to say, about the incredibly tardy response of the British Government. This clear verdict said that these retentions are illegal. So they are still dithering about this; current proposal is that instead of retaining innocent people DNAs indefinitely they retain them for 6 years, it strikes me as a very long time. There's no other country in the world that does that, not even Scotland. So I think my evidence to the Home Affairs committee was blunt, whether it will have any effect whatsoever, I have no idea, but I have done my bit.

PSH. I was going to say, do you think that there is a chance they'll listen, or do you think they're fixated on.....

AJ. Well, there's a great determination to. They are probably thinking in two sorts of ways here. First that a considerable expense has gone into the acquisition of these people. However, there was a statement recently by the chairman of the Human Genetics Commission who noted a claim by a senior Police Officer that some police were seemingly actively encouraged to go out and arrest people just to get a DNA swab off them. So we are now in the position where approximately 75% of juvenile blacks are now on that database, many with no criminal record whatsoever. Diane Abbott was very

concerned about this, reckons it's going to elevate quickly to 100%, the way it's going at the moment. So you're basically branding whole sections of society, juvenile blacks as future criminals. It's an appalling record, but the thinking seems to be that, having spent all this money to get all these people on the database, would be a shame to chuck them all away. There is no published evidence whatsoever on how effective these million innocent people are in solving crime. One of my fundamental objections is that the judicial system of English, Wales and Northern Ireland judicial system relies on one fundamental principle, the presumption of innocence, and the only reason we are keeping these people on databases is on the presumption of future guilt. So you are undermining the very foundation of the legal system that is there to protect the individual. So I have a deep philosophical objection to the retention of innocent people and a deep practical one as well; in my position I meet or am emailed or written by quite a few people who are on that database and are seriously distressed. There is one recorded case of a person who committed suicide because of the shame that he felt of being an entirely innocent person and demonstrably innocent, of being put on that police DNA database. The initial foundation of the database back in '95 was as an intelligence tool so you'd accumulate all your unsolved casework, database all of your criminals and that made excellent sense. What we've seen since then is a sort of creep starting in 2001 with the change in the criminal justice act, which started opening the door for the retention of DNA from innocent people. There are other issues like familial searching, which again is not covered by any legislation whatsoever. So we are now in a position whereby if I as an innocent person were placed on the database, then they could do a familial search, say at the scene of an unsolved crime, and possibly come up with someone who was rather closely matched, for example bringing my brother purely by chance into the frame of a criminal investigation. The next thing there is knock at his front door by the police saying 'we need to question you about such and such a murder' or whatever. That is breach of right to a private family life big time. The response from police and from politicians is that if you've got nothing to hide, then you have nothing to fear about being on the database, which I think is the most wrongheaded way of

viewing this imaginable. If I have nothing to hide, if I am not a criminal and never will be a criminal there is no point of me being on the database, the worst that could happen is a database screw-up or an accidental match that could inadvertently put me in the frame of a criminal investigation and cause untold havoc to me and my family as I suddenly become an entirely innocent suspect in a criminal investigation, or could wind up falsely implicating one of my relatives. I've said enough. The battle will continue but I am not going to let go on this.

PSH. Coming back then after your detour, back to science, there are lots, far too many things that we could go over, but are there any in particular that you would like to talk about that have followed on from that initial phase.

AJ. Right, yea I think that there is quite a lineal sequence here. So we start off with DNA fingerprints which used these, in some cases, fantastically variable minisatellites. We realised from the outset that these things are so variable for one reason and one reason only; they are unstable. So we then started looking in families, actually directly measuring germline mutation rates , which had never been done before in humans, and we found mutation rates at the 1%, 5% level, which was unbelievable. So this was highly unstable DNA. So that then really whetted my appetite about thinking, not so much about patterns of DNA diversity that you see out there in human populations, but more about drilling down below that to start asking more mechanistic questions, like what are the dynamics of the process involved, what are the mechanisms going on. Our first foray showed by pedigree analysis you can directly get a germline mutation rate but then we thought, wait a minute, what are we doing in this approach. We are looking in families using the child as a way of reporting whether a sperm or egg carried a mutation. It then became immediately obvious to me that single molecule PCR, which had just come over the horizon, would be the way forward, by looking for mutations directly in sperm. PCR was of course a major part of the forensic story too that we quickly latched on to, with the development of microsatellite markers

and bone identification, the Mengele case and Cardiff Crown Court, which was where PCR and microsatellites got their forensic debut in the UK.

PSH. I'd forgotten that.

