MS MCDONALD CALLS

+DOMINIC EDMUND DWYER SWORN

+EXAMINATION BY MS MCDONALD

Q. What is your current position.

A. I am currently a senior medical virologist at the Institute of Clinical Pathology and Medical Research which is based at Westmead Hospital in Sydney.

Q. What does that position actually involve.

A. That entails a number of responsibilities. I - the laboratory looks after the Westmead Hospital and that area health service of Sydney which services about one and a half million people. It also provides public health microbiology and specialist HIV laboratory services for much of New South Wales on behalf of the State government. It also - my job also involves clinical practice, which is predominantly in the field of HIV and other viral infections, and it also includes a research component which is predominantly HIV and resistance to antiretroviral drugs.

Q. You mentioned having a clinical practice. What component of your -

HIS HONOUR

Q. Can I take you back a step. It might be a very basic question but what is a virologist.

A. A virologist is someone who looks after the clinical features, the laboratory features, and the public health problems arising from viral infections. It is a subspecialty within infectious diseases if you like.

XN

Q. It actually involves you looking down the microscope at samples.

A. No, because we don't do a lot of looking through microscopes in virology. It is mostly the interpretation of laboratory tests that are done by a range of techniques be it culturing the virus, detecting the genetic material of the virus performing the antibody tests.

Q. You referred to clinical practice being a component of

your position; what percentage.

A. I would estimate that about 25% of my time is dealing with patients, predominantly those infected with HIV. We have an active clinical trials unit which looks after people with viral infections that are placed on antiviral drugs, not just HIV but other things such as influenza and other viral infections.

Q. Do you have another particular area of expertise in virology other than HIV.

A. Yes, involved by virtue of the position of our laboratory in New South Wales in the preparation for emerging viral infections, for new viral infections, so that we have, for example, a new high security laboratory, in fact now probably the highest secure laboratory in the country for human purposes, where we prepare for new viruses that may emerge, as demonstrated by SARS or avian influenza or anything else that may emerge. That sort of work also entails interacting with the public health authorities about the implications of new viruses as they emerge. In other words, what information we would give them that would help them understand the transmission of that virus, the clinical features of that virus and the likely impact on the community as a whole. The public health aspects of virology and microbiology have been now gathered together in the last few years and I am the deputy head of what is called the Public Health Laboratory Network which is now a gatherer of the main public health laboratories in Australia. Again, the aim of having a group that are prepared to handle new viral emergencies if you like.

Q. Is one of the reasons that that new secure laboratory has been opened up concerns about things like biological terrorism.

A. That's right, the funding from that, from New South Wales Health and the Commonwealth, was essentially for bioterrorism but included within bioterrorism are infectious diseases, agents such as smallpox, SARS, flu,

those sorts of diseases that have significant clinical impact.

Q. Have you provided a curriculum vitae for the court.

A. Yes, I have.

MS MCDONALD: I tender that.

HIS HONOUR: Have you seen that Mr Borick?

MR BORICK: Sorry?

HIS HONOUR: Have you seen the CV.

MR BORICK: Yes, I have.

EXHIBIT #P67 CURRICULUM VITAE OF DOMINIC EDMUND DWYER. TENDERED BY MS MCDONALD. ADMITTED.

XN

Q. I won't take you through all of your qualifications, most of it is self-explanatory and I am conscious you have limited time.

HIS HONOUR: I can read it Ms McDonald. If there is anything in particular you want to refer to, by all means.

MS MCDONALD: Yes.

XN

Q. I want to take you to the very end, in fact to a heading on my copy, doublesided, 'Antiviral Drug and Vaccine Trial Participation'.

A. Yes.

Q. Can you just tell us what that is all about.

A. Well, we have a clinical trials unit in my department which is actively involved in clinical trials for viral diseases, both drugs effective against already established infection or vaccines that may prevent disease due to viruses. I have acted in various roles in those sort of trials, either as clinical investigator recruiting patients or as a sub-investigator, particularly in my earlier days, and also as a protocol virologist where we assess the biological testing and so on done for the trial. Most of these are international multicentred trials, that are usually run by government organisations such as national HIV centres, the NIH,

those sorts of things, others funded by pharmaceutical companies. We have been involved in over 50 of these in the last decade or so.

CONTINUED

Q. That's all I want to ask you about your CV for the moment. Have you also provided a report for the court.

A. I did provide a short report on laboratory testing for HIV.

Q. That's a seven page document.

A. That's a seven page document.

EXHIBIT #P68 REPORT OF DOMINIC DWYER TITLED LABORATORY TESTING FOR HIV TENDERED BY MS MCDONALD. ADMITTED.

Q. Before I get to the nuts and bolts, if you like, I want to go back in time a bit to the time you have heard a lot about, the days of Montagnier and Gallo, both beginning to talk about identifying this new virus HIV. Did you have some first-hand experience of all of that.

A. I've had first-hand experience I guess in a number of aspects. I was a junior medical officer, an intern of St Vincent's Hospital in Sydney, where David Cooper had just come back from the United States and at that time, it would have been the late 70s, early 80s, there was discussion then of this new disease that seemed to be appearing in predominantly the gay communities in North America. I remember, in fact, visiting one of the first cases identified in Australia whilst that person was in hospital dying. I then went to Westmead Hospital where clinical practice is different and I did cause a strike in the hospital by writing down a provisional diagnosis of possible AIDS on a patient just to highlight the anxiety and so on that was occurring at that time and nobody wanted to go near that poor fellow.

