Genetic fingerprinting

Sir Alec Jeffreys in conversation

Thirty years ago, the technique of genetic fingerprinting was invented here at the University of Leicester. It can be used to identify family relationships, or if DNA found belongs to a particular person. It has revolutionised the legal system and DNA evidence is now commonly used in criminal investigations. Recently, genetic fingerprinting was used to determine that the remains found in a car park in Leicester were indeed those belonging to King Richard III.

Akanksha Bafna interviewed Professor Sir Alec Jeffreys before his retirement in September 2012, after nearly 40 years working at the University of Leicester.

So, you completed your degree in Biochemistry at Oxford and then you went to Amsterdam for a few years before coming to Leicester?

Not quite. I stayed at Oxford to do a DPhil, which was in genetics. That was in the days just before the beginning of the DNA revolution. Having got my DPhil, I was very lucky; I got myself a European molecular biology organization fellowship to go to the University of Amsterdam. The original deal was that I was going to go over there to work on yeast RNA and having arrived at the department I met up with this guy called Dick Flavell, a brilliant scientist, and we said 'well you might want to do this yeast stuff but we've got this other project on the go which is an attempt, for the very first time, an attempt to isolate a single copy of an alien gene'. And I thought, wow, that is exciting. So this is right at the beginning of the recombinant DNA revolution. And that's what my initial research was on.

Is that when you started looking at variations in human DNA?

Well, that came a little bit later. Let's fill in one or two little gaps. So the two years in Amsterdam, during that time I was the first to develop methods which enable you to detect a single copy of an alien gene, using solvent block hybridization. I then went on, accidentally, to provide one of the very first examples of split genes. Which people forget, but I'm the one who discovered split genes so I was that close to getting a Nobel prize – we were just beaten by Richard Roberts and Phillip Sharp.

It was an extremely exciting postdoc and at the end of that, at the tender age of 27, I arrived here as a temporary lecturer, though that fairly quickly got turned into a permanent position. So the big question was what was I going to work on? The obvious thing was to carry on with the split gene story, but I realized the field would be overtaken by the big groups in the USA and in Europe. So I thought no, that would be an extremely unwise route to go down.

So I've got the ability to detect single copy fragments of human DNA, genes and whatever, but of course I've got a background in genetics – I've been trained in human genetics. I thought why don't I try and put the two together and see if I can detect heritable variations in these restriction fragments that you can detect in human DNA.

I arrived here in autumn '77, by early '78 we'd got what proved to be one of the very first examples of restriction fragment length polymorphism, or snip as you would call it nowadays. Another claim I would make is to be one of the very first people to ever describe variation in human DNA. From that initial, very primitive, very crude, survey we came up with an estimate of how many sites of variation might exist inside the human genome. And the number we came up with was 15 million, which is almost exactly bang on what's in the snip database now.

It was a really exciting moment because before that, the whole of human genetics was based either on phenotypic characters or on things like blood groups and enzyme polymorphisms and so on. All the raw material that one needed to begin mapping the human genome and really in terms of the human genome project I would lay perhaps a little claim to being there pretty close to the beginning.

We then got a bit disillusioned with the single nucleotide polymorphisms that we were detecting. They're easy enough to assay now but in those days horrendous, very slow, very tedious, very expensive on DNA. We set ourselves the quest of trying to find hypervariable DNA, the reason being that if we could develop or detect regions of human chromosomes that vary enormously from one person to another that would be great for medical genetics. It would give you very hardy informative linkage map markers and so on. Then by a series of complete and utter flukes and accidents we stumbled upon a generic method for getting the hypervariable DNA and that led us to the first DNA fingerprint and the realization that within seconds of getting that the work had opened up and answered a completely different question. A question we didn't even know existed; how do you use DNA to solve problems of biological identification?

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And then everything went very very rapidly so the first DNA fingerprint was in September 1984, technology patented by November, improved by the end of the year to the point where we knew it could be applied to real casework. By April 1985 we'd taken on the very first case – an immigration dispute where we saved a young boy from deportation. Summer '85 was the first paternity case then the first criminal investigation that started very early 1986 - a local double rape murder case.

So a lot happened in such a short time?

