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An Interview With Sir Alec Jeffreys

Alec Jeffreys is well known as the man who applied his knowledge of short repetitive hypervariable sequences in the human genome, called minisatellites, to develop DNA fingerprinting. This discovery is the basis for DNA-based human identification. Recently, Sean Donnelly, a former student at the Department of Genetics at Leicester University, had an opportunity to speak to him about the early days of his discovery and how that discovery has changed his life and the face of human identification.

SD: Dr. Jeffreys, it has been more than 20 years since you first developed DNA fingerprinting. How has that discovery shaped your life and your career? Are you surprised by the extent to which DNA typing is now an accepted part of present society?

AJ: The discovery totally transformed my life in a huge and sometimes unanticipated way. Going back to the late 1970s and early 1980s, my basic interests were in trying to develop methods to detect variation directly in human DNA using restriction fragment length polymorphism (RFLP) technology. We were looking for highly informative markers to map the human genome, and our interest in hypervariable regions was really triggered by a paper by Arlene Wyman and Ray White in 1980 (1), where they described the first example of a hypervariable DNA segment. We wondered if that segment was a much shorter version of satellite DNA, which we called a minisatellite. To my delight, in 1983 a few papers were published showing that minisatellites did exist. By a stroke of good luck, we were able to confirm the existence of many minisatellites, and we discovered that minisatellites share a degree of sequence similarity between different loci. This allowed us to develop multilocus probes to detect multiple variable loci at the same time. The result of the first Southern blot using this type of probe was a DNA fingerprint. We had stumbled on the potential for DNA-based biological identification. On that very first Southern blot, there was a family group, a mother, father and child, and the child was a composite of the mother's bands and the father's bands. That opened up the possibility of familial relationship testing. On that very first day, we were thinking of forensic applications. There were questions though. In particular, if you're ever going to use this in a forensic context, did DNA survive? So, on that first day, I ran about the lab, pricking my finger and leaving blood spots on tissue paper, glass and so on—sort of a mock crime scene.

We walked out of the darkroom looking at this complicated mess on an X-ray film and thought "Whoa, wait a minute. We've stumbled on the potential for DNA-based biological identification".

We faced two challenges: first turning the very first DNA fingerprint, which was a smudgy mess, into something informative, and second getting someone to take notice. At the time, I felt that it was going to take years, maybe decades, to move this to casework and that it would be a technology of last resort after blood group analysis, ballistics and fiber analysis. However, we took our first case, an immigration dispute, in April 1985. Our first paternity dispute came a few months after that, and the following year was the first criminal investigation of a double murder. The rest, as they say, is history.

SD: Are there any DNA profiling applications currently in use that have surprised you?

AJ: I think most of the broad applications we spotted early on. The one that I didn't see coming was marshmallow DNA testing. If you have marshmallows with gelatin in them, what is the source of the gelatin? If it's porcine, that's a serious breach of Islam. Some of the more exciting recent applications are physical characterisation and the explosion of DNA marker usage in genealogy, such as examining Y chromosome association with surnames and mitochondrial DNA with matrilineages.

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SD: DNA samples are now being collected from ever larger portions of the population. Does the expanding collection of DNA samples cause you any concern? Are there measures that you would like to see put in place to exert some level of control over the database and its use?

AJ: The way that DNA profiling has spread is unbelievable, and a national DNA database was obvious from the outset. The only surprise was how quickly it was developed and adopted. If you look around Europe now, nearly every country has a national database.

The initial evolution of the database was very much a police operation with little legislation to prevent the police from charging off in any direction they like. Can you blame the police for performing familial searches? Can you blame the police for wanting to get anyone they possibly can onto the database? The only thing that will stop them is legislation, and I think that the legislation is now catching up with the use of the database.

As a crime-fighting tool, the national database has been unbelievable. It has exceeded everyone's expectations. Public opinion surveys have shown a general approval, certainly for convicted criminals who owe it to society to submit a DNA sample to the database. My real concern is what happens if you start extending the use of the database, and things start going wrong. For example, the current database in the United Kingdom uses a 10-marker system, and once the database has millions of profiles, you are going to get adventitious matches, particularly between close relatives. They will be rare, but just one wrongful conviction would be dreadful.

Britain is now one of the most intensely surveyed society on the face of the planet, and DNA is beginning to be seen as part of that surveillance. It is important to keep a distance and use the database sensibly.

There have been many interesting, and in some cases worrisome, developments. Examples are familial searching of the database, retention of DNA from innocent people, and interest by the police in acquiring physical information, ethnic origin and geographic origin from DNA samples.

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SD: But you would say that this has been more positive in terms of the value to society?

AJ: Detection rates in violent crimes, burglary and car theft have gone up eightfold since the introduction of DNA analysis. However, DNA profiling is not just about proving guilt; it's about proving innocence as well. This mirrors something that happened during our first criminal investigation. The prime suspect was shown to be innocent despite the fact that he'd confessed. I think the Innocence Project in the US has now topped 200 exonerations by retrospective DNA testing. Exonerating prisoners, in some cases people on death row, is a very important component of DNA testing.