Q. There was a strike in the hospital.

A. Yes, HIV was around there. Ticked off. But that was just a demonstration of the community attitudes and the health care attitudes at that time. I guess more importantly though I undertook post graduate research at the Institute of Pasteur in Paris in the late 80s. I spent two and a half years in France and I have since been back for a number of sabbaticals in France with people who were in that laboratory originally. That lab

was the lab of Professor Luc Montagnier, so I knew him and I knew his lab and I knew the co-authors on various papers. Of course, that original paper was published in 1983 so it was already some years before I got there, but the lab was going through a very dynamic stage of sort of understanding what this new age virus was. HIV 2 had just kind of not long emerged and how this virus worked and what it did at the basic science level was a very fast moving and exciting field at the time. I also I guess met - the Institute Pasteur used to have an annual closed meeting held off campus where people were invited from the lab with other major players from around the world, just a small meeting of 50 or 100 people. Gallo, for example, came and other high flyers where a lot of arguments about HIV and its function and also personal arguments about who found what first and so on all occurred. There was a strong political overtone over all of this in that - in fact, the time I was there was when Ronald Reagan came to Paris to meet with Jacques Chirac who was then Mayor of Paris to really shake hands over the deal as to who had found the HIV first because of the implications for the commercial production of antibody tests and so on. So this was an argument that ended up being solved at the very highest political level because the scientists themselves were not quite ready to meet, so anyway I guess by spending that period of time there, I saw both the political and the social issues as well as the scientific issues that were hot at the time.

Q. What was your position at Montagnier's lab.

A. I was called a staigaire. It was just a sort of generic term for a researcher, someone usually coming from overseas, so I was a junior research officer, if you like, or fellow in that lab.

Q. Had you gone there because you had a particular interest in this virus.

A. Yes, I went there because HIV was the hot area in virology and people were wanting to come there from all

around the world. We had been fortuitous in our laboratory at Westmead that we had a Belgian guy who had worked with Montagnier many years previously and he was able to make that connection for me which allowed me to go. We met Montagnier when he came to Australia and visited Adelaide.

Q. You have given us something of the flavour at the time of the debate and the political interest. Was that something those working in the labs were conscious of, that is there was some acute public and political interest in finding out what this illness was all about.

A. Absolutely. In fact, it was a very dominant feature of all the work that was done, far more so than I think I have seen with just about anything else, perhaps with the exception of the recent SARS discovery, the SARS virus. There was a lot of pressure, there was a lot of competition, and really all the best minds in virology had gone into HIV, but there was a lot of competition between the French and the Americans as to who was going to produce the first paper, who was going to produce the first genetic sequence of the virus and so on, and it meant that any results that came out of those laboratories, either the French or the Americans or anybody else, were extremely heavily scrutinised before they went out, and I think this was something that I had not seen before and I am not sure that I have seen it very often since, just because of the pressure of either being right or wrong, and people were right and wrong in a range of areas.

Q. Who won in the end by the way.

A. Well, I think basically at the political level the fact that the US President came to France and said well, the first discovery of what proved to be HIV was made in the French laboratory by the French group, by Montagnier's group, but really that work was confirmed and extended by Gallo's group and a lot of others. That's how I see it. I am not sure that the others all see it that way, but that's essentially what it was. They both fed off

each other. For example, in Montagnier's lab the woman who was a first author on that original paper had gone to Gallo's lab the year before to learn some of the techniques, so they worked off each other.

Q. An illustration of the sort of public interest was that Princess Diana visited Montagnier's lab when you were there.

A. Yes, she did, and that was at the time again very much to Princess Di's credit. She was one of the first sort of celebrities to take an interest in people who were then dying of that sort of stigmatised disease, so she was extremely good in going along and shaking people's hands of people dying in hospital, which a lot of people wouldn't do, including health care workers, and that I think was very much appreciated by the infected community. This is at the era prior to antiretroviral drugs. There had been deaths already of celebrities like Rock Hudson and the like which often were not ascribed to AIDS but to other things, with people's sensitivity, but she took on quite an active role so she came to France to meet Montagnier as a discoverer to sort of bestow her kind of glory on the laboratory, but also to show that looking after dying people with this disease was a good thing to do and not a dangerous thing to do, and there was also the off-shoot that people are more likely to fund and support research into this disease that was then a disease of a very marginalized community.

Q. You had an opportunity to see the PowerPoint presentations put forward by the two defence witnesses in this case.

A. I have seen some pictures of some of the PowerPoint presentation, yes.

Q. You have been given a print-out of the slides.

A. Yes.

Q. In particular one that's been labelled A5.

A. I don't have that with me.

Q. But you have seen it.

A. Yes, I have seen it.

Q. Just to refresh your memory you recall within that presentation there are a number of slides in which there were criticisms of some of Montagnier's experiments, Gallo's inconsistencies in the findings. You remember generally those sorts of slides.

