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DNA on the Witness Stand

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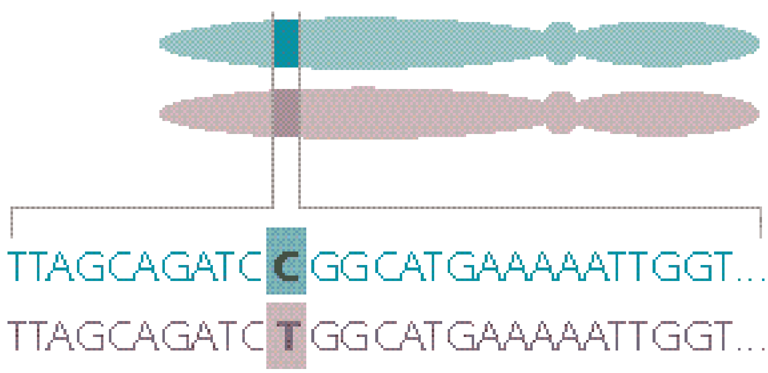
What I would like to talk about today is the use of DNA in identification. I think it does a marvelous job of illustrating the unexpected consequences of discoveries in basic science.

There is a tremendous diversity amongst human beings. What a marvelous range there exists of human diversity, in height, in weight, in skin color, in faces. It's what makes life wonderful, what makes the human species so wonderful. And it makes us wonder what underlies this tremendous diversity in physical appearance. We know, in fact, that in large measure, physical appearance is genetically determined. We know this by looking at identical twins. When you look at identical twins it's not hard to see striking similarity between them. You do indeed see difference, but the similarity is really much more striking. And this tells us that identical DNA tends to produce identical physical appearance.

Now, when it became possible to read DNA sequences directly, it was natural to wonder, how this diversity would be reflected at the level of DNA spelling, on the DNA sequence itself?



How Many "Spelling Differences" Exist in Our DNA?

But in fact, I'll talk to you about a different use of all those spelling differences. How much spelling difference is there? Well, there is almost complete identity between any two human beings. Look at the neighbor to your left and to your right. You're 99.9% identical. That should make you feel very common, part of a common species. But of course, in a genome of three billion letters, even a tenth of a percent difference translates into three million separate spelling differences. And so I invite you again to look to the left and look to the right and notice how unique you are. There is no one in this audience who has the same DNA sequence as anyone else.

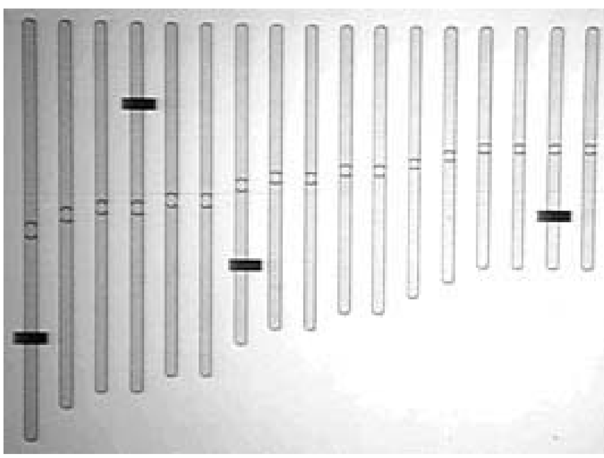
And indeed, your DNA sequence is unique amongst all DNA sequences of any human that has ever lived and will live for quite some time to come. Unless you have an identical twin, in which case you do have someone who has the same DNA sequence. But apart from that, your DNA sequence is yours and yours alone. Should you choose to leave your DNA sequence behind here in some form in some biological tissue, in principle, I ought to be able to look at it and by its uniqueness know whose it is.

DNA Identification in Criminal Courts

Thus is born the notion of DNA identification. And it was quickly realized that this DNA identification would be especially useful in legal cases, in the criminal courts. Of course, law enforcement officials over the course of many years have looked for things that uniquely identify individuals, so as to find evidence that links a criminal to the scene of a crime. In fact, 1992 was the 100th anniversary of the use of fingerprints as an identifier.

They're uniquely powerful. They are essentially unique, and there are computer databases for fingerprints that are online across the country and are used. They're great, except that for many crimes, no fingerprints are left behind. A very common example, and an important example, is rape. For property crimes you may find fingerprints, but for many violent crimes it's harder sometimes to find fingerprints. So scientists look for other markers, biological markers, for example, as you might find in a semen sample from a rape. There has been success looking for protein differences, cell surface differences, things like the HLA complex and blood groups. But in fact, the variation is nowhere near as spectacular as in fingerprints – that is, until it was possible to read DNA.