Yeah, it's unbelievable. Well, the Queen once used a phrase, about a really bad year she'd had, as 'annus horribilus', this was my 'annus mirabilis', my miraculous year. The question is, why did it go so fast? Because we hadn't realised the world desperately needed a new technology that could provide definitive answers in identification and sorting out family relationships. Once we'd done our first immigration dispute, that got a lot of press coverage and of course unbeknownst to us there were a huge number of families out there all trapped in immigration disputes where there were doubts about plain family relationships. So what do they want? They want DNA testing. As soon as we did our first paternity case the same happened with paternity disputes. It was a flood gate. There was this huge dam in front of us which we couldn't even see and then the walls broke on it and it was a deluge, very exciting.

With the present state of DNA fingerprinting it's easy to disprove paternity but proving paternity is impossible. Could you ever see DNA Fingerprinting ever doing that?

Well, no. Current DNA testing can only prove that a man is not the father. If it fails to exclude that possibility then there's a chance the man is the father. The traditional way of looking at this is so called paternity index. In other words, how sure given the genetic results, that this man is really the father. In your blood group days you had a paternity index of 99%, 99.99% was the best that you could get. With DNA you can add a lot more nines!

So it's a game of probabilities...

It always is. There is a possibility that your DNA profile might be the same as mine. That probability is 1 part in 10 trillion. Is that a zero? No. Therefore, it is possible that your DNA profile is the same as mine. Do I worry about that? Not in the slightest because ▶

it's incredibly unlikely. This technology delivers definitive results in the paternity cases. And remember that in UK law, a paternity case is a civil dispute where you have to prove the case on the balance of probabilities.

> "I arrived here thinking that I would give it a year or so and then move on but I just fell in love with the place"

So if you can show, that it's in all likelihood for this man to be the father against not being a father, say 51:49, you have proven your case with that. But the DNA can never give you 100% proof, nothing in science can give you 100% proof but it will get you so close to it that it makes no difference and if you're worried about that 1 in a zillion chance that may gave the wrong result, test more DNA markers. So I profoundly disagree with your comment that you can't do a paternity test. You certainly can.

So what would you say is the absolute highlight of your career to date?

If I had one single moment where I suddenly realised what we had accomplished, it was at the immigration tribunal for the first immigration case. DNA evidence was provided at the tribunal, and they dropped the case against the boy, so the boy was now going to go back to his family as a full UK citizen. I was there when the mother, who had been fighting this case for two years and made her very ill, was told that they have dropped the case against the boy, and that the boy was now going to go back home. It was the look in that woman's eyes. It was the sudden realising that this was no longer just an academic finding. This was something that had reached out and had profoundly touched another human being. That was simply magical.

You've been here for almost forty years now. What made you want to stay in Leicester for so long?

I love the environment here. I went to the very competitive environment of Oxford University, and then on to Amsterdam, which was less competitive, but still fairly high-pressure. I arrived here in this department, as a temporary lectureship thinking that I would give it a year or so and then move on. But then, I just fell in love with the place. I think it was all down to a guy called Bob Pritchard, who was a founder of this department, who created this very egalitarian atmosphere. There was no police, there were no cowboys, he just simply said "have fun here, don't cause me any trouble, and I want cause you any trouble". In other words, he just said: go and do your own thing. It was just complete academic freedom. That's what I love. Over the years, I've been very lucky to have a great number of people working with me, and everybody that has worked with me in this lab has been fantastically loyal. So we've built up a big, happy family atmosphere in this lab. I'm not treated in any way special; if I make a mess, I have to clean it up, and if I don't clear up, then somebody will come and give me an earful, which is how it should be. The thing I cannot suffer is these prima donnas. The scientific world, like any other human endeavour, is full of prima donnas unfortunately.

How has science changed since you started your career?

If you look at biology and medicine the model when I started was essentially a cottage industry. It was a one man and his dog show. There was a PI [principal investigator], there might be a technician, you might have a PhD student, and if you are very lucky a post doc. This would form a critical mass so that you would be able to do some really good, imaginative science. What's happening now is that biology is going down the road that particle physics went down many decades ago. It's got very big, expensive, corporate, and you have got to do it in factory mode. Now you have the big genome centers with big armies of people with great big machines, churning out great quantities of data.