A. Yes.

Q. Were those sorts of issues arising at the time you are talking about.

A. Yes. I mean I think, having been involved in sort of the description and discovery of emerging viruses in a number of areas over the last 20 odd years, there's always difficulties at the beginning in trying to ascribe a cause of what is a new disease. So you then call in all the ability of people, both the epidemiologists and the public health people, to work out what's going on in the community with this disease, how the disease is being transmitted, how people are faring with it, the mortality rates and so on. At the laboratory, at the basic science level, you are trying to identify what is this pathogen that is causing a disease. At the diagnostic level you are trying to work out what test can he do to get out there to at least start being able to diagnose what is going on. And the way we went through HIV is just the same way we've been through things like SARS and like avian influenza, the technology is so much significantly better and the knowledge of different pathogens is so much better than it used to be. So with technology and the speed that all this discovery and so on happens is much, much quicker than it used to be, but people still make mistakes, and even with something like SARS there was still great arguments in the early weeks of SARS on is it this virus or is it that virus. Careers rose and fell on this, but even then quickly that was sorted out. The same thing with HIV, again there were a lot of causes that people thought could be responsible, viruses, other things as well, and really as the bits of

information came through, and they often are tidbits as they come through, improved by further experimentation, improved by newer technology, particularly the molecular technology you have been mentioning before, the case gets stronger and stronger so that, if you like, the discovery of AIDS is really like all of these other discoveries. The reason we keep referring back I suppose to the 1983 paper of Montagnier, or Barre-Sinoussi, she's a legal author on that paper, is that with all the work that's gone on since, it all shows that really what they were doing was going in the right direction, no doubt about it. There were lots of other papers published at the time saying it could be a herpes virus or it could be CMC, it could be drugs or it could be this, but none of the evidence at the diagnostic science level and the clinical epidemiology level ended up supporting that, so they fell away. You don't hear of those any more. That's why that paper takes on the importance it does, not because at the time it is definitive, but because it proved to be the first of what I regard as the ultimate sorting out of what was the cause of AIDS.

Q. So in your view and in your experience when was the virus first identified.

A. I think that the first evidence of this virus is in that 1983 paper by Montagnier and his team.

Q. Is what you are saying in your evidence that once it might have been definitive in that time, everything that's followed has now pointed to that being the first identification of the virus.

A. I think that's reasonable, yes.

Q. You have told us about the sorts of debates that were going back on in the early days. Are they still live issues in the scientific community.

A. No, they are not. I think that, as I said, with any new pathogen, particularly those with significant public health import, there's a discussion about what the cause is and, as that cause is determined, the others drop out

or change or come round to it. So, for example, again with something like SARS, the two people in Hong Kong who are most arguing about the causative virus, eventually the loser had to admit really that oh, well look yes, it's a new coronavirus, and that's of course SARS. I don't think I ever heard him say 'I made a mistake' but he certainly backed off and didn't put up his virus as a cause. And that's what happens, those debates die away as evidence comes in. To my mind, the debate about the cause of HIV being the viral cause of AIDS was over before I got to France in the late 80s. I think it was over. There's a lot that was not understood and there's still a lot that's not understood, but I think in terms of that virus causing the clinical syndrome of AIDS was accepted. So I think the debate about whether HIV is the cause of AIDS or not is long over and I think that to argue the case otherwise is completely overdoing it.

Q. I want to move on to HIV and look at the virus and the isolation of the virus. Have you produced to the court to assist a diagram that explains the life cycle of the virus.

A. Yes. I did have a picture here that is a cartoon sort of replication of the virus life cycle because if you understand the life cycle of the virus you then understand how the drugs work, how the disease is caused, what the target of the virus is, what the long-term effects are and so on, so with any new virus determining this life cycle is fundamental.

Q. Do you have a copy of that there.

A. I do have a copy. It's very similar to all the other ones that I've seen around here and very similar to the ones you can get off the web or out of textbooks and so on.

EXHIBIT #P69 DIAGRAM OF THE VIRAL REPLICATION CYCLE TENDERED BY MS MCDONALD. ADMITTED.

Q. Can you just talk us through what it is that we see in

that diagram.

A. This is the sort of replicative cycle of HIV. Really it's the sort of thing that happens with any virus. They all have differences in the way they bind to their target cell and the way they interact with their target cell, but the general principle is it is coming along, binding to its target cell, entering the cell, either killing the cell or causing disease inside the cell or taking over the cell machinery to then produce the virus to go out of the cell to go and infect other cells. That's the basic principle of virus replication. With a virus such as HIV there are unique features and HIV has got some very elegant virologic features. Basically what you have, if you look at the left-hand side you have the three viruses, the virion, a single viral particle comes along and attaches to the cell using certain receptors. All viruses use receptors to hit the target. The genetic material of the virus goes into the host cell. In the case of HIV it's an RNA virus. It undergoes an interesting mechanism where it is reverse transcribed to DNA which is the opposite of what we are all taught in sort of high school biology where you go from DNA to RNA to protein so here you have this reverse step. That DNA is then transported into the nucleus of the cell and that DNA then integrates into the host cell genetic material or the genome of the host cell where it then sits. There's some little bits and pieces that might hang outside the genome but, for all intents and purposes, that's what happens. So that virus is an integrated part of the cellular genetic material.

CONTINUED

Then when that cell is sort of stimulated, for whatever reason - it is exposed to another infection or something like that - it can turn on virus production from the genetic material. You then get the process of transcription to RNA, which then goes out into the cytoplasm of the cell. The RNA produces proteins and those proteins are gathered together underneath the cell membrane and eventually bud out to go off as a free virus to go and infect other cells. All of this is typical of viral infections. It is just that retroviruses and HIV have few very interesting unique features and because they are reasonably unique they become drug targets. If you have targets that target the reverse transcriptase, that is very good because that then works on the HIV, not other viruses that might be present or ordinary cells that might be okay. Similarly, the integration, where the virus inserts itself into the host genetic material, is also a target. There are numerous targets in the life cycle for anti-viral drugs, or even vaccines for that matter, that's why you need to understand the sort of picture. This is not unique to HIV. The other retroviruses, which HIV is one, and there are plenty of others - animal and human - have similar but slightly different replicative cycles

Q. Turning to another set of images that you have produced for us, have you also produced a series of pictures of HIV but comparing them to other viruses.