DNA gives us rich results – and, in principle, just as detailed as a fingerprint



You might think what we do is to take a sample and just read out a DNA text in its entirety. It would be a wonderful thing if we could get that from a sample, but that is the business of the Human Genome Project, not the business of the local constabulary....yet.

So when we do DNA comparisons, we can't read all three billion letters. What is done instead is that a very small handful of sites of variation are examined. Sites of variation here on this chromosome, perhaps, or one here, or one here, and one picks enough sites of variation to be able to have enough markers of difference.

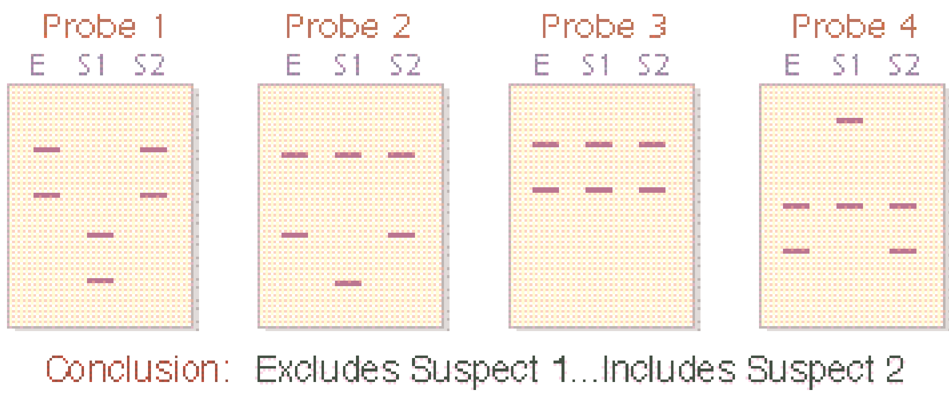
DNA Forensics

At least in the forensic applications commonly done today, people don't actually read out the sequence. For economic reasons, for being able to do this more quickly and more cheaply, they look instead at regions that have spelling differences that are due to repetitions of some sequence. There are repeat sequences all over the genome and, in any particular region, let's pretend this is chromosome #1, you may have three copies. I might have four copies, someone else five copies, someone else one copy - typically, an unimportant repeat that has no biological function, but we all might differ.

DNA regions with repeat sequences can be highly variable

By taking that DNA and cutting it with an enzyme that recognizes a distinctive site here, running it out by electrophoresis to be able to separate these fragments by size, and probing it with a piece of radioactive DNA from this region, one can visualize bands corresponding to the lengths of these fragments. And each of these different chromosome configurations, each of these different spellings due to different numbers of repeats, can be visualized as different-sized bands on a ladder, much like a bar code. And so a forensics scientist, examining an evidence sample E here, might probe it first with Probe #1 for the first site of variation and see the pattern. Then he or she might probe it for the next site, the next site, and the next site, and compare it to the DNA patterns taken from two suspects, Suspect #1 and Suspect #2.

Schematic of DNA Fingerprinting



If Suspect #1 has a different DNA pattern than the evidence, the suspect is excluded from having committed – well, more exactly – from having left this evidence. It's another question of how the evidence relates to the crime. But that evidence sample of DNA cannot possibly be Suspect #1's.

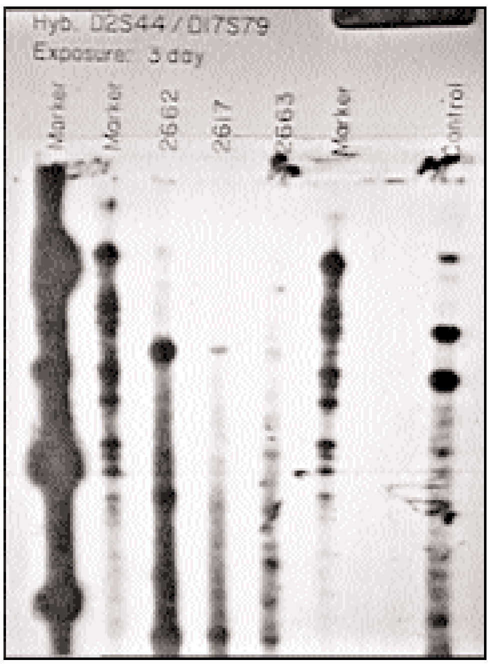
Suspect #2's DNA corresponds perfectly at each of the four places of variation on the human chromosomes examined. Does this mean that Suspect #2 is indeed the person who left that evidence sample? What does it mean, to say Suspect #2 is included amongst those who left it? Of course, to know how strongly we should take this evidence, we need to know how rare that pattern would be - if it's a question of population genetics - and for that purpose databases have been assembled of how frequent these patterns are in the population. These are tricky questions, and we'll return to them very briefly.