It has become much more difficult for the individual to make their mark. The people that do tend to make their mark these days tend to be very talented science managers, rather than the people that actually come up with the scientific idea in the first place. I think it's a tougher world out there - not more competitive - but it is certainly a very different world. It's also a world where, perhaps rightly or wrongly, both the government and research councils are much keener on focused research, and research that could have more impact than the sort of blue skies research which I have lived through in my career. That's fine but there would be no such thing as DNA fingerprinting if the job had been given to applied

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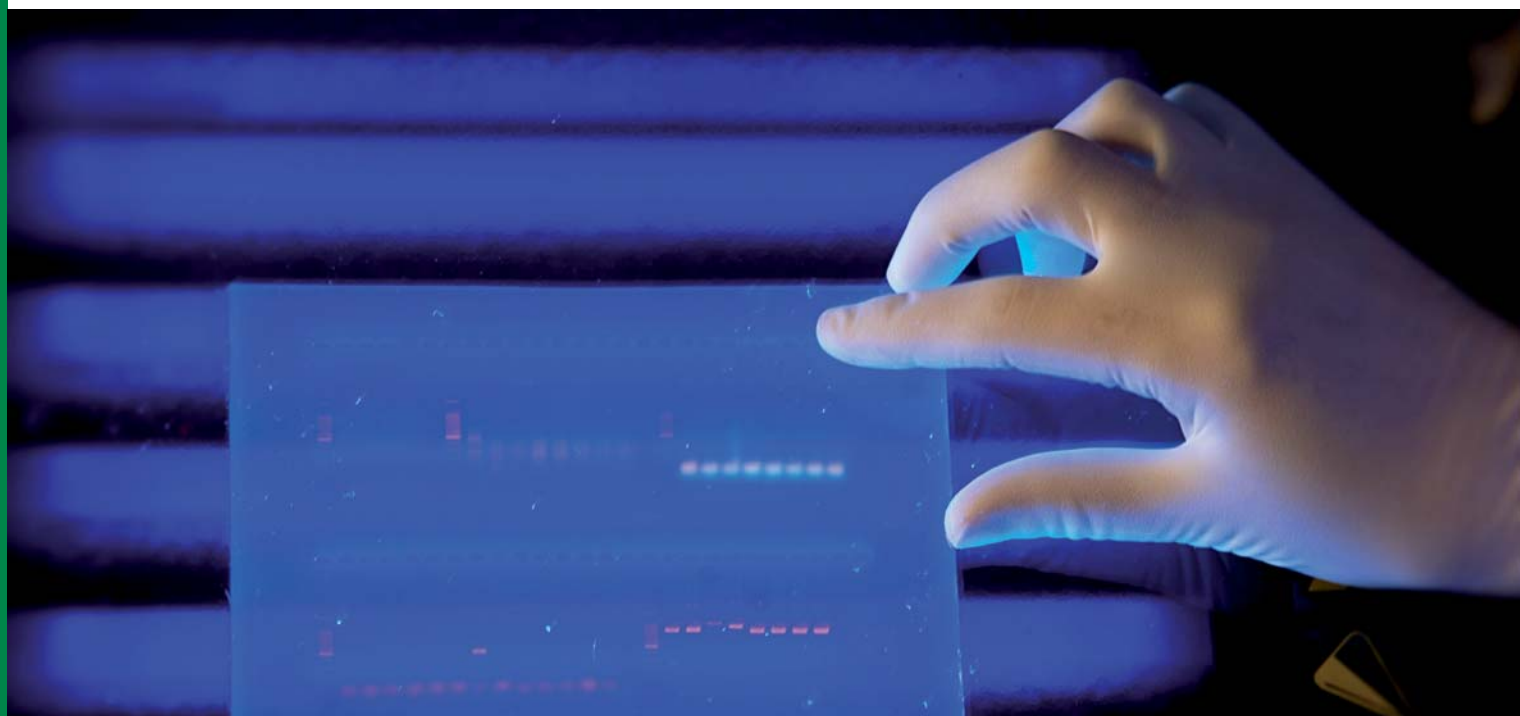
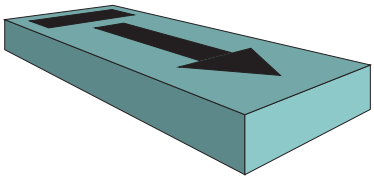
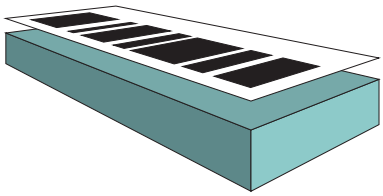