A. Yes. I was just asked to show an electron micrograph of HIV, which I have given.

Q. Where did you obtain these images from.

A. This comes from a recent article on electron microscopy of viruses which I can give you the reference. I have the article here. It is in a recent publication and I guess one of the reasons - yes, it is in a recent publication that I have here - it is something called 'Current opinion in microbiology'.

HIS HONOUR

Q. What is the title of the publication.

A. It is 'Current Opinion in Microbiology from 2006' and the article is called 'Structure of complex viruses and virus infected cells by electron cryotomography'. I guess I put that in because -

HIS HONOUR: Mr Borick, obviously you haven't seen that article?

MR BORICK: Personally, I can't remember whether I have seen that or not at the moment, but if I can have a look at it and get the full note of it.

HIS HONOUR: We will copy it and provide Mr Borick with a copy, unless you have a copy, Ms McDonald?

MS MCDONALD: No, I don't.

EXHIBIT #P70 DIAGRAM PICTURES OF HIV COMPARED WITH OTHER VIRUSES TENDERED BY MS MCDONALD. ADMITTED.

XN

Q. Can you tell us what we see in the series of images.

A. This is the series of sort of electron micrographs. It is a new technology of electron microscopy. Electron microscopy, like all technologies, has improved over time. This wasn't available in 1983. As the technology becomes better, you get better pictures of viral particles. This just happens to outline this particular technology and with pictures of a couple of viruses. The first row: Herpes Simplex virus, which causes various herpes infections, the second one is Vaccinia Virus and the third one is HIV. The beauty of these newer pictures is that often you can use the newer technologies to better look at the sort of core of the virus, the structure of the virus - the morphology of the virus. These were prepared by HIV cultures, and the reference is in that article, where you grow a virus in a tissue culture, you grow HIV, you purify it and then you take electron micrographs of that purified material. The technology for doing that is much improved over the decades.

Q. Are the images that we see in the two left-hand columns images using altered technology.

A. No, it is just the way they are scanned. The colour is just colour. The computer puts the colour in and it is not really colourful. Those pictures are just different slices, if you like, of the virus structure.

Q. You know that in this court the proposition has been advanced that HIV has never been isolated. What do you say to that -

HIS HONOUR

Q. What do you understand by isolation of the virus; firstly. We need to get the terminology right, so we all understand what we're talking about.

A. The term 'virus isolation' and 'virus culture' are used interchangeably in this discussion by laboratory people and medicos and so on. Really, the term is virus culture, because viruses need living cells to grow, so a virus culture or virus isolation is putting a clinical sample through a particular cell line, or particular cells, that will then produce free virus at the end of the culture which you can then measure or assess.

XN

Q. Has HIV ever been isolated or cultured in the way you have described.

A. HIV was isolated in a 1983 paper by Montagnier's group. It is not the way we do it now but it was done then and we now isolate HIV by other somewhat quicker techniques and so on and we do it in our lab many times a year. It is a routine procedure. It is not done much for the diagnosis of HIV because it takes a few weeks and it is also expensive, so we tend to do it, I guess, for research purposes but we still occasionally do it clinically, where it is felt to be necessary or where the other tests are not working or what have you.

Q. When you say you 'do it clinically where it is felt to be necessary'; in what sort of circumstances.

A. The main circumstance that we would do, culturing the virus now for diagnostic purposes would be still in

babies born to infected mothers. If you have HIV-positive mothers, because it can be difficult to interpret the laboratory tests in the baby because the babies are carrying the mother's antibodies, for a whole lot of things, because if the mum has HIV seropositivity, the baby will for a certain period of time, whether it is infected or not. Then you need to use other tests, independent of the antibody test, to determine whether the baby is infected because you want to treat that baby as quickly as possible. You then either do genetic testing or isolation culture to see if the baby is carrying the virus. If those tests are negative - we sometimes repeat them to be doubly sure and so on because of the implications of the baby - but if they're persistently negative, we would say that baby does not have HIV infection. Then what you see is you follow the baby over the next 12 months or so and the antibodies that they have carried from their mother then go away, drop off over time, and the baby is left completely negative of HIV by whatever testing you do. That would be the main reason we would do virus isolation nowadays, for clinical purposes. We do bucket loads for research purposes.

Q. Bucket loads.

A. We grow lots of viruses for our research colleagues. We look for viruses from unusual clinical samples or from unusual parts of the world. We do a lot of work with HIV in other parts of our region - Timor, New Guinea, etc.

Q. Is it necessary to culture viruses for the purpose of development of vaccines or medication.

A. Sure. You need to be able to know what strains of HIV are present to develop an effective vaccine. You can do some of that work at the molecular level but you do need to grow the virus and you need to grow it consistently for that purpose. For vaccine development, virus isolation is important, just like it is crucial for influenza vaccination or measles vaccination or any

other vaccination we have.

Q. Is the process that you're describing any different compared to other viruses, like rubella or measles.

A. The general principles of virus isolation are the same. The techniques for doing it vary from virus to virus. You need the clinical sample, which might be blood for HIV, it might be respiratory secretions for influenza or whatever. You then take that material, you put that into a flask, or a bottle, or a tube, depending, and you have cells in that tube or flask, that you know is permissive for the sorts of agents that you're trying to grow. For example, if you want to grow HIV, you take lymphocytes from a negative person and we grow those, stimulate them and put them in culture with the clinical sample and then measure and see if the virus is produced. If we do it for influenza we take other cells that are now commercially available and you take those and you put the respiratory tract sample in there, you treat the cells and you measure the virus produced at the end. That is the general principle for most forms of virus isolation. In all cases you need living cells to grow the virus. The living cells will vary but they'll all need treatment of some form to make them, I suppose, permissive for the virus. At a very basic level, most cells don't want to be infected by a virus, so they have things that kind of stop virus infection and sometimes you treat the cells to make them permissive so you can grow the virus. With HIV, we take lymphocytes that we get from the blood bank, we know they're HIV antibody negative, we stimulate them with compounds such as PHA and there are other things you can use and you add a clinical sample and away you go. For influenza, we use other things, like trypsin, an enzyme we use to make the cell permissive. They all have serum in them, calf serum, again to keep the cells happy - if cells can be happy - sort of permissive and receptive to pathogens. That is the general principles of manipulating the cells a little bit, all culture quite

typical of virus isolation work.