People tend to forget the huge impact on paternity testing as well. In paternity disputes, British courts will tell you to get a DNA test; it's as simple as that. Also, resolving immigration disputes was the first volume application. Thousands of families have been reunited through DNA testing.

SD: Obviously DNA typing has a huge societal impact. It can provide resolution to grieving families, provide proof of parentage and even shed light on family genealogy. Are there any cases that have been resolved through DNA fingerprinting that have had a personal impact on you?

AJ: Obviously. All the cases we've been involved in. One big case was the first immigration dispute in which a lad was facing deportation. The look in his mother's eyes when the DNA evidence was accepted was pure magic. Also, the Enderby murder case, which was the first time I handled real forensic specimens, was quite distressing because suddenly I realized that this wasn't just research anymore. These were dead girls. Finally a meeting with one of the very first people to be exonerated by retrospective DNA testing was an emotional moment. I was at a ceremony to accept a lifetime achievement award, and for each person receiving an award, the organisers brought in a surprise guest. For me, it was Kirk Bloodsworth, a man who had been convicted of the rape and murder of a 9-year-old girl and was sentenced to death in the U.S. in the mid 1980s, about the time we were establishing the technology. DNA had exonerated him, and he had been flown over specially to say "Thank you", not so much to me, but to the technology.

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SD: In the 20 years since your discovery, research tools have much improved. Are there tools you now use that you would have liked to have had two decades ago?

AJ: The polymerase chain reaction (PCR). The whole of forensic DNA analysis, including the legal arguments and precedents and court appearances, was founded on prePCR technology. The National Research Council reports on DNA were on RFLP technology and Southern blots, no PCR at all.

SD: Looking 10–20 years forward, do you see any specific laboratory tools developing, or are there any tools you would like to have at your fingertips?

AJ: In the forensic field, I see miniaturisation, automation and scene-of-crime detection. Also, the possibility of far broader DNA identity databases using the notion of DNA as a personal identifier. You would encrypt a DNA profile, and wind up with a DNA personal identification number from which you cannot extrapolate back to the original DNA profile. This would automatically strip out any information about ethnicity, conceivable disease association and family relationships.

Also, mass sequencing and forensic metagenomics, where instead of typing one thing at a crime scene, you type absolutely everything, and things like physical identification, although I'm a little concerned about that because of the issue of breach of genetic privacy. Genes that control facial features could also impact disease risk and dysmorphologies.

Markers of the current 10-locus system have virtually no disease association. In the future, I would prefer to see markers used that are even less associated. Let's suppose that no one had ever thought of a forensic DNA-typing system, and you decide to build one now. Would you use the markers that are currently being used? The answer is almost certainly "No" because most of these markers are very close to genes, and one would like to reassure the public that all we are getting is some boring STR short tandem repeat numbers, and there is nothing else that we can divine from the profiles. Given the availability of the human genome sequence, the International HAPMAP Project and knowledge of recombination hot spots, I would target microsatellite sequences that are away from any genes and are unlikely to show any association at all.

All the cases we've been involved in have had a personal impact on me. The Enderby murder case was the first time I handled real forensic specimens. It was quite distressing because suddenly I realized that this wasn't just research anymore. These were dead girls.

SD: What are you learning in your current research efforts?

AJ: Our broad interests are the two great agents that create all diversity: mutation, which creates genetic novelty, and recombination, which is a reshuffling process. We are currently trying to understand recombination hot spots: how they work, their morphology, how they evolve and the different types of recombination processes such as crossing over and gene conversion. All of this work stems from DNA fingerprinting because the minisatellites we studied are highly variable and therefore forensically useful because they are destabilised by recombination. There is a huge amount of interest in copy number variation, much of which is driven by ectopic recombination, where repeated sequences in the genome misalign and exchange information. Ectopic recombination is important in a whole range of diseases and is the process that creates new genes, making it one of the most important drivers in evolution.

We are developing a suite of single-DNA-molecule technologies that enable us to analyse somatic and germline DNA and characterise new mutation and recombination events. We can see human DNA evolving in real time, seeing how these mutations occur and how people differ in the dynamics of this process.

SD: Do you see your current research impacting DNA profiling some day?

AJ: Very broadly. Information on DNA diversity, by definition, is going to feed directly into forensic genetics, but in terms of direct technology, I have no idea. If you had asked me in 1980 if what I was doing would have a forensic application, I would have said you were mad. I'm a firm believer in the applications following the technology. That's one of the great things about pure science: you don't know what's around the corner.

REFERENCE

1. Wyman, A.R. and White, R. (1980) A highly polymorphic locus in human DNA. *Proc. Natl. Acad. Sci. USA.* **77**, 6754–8.