Those are simply the ideas underlying DNA fingerprinting, as it's popularly called, or DNA typing or DNA identification, as we prefer to call it. Within five years of the notion of DNA spelling differences being used for medical purposes, there were already private companies, Selmar, Lifecodes, and others, which grew up to provide DNA typing services to law enforcement officials, and by 1989 the FBI had its own DNA typing lab in the Hoover Building in Washington. There were dramatic ads in the appropriate press, such as this one here from Selmar (showing ad). "DNA Fingerprinting Links the Criminal to the Crime," with the handcuffs here being a double helix.

For the most part, this has been a dramatic and broad success. Increasingly, in rape cases, there is no need for a victim to testify about whether a sexual act took place. There's no question, typically, about mistaken identity being the problem, because DNA from a semen sample can be used to link a suspect to that semen sample. In fact, it has been useful for excluding innocent people. The FBI says that, of many test results, that they could never exclude with standard blood markers, nearly a third of those people are exonerated immediately upon DNA testing. Many rapists, because of this, now plead guilty.

Standards For DNA Identification Practice

In essence, DNA evidence is rapidly becoming, in principle, an irrefutable proof of identification. But of course, nothing is ever so simple. Scientists are a demanding lot, a skeptical lot, a rigorous lot. It's not enough to say it's okay in principle – it must be okay in practice as well. And although everyone agrees that this is a spectacular technology, controversies have erupted in the scientific community from time to time over whether it's really being done right. Fights erupt over DNA fingerprinting because it's such an important technology.



What have these fights been about? They have not been about how to do it in principle. They have been about how to do it in practice, and how well-regulated the practice is. For example, DNA fingerprints should look like bar codes. Here is a not-very-good example of a DNA fingerprint, which was used in a criminal case in New York. It's one I know well, because it was one where I was asked to serve as an expert witness, which is how, from my medical genetics background, I got deeply involved in this.

It was an interesting case, because it showed what scientists can do when they put their heads together. Halfway through this case, when all the evidence was being considered, all the scientists who had testified as witnesses for the prosecution, and all the scientists who had testified for the defense, met outside the courtroom without the lawyers present and talked about the evidence. And at the end of the day we agreed the evidence was terrible, and we went back to court with a joint statement for the witnesses on both sides, saying the evidence was no good. It was the first case in which DNA fingerprinting was actually thrown out because of the way it was practiced. It was also an example, I think, to the legal community, that scientists are not necessarily hired guns to say whatever you tell them to say.

The other controversy that has arisen is about how to interpret a match. What frequency should you put on it? How rare is a pattern? How odd is a match? And for this, the controversy is a technical one and a complex one, but it has to do with the fact that the frequency of the different DNA patterns of different genes vary across the population. This is actually a blood group frequency distribution. Similar things are known for other types of DNA differences. And so there has been active controversy about exactly what weight we should put on samples. Are the odds being quoted one hundred-fold too high? Are they exactly right? Maybe they're one thousand-fold too high. Scientists are arguing actively about this.

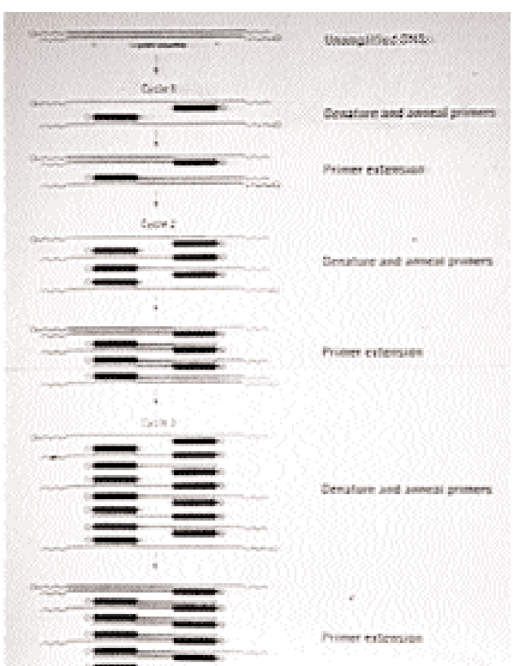
There is a good mechanism in the scientific community for focusing on such arguments. It is the National Research Council Committee from the National Academy of Sciences. For my own sins in that New York case, I served on this Committee for a period of three years, which finally culminated in the production, after a very, very long gestation, of an NRC report called, "DNA Technology in Forensic Science."