Q. What do you say to the suggestion that because you need the cells to culture the virus, you can never actually properly isolate it.

A. That doesn't make sense. You have to do that to the cells to produce the virus.

Q. How do you know that what you have got then is virus and not some contaminant caused by the cells.

A. That's a very good point because you can have contaminants that come out of cell cultures. You see that a lot. For example, we already do that with our cell cultures. If we grow HIV from cell lines, we need to check the cell lines before we add clinical material to them, to make sure they don't have other things in them, like mycoplasma or foamy virus, to make sure we don't have them in there. Similarly, we do the same thing with our other cell lines for other viral infections. Things can come out and other viruses have been discovered when trying to culture something else. If you take lymphocytes from a donor, an HIV-negative donor from a blood bank, you can culture other viruses out of them very, very occasionally. Viruses like some of the herpes viruses - HHV6, HHV7 - they arose, unrecognised, out of cell cultures and that was a very exciting discovery for that particular person. Because we have been doing this for a long time now and we know how to look after the cells and this is all a biological process, we know how to look after the cells and because of the tests we do on the material that is produced from the infected cultures, we know that that is not something other than HIV. If there was something else there, we might say 'There's HIV there and there's something else' and get excited and go off and try and find out what it is'. Cell lines, using culture, can produce other viruses - a whole range of them over the years.

Q. When you say 'because of the tests that we do, we know it is HIV'; what tests are you referring to.

A. There are a range of tests that we do. In the routine sort of scenario - in the research scenario as well, I guess - we do a couple of things. We look to see what the cell lines are looking like. If you add a clinical sample into some lymphocytes to grow it or into a T cell line, which is like a continuous lymphocyte, the virus will often cause cytopathic effect, or CPE. In other words, because the cells are infected, they look as though they're going to die and they are dying, in fact, and sometimes they all clump together and they take on a very bizarre shape and that's why, when we have our cultures, we look at them every couple of days under the microscope to see whether the cells are looking ill or not and, again, this is a principle for all viruses that we culture and we put them into the cell culture. They'll kill that cell, generally - not always but mostly - same with influenza or measles or whatever we culture. An experienced technician or scientist can tell that the cells are infected. That is the first thing; what the cells look like. That is not specific, it doesn't say 'it must be HIV that is causing that effect' or 'it must be influenza causing that effect'. We do other tests. In the case of HIV, we look for the production of P24 antigen which we know to be an HIV antigen or we look for reverse transcriptase activity or you can look for genetic sequences of HIV in that cell. Which one you choose depends entirely on the cost to your laboratory. Again, that's the same principle that we do with other things - like influenza cultures or measles cultures - you look to see what the cells look like. If they have a cytopathic effect, then you have the various messures of the viruses in that material.

Q. You referred to one of the options being to look for the P24 antigen, is there a P24 that is unique to HIV.

A. There is a P24 that is unique to HIV and there is a protein of that size that Dr Dax discussed yesterday. There are many proteins of that particular size, if you ran them out on an electrophoretic gel. The P24 that we

use is a commercially available one and it is HIV specific and it doesn't pick up non-HIV proteins of that size. If I could just make one comment, when we do all these cultures - because they're asking about 'could other things emerge?' - when we do the cultures, we always run a culture that is a controlled culture - it doesn't have any of the patient's material in it. We look at the controlled culture and do all the measurements that I have just mentioned on that control culture, as well as a sample that we're after and if all those control things are negative and the things we're looking for are found in the clinical sample, then that helps us say there is nothing wrong with the donor cells that we have used.

Q. You have also talked about reverse transcriptase as being something that can be looked for. This might, in part, be answered by what you have just told us, but is reverse transcriptase found elsewhere in the body.

A. Reverse transcriptase is an enzyme that performs a specific function, I guess, of converting backwards from RNA to DNA. A number of viruses and cells can do that function and I think there's a lot to be discovered about that. Retroviruses do it as a group of viruses, or as a family of viruses. Some other viruses, like hepatitis B, there's an enzyme that has that sort of activity and there are cellular enzymes that also have a reverse transcriptase effect. The reverse transcriptase of retroviruses is somewhat unique, in the sense that it has particular electrolyte dependency, and so on, that other forms of reverse transcriptase don't have and we know actually in the case of HIV what that reverse transcriptase enzyme's genetic make-up is.

Q. You actually know the genetic make-up of the reverse transcriptase you're looking for in HIV.

A. We do.

Q. It's a bit like P24, you might have other proteins of a similar molecular weight to the P24 but you know because of the other research that's been done that there is a P24 unique to HIV, that's right.

A. Yes.

Q. The third that you mentioned was genetic sequences, I turn to deal with that as a broad topic. Nucleic acid testing is something that has been referred to during the course of the evidence of other witnesses. Can you tell us, from a virologist point of view, what nucleic acid testing is.