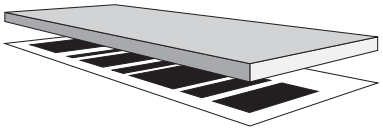
1. A DNA sample is broken up and the fragments separated by size.



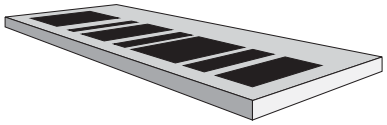
2. The DNA fragments on the gel are transferred on a nylon membrane.



3. A piece of X-ray film is exposed to the nylon membrane after radioactive probing.



4. This produces a pattern of stripes that resembles a bar code.



DNA fingerprinting at a glance: These steps outline the process involved with DNA fingerprinting, from obtaining the DNA to (in this case) performing a test to determine parentage

translational research. You needed blue skies to get it brought up in the first place. If you look at the big transformative discoveries in science, most of them were completely unexpected.

"you need mavericks just to open up completely new doors"

For example, the discovery of penicillin was a complete accident. When Charles Darwin signed up for his four years on the Beagle, would he have written an impact statement on his grant application stating that "I will use this voyage to transform the entire way that we will think about our origins and our place in the universe"? No, of course not. The guy who invented the laser was told to stop messing about by his supervisor because he thought it had no use whatsoever. So you need to retain a vibrant and blue sky state of mind, and work not through any desire to solve things like overpopulation, global warming or cancer. Do it because you are curious.

So would you say science works as a relay, rather than a sprint, or a marathon?

Actually, it's none of those. It's more like a large head of cattle, all plodding along in the same direction. Most of the science done is safe science. A much better analogy for the science that I'm doing is the current Curiosity mission to Mars. They finally managed to build themselves a robot big enough and clunky enough that it can actually drive around, drive on the tops of mountains and so on, and Lord knows what that's going to find. You don't care. The point is, really interesting discoveries are by their very nature, unpredictable. Because of this, it often very incompetent people who do all the best stuff! For example, Christopher Columbus. He was looking for a western route to the East Indies, he crashed into the West Indies, and when he got there, he still insisted that these were actually still the East Indies! But, you need mavericks like that just to open up completely new doors. I'm not saying you shouldn't do applied research, of course you should, but behind that has to be a very important engine, and that's called basic discovery research.

How important is the 10th of September to you, the day when you actually obtained your first DNA fingerprint?

Actually, I had forgotten about it! It's a big day, though, especially for me personally. It was actually not even a day; it was a five minute interval when my entire life changed. Everything went shooting off in a different direction. My first DNA fingerprint was pretty horrible looking, but I could see the implication. And it was pretty obvious where this could go. Rather than saying, "That's potentially interesting", and putting it on the back drawer somewhere, we just ran with it immediately. So, the thing about science is keep your eyes open and keep your mind flexible. Another thing is, and this is terrible advice, but don't read too many scientific papers. They merely constrain you into thinking with orthodoxies. Instead, it's much better to just let your mind wander.

"Have fun, and treat science as a hobby. It's not a job!"

I'm sure that's a piece of advice that every student would love to follow!

Yes, I will probably get sacked for that! But, reading zillions of papers does not necessarily make you a great scientist. It's keeping that excitement and imagination in your work. Those are the two most important words. Forget the intelligence or learnedness. It's excitement and imagination. Really good science is no different from really good art. You are creating stuff. It doesn't matter whether you are coming up with a new theory, or painting a wonderful new painting or composing a fantastic new bit of music. They are all ultimately an act of creativity. It's all about keeping those creative juices alive and thriving. That is probably the biggest challenge as a scientist.

So finally, what advice would you give to future researchers who seek to follow in your footsteps?

Oh, have fun, and treat science as a hobby. It's not a job! ■

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