The really important thing the committee has done is calling for defined standards for laboratory work. For new standards of statistical calculations. And most importantly to my mind, it called for a mandatory proficiency test – that the laboratories that are doing this work should be subjected regularly to blind proficiency testing, to insure that they did the work well on a regular basis. It is in some sense appalling that there are no mandatory standards for something as important as forensic testing. There are higher standards, indeed for the laboratory practices of someone who will diagnose strep throat than for the laboratory practice of someone who will create a DNA fingerprint that could be used to send someone to Death Row.

DNA Databases

Another point to mention is databases. There has been discussion about creating national databases of everyone's DNA type. That way, when a rape is committed, there's no need to find a suspect. You take the semen sample and get its DNA pattern, and compare it to a database of everyone's DNA pattern and find out whose it was. There are many people who feel understandably uncomfortable about such a national database. So legislatures have instead decided in some states to set these up, not for all citizens, but for only those convicted of, say, sex offenses, and other states for those convicted of any felony.

There is a lively controversy over what sorts of databases should be set up and there are those who say – why should it matter? Why should you care if you're in a database? After all, if you're innocent, there's no chance the technology will do you any harm. Well, even if standards are being discussed and looked at, and I'm an optimist, I feel that the standards are being worked out well. I think the Academy's report and many other steps are doing a great job of putting this on the most rigorous footing possible.



Polymerase Chain Reactions

New developments occur at a dizzying pace. For example, Polymerase Chain Reaction is a marvelous technology to amplify DNA. It allows you to take a specific region of DNA on the chromosome, and by using little black primers here and copying back and forth, back and forth, just the particular region you want to copy, making two, then four, then eight, then sixteen, up to millions of copies of a particular region, and so in principle it is possible to start from the DNA of a single cell and get enough DNA to analyze it. That makes it possible not just to analyze blood stains of the sort that were seen before in which you could get one microgram, one millionth of a microgram of DNA, or semen swabs from a rape, some of which give you enough to analyze by standard techniques, but in fact even shed hair has enough DNA at its root. A urine sample, saliva sample, will have enough DNA in most cases. It's possible that by licking an envelope you deposit enough DNA to trace from the seal of the envelope.

Obviously, a technology that is so powerful and that is that sensitive must be used even more carefully, since you can imagine that if I sneeze on something, my DNA is there, too. And so there is tremendous need to avoid contamination. Proficiency tests have to be put in place to guarantee that laboratory practice is up to that. These are questions under debate**.**

DNA Identification Applied to Human Rights

Let me shift gears, and talk about a different application than the United States criminal courts. It's an application to a human rights problem, the work of a colleague of mine.

In 1975, the military in Argentina overthrew the government of Ysabel Peron, and this was a very rigid ideological military. It was a military which said such things as the following quote from the military governor of Buenos Aires, a direct quote from a speech to the public: "First, we will kill all the subversives, then we will kill their collaborators, then their sympathizers, then those who remain indifferent, and finally, we will kill the timid."

They had a lot of enemies indeed. I note for you just briefly, the roots of their "tree of subversion" are Marxism, Zionism, and Free Masonry. But other important branches included liberals, evangelicals, the Anglicans, and even the Rotary Club.

The military junta set out in a systematic fashion to eradicate the opposition and to terrorize society, and did so with sweeps through neighborhoods, picking up subversives and non-subversives, rather indiscriminately, taking whole families....at times, young families. Many people disappeared, and no one knew because of the lack of coverage, the actual scope of what was going on. They only knew their own children had disappeared.

The Grandmothers of the Placo de Mayo

Eventually, after the fall of the government, the Commission on the Disappearances of Persons found 9,000 documented cases of disappearances. Correcting for underreporting and the lack of documentation, it's estimated that about 15,000 persons were "disappeared." Well, as these cases began to build up, older women, grandmothers, typically, of young men and women in their 20s and 30s began to get together in the main square, the Placo de Mayo in Buenos Aires, and began to talk, as support groups for one another, looking for their lost children. They began to talk – and they began to march – and they began to protest.