A. Well the core part of a virus, or of any living material for that matter, is a genetic material contained within it; in the case of a virus that's either RNA or DNA. What nucleic acid testing means is using methods to identify what that genetic material is, and you can do that in a number of ways. You can sequence the virus, or the sequence material where we look for all the building blocks of DNA if you like in a regular fashion, and then we can take that sequence and compare it to all the known sequences in the world that are in various database and so on and say 'it's exactly like that one, that's what it is', or 'it's more completely new, this is interesting', or 'it's slightly different from what's in the data base'. Rather than detecting the whole part of the genetic material you can also look for particular parts of the genetic material, and that's what we do in the diagnostic lab. So we look for short segments of genetic material that's unique to that virus and use these assays to say 'yes, that material is there' or 'no, it isn't', that's what we call a 'yes' or 'no' PCR, or you can quantify the amount of that material in the sample and give some idea of how much is there.

Q. Do we now have the full genome of the HIV.

A. We have thousands if not tens of thousands of copies of the full length of the HIV genome.

Q. So we don't just know what bits and pieces are but we have many times established the full genome of a virus.

A. That's right, I mean the French group within about, I can't remember the exact detail but within a year or so of that original publication of the 1983 paper of the isolation of the virus sequenced the whole virus and these were in the days where sequencing technology was complex and slow, it took them about six to nine months to sequence that whole genome with five people working, in fact almost around the clock to do it. Now with nucleic acid technology we can sequence, should I say define, a whole HIV genome in 48 hours.

Q. Does it happen in your lab.

A. Well if we need to we do yes, we don't do that as a routine let me say, we do it with hard to get research money but you can. In order words, the point I'm trying to make is that the ability to do sequencing of virus, be they HIV or otherwise, is dramatically easier, in fact it's almost a diagnostic test and we use sequencing in our lab for HIV as a diagnostic test now.

Q. So those whole genomes that you have talked about there being many thousands of, are those the sort of thing that is stored in that database we have heard about at Los Alamos.

A. Yes, they are, there are a number of databases, the main sort of ones in the USA where these data bases - where that Los Alamos database is, Los Alamos is one of the major, well, military laboratories, originally, but molecular laboratories. But even labs would have their own database so, for example, I know that in South Australia that the laboratory in South Australia has an extremely good database of the genetic sequence of HIV circulating in South Australia and we have a similar one in New South Wales, and in fact we are putting together a national database in Australia of the sequences of HIV here for kind of local purposes.

Q. With an HIV genome are there certain areas that are consistent between all HIV viruses.

A. Yes, there are. The genetic structure of HIV is I guess complex, certainly is complex. If you go across the

whole genetic material there are parts of the genome that are sort of very much the same in everybody and then there are others that will vary very significantly between people. And the virus can mutate very quickly and often those areas of the genome where there is a lot of variation are targets for things like drugs and targets for things like immune responses, antibody responses, so there are responses and so on. So in fact it is a defence mechanism of many viruses to keep its genomic structure but it varies in certain regions where it us under attack, if you like, in the immune system. Irrespective of that, if you look at the databases of Los Alamos or your local ones and so on you can line them all up under each other and you can see where the variation is or isn't and there are certainly parts of the genome that are crucial for virus replication that don't change. And of course there are now diagnostic tests for PCR nucleic acid testing besides that.

Q. We have heard some evidence in this court that not only does the virus vary between individuals but it can vary within the one person.

A. Absolutely, there is a term called quasi species, which means that in an individual infected with HIV every single virus, at some tiny genetic level, will be subtly different to another. They are still all HIV and all the ones in that particular person are much closer together than all the ones from another particular group of people, of other people, but even so within that individual, even within a cell in a person you can see different HIV strains. That is not just the feature of HIV but influenza is like that. Most of the RNA viruses of which influenza is one, HIV is one, they all have this genetic mutability and variation.

HIS HONOUR

Q. So, just so I can get it clear in my own mind, let's take influenza, if you were to take the genetic sequencing from someone who had influenza, someone who contracted it and you compared the two you might be able

to say 'well you contracted influenza from person A rather than person B'.

A. Yes.

Q. Although person B also has it.

A. That's right and we do that for influenza already, in outbreaks in nursing homes and so on and you can do it in a lot of viruses, HIV is one.

Q. But there would be certain common features about all of them that determine that it's influenza.

A. For sure, exactly.

XN

Q. Is it the case that scientists can use both aspects of the virus, that is those that are static between the viruses and those that vary between person and person for different sorts of purposes. So, for example, do scientists look at those areas that are consistent between the viruses for the purpose of nucleic acid testing.

A. Yes. That's right.

Q. What does nucleic acid testing actually involve looking for.

A. Well, in the diagnostic sort of situation what that really is looking for is looking for presence of those conserved bits of genetic material that you know to be the pathogen, be it HIV or flu or whatever, you then use that technology to see whether those sequences or those bits are present in something else, in another clinical sample, for example. And that really now has become, you know, the main method of diagnosis of many many pathogens in a laboratory now. In fact most of the laboratories around the world are giving up doing virus isolation as a diagnostic test. We still do it because we have reference laboratory functions but most people have gone straight to genetic testing now.

Q. Particularly with those new sorts of viruses you told us about, things like SARS.

A. Yes, that's right, I mean with genetic testing - I guess the upside of course is you can do it on everybody, it's

pretty cheap, it's extremely reliable and robust, the downside is that you have to know the genetic structure to begin with, you have to have the genetic sequence of what you are after. So when the a new virus emerges, like SARS, you can't necessarily use, reliably, nucleic acid testing until you get the sequence of that new virus for the first time. So then in fact you are in a first identifier, you are required to use these more traditional methods of virus culture and microscopy and so on. But of course the speed at which that can be done now is extremely different. So that with SARS they grew the virus, they saw the effect in the virus, they then sequenced it. In those days, instead of taking, you know, nine months to do they sequence that virus in 48 hours, it was available on the Internet within that time and people were then able to look at the genetic structure of it, design their own nucleic acid testing things to then use on their clinical samples. Whereas with HIV this is a - influenza took, you know, a decade.