AJ. Yes, the Karen Price body in the carpet case. So ok, looking at mutation of these minisatellites you don't need the kids anymore – with PCR and the ability to go down to the single molecule level in sperm, you can transform analysis of human germline processes from the strictures of limited family size into a numbers game that the yeast people and the E.coli people have been enjoying for years. This turns humans into E.coli basically, you know, with one ejaculate, one hundred million sperm, you're in seriously good business. That concept has really guided much of what we have done ever since. So we developed single DNA molecule methods for getting at minisatellite mutations so suddenly we could not only measure mutation rates, but rates at the level of the individual man and start looking at differences between men in levels of instability. We also started asking mechanistic questions, ok these minisatellites are pretty unstable, what is the mutation process? To get at that we made use of the fact that minisatellites are not homogenous repeats but that the repeats come in variable sequence types – it's like beads on a string, minisatellites are not just a string of white beads, it's a string of white, yellow, red, blue , green, purple, indigo beads, coming in many different combinations from allele to allele. We then developed in 1990 a PCR method that we called MVR PCR, minisatellite variant repeat mapping by PCR, which we thought was going to be a great forensically as a digital DNA typing method, but there was one basic problem, I got too bloody clever by half and it went straight over the head of the forensic people. But it was superb for studying minisatellite mutation – you could not only get as many mutants as you liked but you could get these fantastically detailed allelic structures before and after mutation. This immediately showed that meiotic recombination was the main driver of minisatellite instability.

This became clear by about ’94 so we then embarked on a major investigation of minisatellite recombination. The main minisatellite mutation process seemed to gene conversion, with minisatellites mutating by alleles coming together followed by copying and pasting of repeats from one allele into the other, changing allele structure. One question was whether this instability was an intrinsic property of the repeat array or could something else be going on. The answer emerged at two or three loci that we looked at in detail to see if we could also detect genuine crossovers in sperm. We then started designing methods for panning huge numbers of sperm for crossover molecules; that worked, and that led to the definition in the 1998, of the first meiotic recombination hotspot to be defined with any degree of precision. Before that it was all indirect inference mainly from population genetics, looking at haplotype diversity and showing the non-random distribution of historical crossover events. One minisatellite that we looked at in considerable detail seemed to be a parasite of a hotspot, engaging in the recombination machinery and creating all these wonderful new variants.. So no, this minisatellite at least seemed not to be intrinsically unstable, but rather was made unstable by a nearby hotspot.

So, the next question was, was this narrow hotspot phenomenon, just 1 kb or so wide, something weird to do with minisatellites was it more general in the human genome. There was a paper from Mary Carrington and others on the so-called Tap2 Hotspot, where they’d done some familial work which seemed to suggest that there was a genuine hotspot within the major histo-compatibility complex. So we thought, that’s a good place to start, went in there, did all the sperm crossover analysis, and it worked and revealed another narrow hotspot but this time with no minisatellite near it, but nevertheless looking like our minisatellite-associated hotspot.

So then we then broadened that out to a bigger survey within the MHC, looking at patterns of haplotype diversity and then looking at sperm recombination events to see if they were correlated. I do take great pride in that paper in 2001, because that was one of the first descriptions of

haplotype block structures in the human genome as well as providing a clear explanation of why it was blocking because of the highly non-random distribution of crossover events. I think that paper certainly played a significant role in the thinking of the HapMap people as to why HapMap was worth initiating. Before 2001, there were theoretical papers saying that linkage disequilibrium in the human genome would decay rapidly over short distances, but we and others were saying that no, this is a far more structured thing. And of course the implications for this block structure on genome wide association analysis was clearly going to be big. So yes, we did take great pride in that first paper, I mean it sort of hit the right place at the right time.

Since then we've been doing a lot of work on allelic recombination, defining hotspots and showing that these are frequently polymorphic in human populations and are rapidly turning over. They have properties which guarantee their auto-destruction, making hotspots actually theoretically impossible. This is the so-called hotspot paradox, whereby the recombination machinery will favour any variant that will shut a hotspot down, so there are some wonderful puzzles there. Meanwhile we've also been extending this work into ectopic recombination, to look at processes underlying copy number variation, what drives this variation into the Human Genome, again trying to answer questions such as what's the role of meiotic recombination, what are the dynamics and so on and so forth.

And then the grand minisatellite circular tour was closed off most satisfactorily by three papers just appearing in Science. It was clear from our work and others that hotspots are ephemeral and that there are not only cis-acting elements that control hotspot activity but probably trans-acting elements as well. There were three papers, none from this lab, I hasten to add, where in a beautiful series of studies, they basically identified what appears to be a major trans-regulator or trans-specifier of human meiotic recombination hotspots. It's a zinc finger protein called PRDM9 where the zinc finger array recognises a motif that is associated with a fair number of recombination

hotspots, and that zinc finger array is coded by a highly, well fairly variable minisatellite. So we're right back to square one, we have a minisatellite specifying the location of what appears to be a significant proportion, what that proportion is we don't know yet, of the locations of human meiotic recombination hotspots , some of which in turn generate minisatellites. So it's intellectually colossally satisfying for me, as now we are back in the minisatellite world.