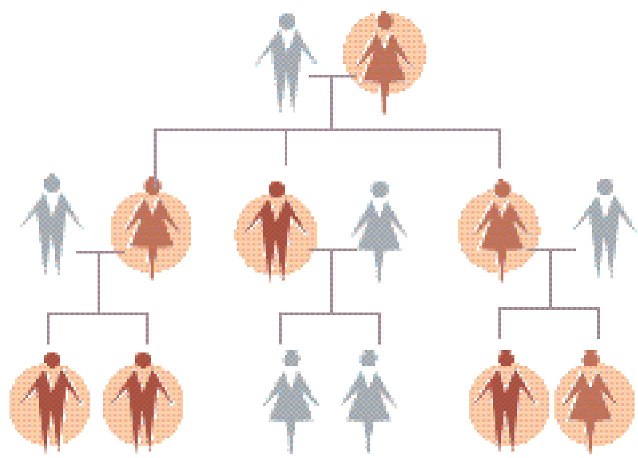
And as they protested, people came to the square and shared with them stories and the stories said, we've heard of cases of children appearing in military families that were previously childless, and the wife wasn't pregnant. They would occasionally have stories from people released from prison saying that their friend had been seen alive in prison and had given birth. Midwives and obstetricians were at times kidnapped and blindfolded from the streets of Buenos Aires, taken to military prisons, forced to help in the delivery of children, then blindfolded and put back on the streets. Sometimes during the delivery, a woman might say to such a midwife or obstetrician, "My name is so-and-so. Please tell my mother." And in once case that has been documented, the midwife did this favor, and she was later killed for it.

Phony birth certificates began showing up at the schools a few years later, and registrars quietly told the grandmothers at the Placo de Mayo – or told someone who told the grandmothers – and the grandmothers took notes. By 1983, when the Falklands war led to the fall of the military junta, the grandmothers contacted the AAAS, the American Association for the Advancement of Science, and asked for help in identifying and proving that these were their children, and they demanded that genetics be used to do it. They got in touch with Mary Claire King, a professor at the University of California Berkeley – a true hero to me – a friend and colleague, whose work I am describing.

Mary Claire King worked with the grandmothers of the Placo de Mayo to begin "searching for two generations." She began to try to get court orders for some of the children taken into military families, to do some sort of genetic typing and show that, indeed, they belonged to these biological grandparents, rather than to the alleged adoptive parents**.**

Tracking Maternal Mitochondrial DNA

Originally, simple HLA typing was used, typing of cell surface markers, but this was not terribly powerful in these cases. DNA fingerprinting of the sort I described before was used, but for technical reasons I won't go into, was not as powerful. More powerful, unique sequences of DNA would be needed. And so Dr. King's group turned to looking at a particular bit of DNA called the mitochondrial DNA.



Mitochondrial DNA Inheritance

It exists in a little organelle – a little package outside the nucleus of the cell. It's a small bit of DNA, and what's important about it is that you get it from your mother. It's only passed on in the egg, not the sperm. And so mom passes it on to all her kids and every female passes it on to all of her kids. If I can read snippets of unique, variable sequence mitochondrial DNA, I can trace maternal lineage.

The Case of Heidi Llemos

The older woman at the top is Heidi Llemos, and these are two of her grandchildren. She and her adult daughter and her son-in-law were all kidnapped by the military. She was tortured and eventually released. Her adult daughter and her son-in-law were eventually killed. But the daughter was two months pregnant when she was picked up, and a prisoner told Heidi that her daughter had been kept alive and had given birth in prison.

Heidi spent ten years looking for that grandchild of hers. She eventually found a child living with a woman who had been the military guard in charge of female prisoners at the prison and, it was quite plausible that this child was her daughter's. She demanded that the courts do DNA testing. Mitochondrial DNA sequences were obtained under court order, and were found to match perfectly between this girl and Heidi. She went to court and demanded the return of the granddaughter.

The military family made the argument, "How can you return this grandchild to a family she's never known?" claiming it wasn't in the child's best interests. The girl didn't even know Heidi Llemos. The grandmothers of the Placo de Mayo said that when the society knows that these people murdered her parents, how can you not release her, because when she becomes an adult she'll find out. Is it worse to move families now, or to find out when she's an adult that she's been raised all of her life by her parents' murderers? The supreme court of Argentina agreed.