Q. When someone speaks about measuring someone's viral load are they there measuring the conserved genes that you have told us about or some other area.

A. It depends on the technology. The original measures of viral load were done by isolation so that you grew the virus out of the cells of the person or the plasma of the person and there was a technology of dilution where you can work out how many viral particles were cultured from that person, samples. And there is a seminal paper published in the New England Journal by David Ho group that showed that in fact you could grow the virus from virtually anybody that was HIV positive, always on the lymphocytes and most of the time or much of the time from the plasma as well and you could quantitate it. So that was the first measure of virus load. The trouble is that's not practical from the clinical management point of view or testing out new drugs, so then people moved to the molecular ways of doing it which is just an advancement of nucleic acid testing, for PCC and so on,

to measure those conserved regions as you say and measure how much there was. And in fact that's more reliable, it's more sensitive than virus culture, so now we do our viral load measurements using nucleic acid testing, but you could do it in other ways if you wished.

Q. It's this nucleic acid testing that's used to screen blood donations.

A. Nucleic acid testing is used to screen blood donations, it's not quantitative but it is done as a standard test in Australia.

Q. Is that to try and meet concerns about that window period in which a person might not yet be producing antibodies.

A. Yes, so in any infection, HIV or otherwise, the period of time where the person is first infected and then it takes some period of time, weeks or so, before you start to see evidence of a person either getting sick, say clinically converting to the disease, or before we see laboratory evidence of that occurring. When you just do antibody tests, depending on how good your antibody tests are and what generation they are and so on, it's some weeks between the initial infection and when the antibody test become positive and that is usually around the time when the person's first getting sick, but if you've got more sensitive methods such as nucleic acid testing you can pick up a bit closer to that original exposure positive activity. In other words they can be positive prior to the antibody test becoming positive and the beauty of that is for the blood supply is that you can get out those people who might be donating blood who aren't yet antibody positive but who are brewing the infection if you like and by doing that you have virtually eliminated transmission of HIV by blood in Australia.

HIS HONOUR

Q. You can also start treating them earlier I presume.

A. That's right, you identify them, that's the whole other

issue is how quickly to get treatment into people who are first detected by these genetic tests, yes.

XN

Q. With the using of nucleic acid testing is there any window period left before a person will tell -

A. Yes, you have to remember that if you look at the virus cycle that we discussed before, P69, you know this takes a period of time for the virus to get in, to insert itself the into the host cell and to be released in enough volume to be detected. So there's still a period of time where - they may not necessarily be infectious during that time of course but they are brewing infection if you like.

Q. Turning to the flip side, and that is the areas of the HIV genome that vary between people, can that also be used by scientists for a variety of purposes.

A. Absolutely. It's been a great research interest of mine, to look at the genetic variability of HIV and we use this as a way of what we call molecular epidemiology, so the strains of virus that are in Africa, are different to the strains of virus that are in North America or Australia. The viruses in India are a bit different again and you can track the movement of people with infection around the world using the various parts of the genome. You can do this with very very old viruses like HTLV 1 and HTLV, two which are retro viruses, which we have discussed here. They are very old viruses, have been part of mankind ever since we came out of, from all the slime. And so you can follow the movement, very old viruses for different populations, which is why they are focussed in certain parts of the world, like Southern Japan, the Caribbean. With HIV it is a new virus and with genetic variability we can track the movement of viruses in different parts of the world. You can do it at local level, you can show how certain strains are being moved from one individual to others. You can do it at original level to show that Australian viruses are a bit different to

Thai or significantly different to Thai or Indonesian viruses, you can do it to see public health problems such as you can track the movement of viruses across transport groups in Northern India or throughout Africa as a truck drivers go along infecting people with their local strain as they traverse the continent antecedent so on. So looking at the genetic variability has been extremely important in understanding the epidemiology and the public health implications of infection. You can also look at it to see who gave what virus to whom, as you mentioned with influenza. So that if someone has infected another person you can analyse the various parts of those people's genomes to say that it's highly likely they got that virus from that other person, and that's been done in many instances. We have done it in the Florida Dentist Case, which I have seen referred to here, it's been done in a number of court cases in other states of Australia and around the world. So that's another thing. The last area where genetic availability is very important is understanding where HIV came from in the first place. So by understanding the genome in humans and then by looking at the genome variability in monkeys from Africa, we can show that HIV is most likely originated from non-human primates, and that's not terribly surprising because in fact 75% of all the viruses discovered in the last 15 years have an animal origin. They nearly all come from animals. So, anyway, that's a very long-winded way of saying that genetic variability is extremely important in HIV research and epidemiology and so on.

Q. You probably touched on it in passing but it's also this variable area that we look at in terms of appropriate antiviral medication.

A. Yes, well it's not quite focussed on the variability in that situation. We use sequencing routinely, as do a number of labs around the country, to look at people's HIV genomes to see if they are going to respond to the drugs or not, so if they are carrying a resistant virus

because they have a mutation where the drug is supposed to bind, then we continue to give that person the drug. Just like antibiotic testing if you like, if you have a urinary tract infection and the lab says 'No look it's not going to respond to that antibiotic but it probably will respond to the other' then we will use the one that it looks as though it is sensitive to and we do the same with HIV. It's more of an issue of people being on HIV treatments for a while where their viral load has gone down, they are getting better load, it's come down, it's stayed below detection or very low and then the virus becomes resistant and you start to see the load come up as the virus is evading the effect of the drug, so you do some sequencing at that time to say 'we had better switch drugs here'.