We had a departmental Christmas review on one occasion and one of the standard jokes was: why are minisatellites like BBC TV programmes? Answer: Because both are boring and full of repeats! Well they are not boring, and some of these minisatellites we know have clear influences on insulin gene expression, diabetes risk, there's a Harvey Ras minisatellite with associations with breast cancer, myoclonus epilepsy caused by a minisatellite expansion, and so on. And now we have a minisatellite regulating one of the most fundamental biological processes of all, namely meiotic recombination. So as I approach the end of my active experimental career this is enormously satisfying. A sort of lovely symmetry to the situation.

PSH: Alec, there are lots of other channels we could go up or down, but we haven't got time for it. But there's one question, I suppose it's two allied questions I'd like to ask. One, you just referred to; you've kept an active scientific career throughout, rather than getting diverted into higher spheres of policy and all the rest. I know you have done a lot besides, on policy, besides active science but you've never lost track of it. Why do you think that is? Is it because you like it?

AJ. I love it. That's what I do, I mean. I will make an analogy, it's rather like taking a really talented composer and saying 'why are you still composing, why aren't you off running a composing school or advising government on composition or something like that'. I mean you would never think of asking that question, so I find it in a way slightly alarming that questions like that are asked of scientists. One of my heroes in science was Max Perutz, a great guy,

a gentleman I knew well and dearly, and he stuck at the lab bench right to the end. You know, the equipment may have been slightly archaic but he was still producing, because that is what he loved doing. Of course he'd had major impact at higher levels of policy, but drill down, that is what he really wanted to do. I always tried to, not model myself on Max, but to keep that philosophy very much alive. I am an unapologetic experimental scientist, I am never happier than when I am at the bench and that's what I do. I think the alternative would have been to run an Institute or something like that and I am a lousy administrator I'll be honest, so I would be, frankly, a disaster. There are other people far better qualified to run that sort of stuff.

PSH. I mean in a way allied to that you told me how you loved Leicester when you came, but there must have been lots of times when people tried to lure you away to here or there. How come you stuck with Leicester?

AJ. There are various reasons. The first one is family. Fairly shortly after arriving in Leicester we started a family and had two daughters, both of whom are Leicester born and bred and I do have a great loyalty to the place. I also enjoy the department. It is a terrific department, friendly, relaxed, informal, everybody equal, no prima donnaishness. Yes, I have had offers over the years but they've all tended to be moving me away from science and very much towards science management and administration, which is not what I am good at. I don't think I could contribute terribly well there. So, you know, I just stick with the science. My Royal Society research chair does insulate me from a lot of the more tedious work that one has to do in a University, though not all of it. It does protect my research time to some extent. I've got the dream job. Why chuck it out. It's as easy as that!

PSH. I've been asking everyone I have seen two questions, just to finish up. One has been, like a sort of desert island question.

AJ. Well you know I have been on desert island discs.

PSH. Oh, I hadn't known that. Well, I'll bet they didn't ask you, if you had to keep just one of your pieces of work, which do you feel the greatest affinity with? I guess I might allow you two because the DNA fingerprinting is such an obvious one

AJ. I think, that's a hard call, but I think it would have to be, the DNA fingerprinting paper and the Intron paper. Ok, so both go back a long way. But they were both pretty significant in their own ways. The trouble about the Intron paper is that everyone has forgotten about that. I am sort of branded as Mr DNA fingerprint now. Most people have no idea that I had an existence before that. I remember on one occasion I was over in somewhere in India and I was asked to give a talk in a research institute and I thought, blow all this forensic stuff, I'll do it about recombination, it's what we are doing now and about half the audience walked out within ten minutes, simply because I wasn't singing the old song – I sometimes feel like a superannuated popstar, if you don't stand up and sing the old numbers your audience gets the sulks. It's sometimes a bit of a burden I have to say, but by and large it's a real joy.

PSH. The other question I have been asking folk, I kind of touched on it before, is there any person or particular people who stand out in terms of their influence on your career and development?

AJ. It's just Max Perutz. He's my hero. There are so many other people that have influenced me, all the people I work with, Dick Flavell had an enormous influence, Ed Southern, people like Bob Williamson, tremendously helpful, there is just so many of them but if I had to pick just one out as a role model it's Max.

PSH. Any other things that you would like to bring up before I switch the machine off?

AJ. I think we've covered. Yes, actually, one thing, yes that I think is actually quite important. The thing that has given me as much pleasure as anything else, and I have had a lot of pleasure out of our work as you can probably gather, is the fact that we've got a story which is of considerable public appeal. I mean if you can't stand up with a story of molecular genetics with added rape, murder, mayhem, immigration, paternity disputes and use that to get something exciting about Science across you may as well give up. So the result of that is I spend a lot of my time going around giving lay lectures, school lectures and so on, really using the gory bits and pieces as a platform to inform people about the science and where human genetics is now and where it's going. All the publicity we've been given over the years, that's given me outreach in a very positive and affirming way. So that to me counts for a lot. So as I retire from running an active research laboratory, not yet but in the not too distant future, the outreach activities will keep on going. As long as I can stand on two feet and get a reasonable, coherent sentence out of my mouth, that will carry on going.

PSH. Alec, thanks very much indeed.

AJ. You are very welcome.