Overall, about 51 living children have been identified, and most of these have been restored to their natural biological families. Many of the children are now reaching the age of majority, so are now able on their own to look for their natural families, when they know that something was amiss. Even as the grandparents are dying, they are leaving behind their DNA in the DNA databank so that the children, as they come to ask, will have it.

The Manfil Family

Sometimes the stories are about things that are less happy. The Manfil family was abducted in 1979 from their home in the middle of the night. Eventually the mother, the father and the son were all murdered. Carina and Christian were wounded but survived, and Graciella was actually sleeping over at a friend's house when her parents were taken in the night. The bodies of the parents and this son were not found, at least not for many years.

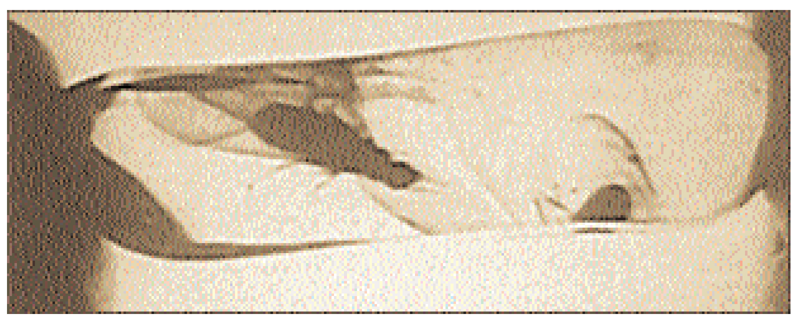
Then, mass graves began to turn up. There was a mass grave site that was a plausible site to contain the remains of the Manfil family. And so, one was faced with the prospect of multiple skeletons and skulls, and trying to identify which were the remains of the Manfil family. Dr. King's group at Berkeley worked out ways to sequence the DNA. They obtained DNA from the teeth of the skull by sawing the tooth in half under sterile conditions and extracting and sequencing mitochondrial DNA. They tried it out first at Berkeley with the baby teeth of lots of residents of Berkeley. When they found they could do it with baby teeth they began to do it with skulls.

They found, in fact, that the skulls of the male child and the mother matched the sister, because they all had the same mitochondrial DNA. The DNA sequence from the molar of the presumptive father also matched his grandmother. Thus these mitochondrial DNA sequences establish they are indeed the Manfil family. The remains have been re-buried in the family grave. It's unlikely much justice will come in the case because the military has declared an amnesty at this point for crimes committed during this period.

DNA Identification in Agriculture: Protecting Plant Varieties

Let me also mention to you two other applications of DNA identification technology. It turns out to be useful in identifying not only humans, but plants as well. One of the great uses of DNA fingerprinting turns out not just to be in the criminal courts but in the civil courts - for corn and tomato cases. People spend a tremendous amount of time developing strains of corn by old breeding techniques, and they can never gain intellectual property protection for it, never get patent protection on it, because there's no way to prove this corn plant was theirs. So they put all this work into developing the strain, and someone steals the strain, and they can't prove anything about it. Well in fact, now you can do DNA fingerprinting on corn plants, and many large seed companies routinely maintain databases of the DNA fingerprints of all their important varieties, so they can go to court and prove their ownership. It creates economic protection, and it gives people an incentive to develop things.

The Ultimate Paternity Test



And then, the ultimate in DNA paternity testing. As I was getting on the plane yesterday to come here, I found in the New York Times a story about DNA taken from a 40-million-year-old termite, preserved in amber. And DNA sequencing by PCR has been done on this termite to answer questions about who is the parent of the modern-day cockroach - was it really the termite? They are comparing and finding all sorts of novel things out as to whether the termite really was or wasn't the evolutionary ancestor of the cockroach. Indeed, if we take DNA paternity testing way back, it brings us to our common origins as a species, and to the common unity of life.

Basic Science

Basic science. It leads us in unexpected directions that have social consequences. No one sets out to develop DNA identification, the looking at DNA spelling differences for the purpose of criminology applications. The research was driven by a whole different set of challenges and questions, and yet the capability to read and interpret DNA spelling differences has had consequences in all of these areas.

As a society, we can be pleased and proud that our technology, that our science, has had social applications, but what we must do together as scientists and as a society is to make sure that we apply these technologies with the highest of standards. We must strive to apply them – as with Argentina – to the highest of purposes

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