CONTINUED

So that resistance testing is done over quite a chunk of the genome I might say. It's a fair proportion, 20% of the whole viral genome is done for resistant testing and that has become a crucial part of viral load management -

Q. Is that management of viral load relevant to the question of transmission of the infection.

A. Very much so. Absolutely, there is now - there are papers which show that, in a number of situations, be it heterosexual transmission or transmission from mother to baby, that the higher the viral load - the more virus in the blood, the more likely the other person is to be infected. The whole point of antiretroviral therapy in infected mothers, which is the biggest public health intervention in HIV medicine is to reduce the viral load in the mother. If you drop the viral load to below detection, it's very, very uncommon for the baby to be infected - still possible, but very, very uncommon. If the mother is untreated and has a high viral load then the chances of the baby being infected is far higher. The same with sexual transmission. If your viral load is below detection because you're on successful therapy then you are very unlikely to be able to transmit to other people - not impossible, but very unlikely.

Q. By reference to P69, that's what you've described as your cartoon diagram of the life of the HIV, by reference to that, can you explain to us how it is that reducing your viral load right down to an undetectable level results in your being less likely to transmit the virus. Presumably there is still some virus in your body.

A. There is still virus in your body. Everybody who has established HIV infection will have evidence of the virus in their body; okay. And that can be really at the integrated level here that is on that diagram; in other words, once someone has been infected, the virus has gone in and integrated, the virus will always be in some cells in the body and in some parts of the body

more so than others. But if your drugs work at these various parts that I alluded to before, various parts of the life cycle, you prevent free virus from being released. In other words, if you cut off the virus being produced then you don't have free virus around and it's generally the free virus that is what is transmitted to other people. You need the free virus to go and infect other cells. You can spread virus between cells of course but, in the context of spreading to other people, you need to have the free virus.

ADJOURNED 11.48 A.M.

RESUMING 12.08 P.M.

Q. Just a final few questions arising from the evidence called by the defence witnesses, Doctor; is electromicroscopy used for HIV diagnosis.

A. It's not used for HIV diagnostic purposes, no, and really never has been. Electromicroscopy is very occasionally used in diagnostic medicine for other purposes and occasionally in other viruses but for HIV it's never been used as a diagnostic test.

Q. Why not.

A. Because you've got to have an electron microscope in your laboratory and they are extremely expensive. But the main problem is it's very insensitive and labour intensive, and an intensely difficult thing to do. It is used much more on the research side for understanding what the viruses really look like or how they might interact with cells.

Q. It's been suggested there is no agreement about the genus or family to which HIV belongs; do you agree or disagree with that.

A. I don't think there is any disagreement with what HIV is in terms of being the member of the family Retroviridae. They are certainly, like we see with all organisms, organisms move place within their classification of families and sub-families and genre and so on, and even order, and much of this has come along with molecular data where, once you have the sequence of something, you

see it's not really there, it's really one of these, so the original discussion about where HIV should sit in the early days when it was first discovered related to some of the electron microscopy appearance, and people thought it looked like a certain type of particle but they are very rough measures or imprecise measures of where the virus should sit in its family, so really the definitive way now of putting viruses in their families is done on the genetic sequence of the virus and the genetic organisation of the virus rather electron microscopy.

HIS HONOUR

Q. When did that process develop.

A. I think, really, once sequencing viral genomes became reasonably easy to do, that's when it took over from electron microscopy as one of the ways of putting them in order. Even now we're still adding viruses into different families now based on their genetic sequence so it's an evolving sequence where you establish these.

Q. I understand that because your evidence was they were able to sequence HIV not long after it was first identified by, not Gallo but by Montagnier, but really what I wanted to find out from you was when did it become sufficiently advanced so that -

A. Look, I'm not sure I could put a date as to when it -

Q. Not an exact date, but approximately.

A. It was within a couple of years of the discovery.

XN

Q. What do you say to the suggestion that there is no agreement as to what HIV particles look like or their morphology.

A. I think there is agreement of what HIV particles look like on an electron microscope. As I said before electron microscopy is sort of imperfect and, again, technology with that has changed a lot but I think now, with pictures you see - electron microscopy pictures of HIV, there is no doubt about what they look like. They have a pretty characteristic appearance; not to say that

is unique, but it is characteristic of HIV, and I think just going back to what you said before, your Honour, about where organisms are put and classified, there is an international taxonomic society which meets on a regular basis to determine where viruses - and there is a bacterial one and fungi one and so on, all four, and that's published regularly, and that's really sort of the gospel, if you like, of where organisms sit.

Q. Following on from that, you're aware there has been a suggestion that Montagnier had said there had to be 80 knobs for it to be HIV, and that was compared to Dr Dax, who is reported as having referred to 72 knobs; is there any comment you want to make about that.

A. I'm not quite sure how that all came up in context, but I did seem to remember reading that Montagnier didn't say '80', he said 'approximately 80' or 'around 80'. These sort of capsomeres and so on, and numbers that people have, are based on the mathematical modelling of what a virus looks like, which is not necessarily what you see on an electron microscopic picture, but there is a mathematics of how viruss are packaged, and they're icosahedral in structure, or some viruses are like HIV and, therefore, if you accept that mathematical model, you can then count exactly how many capsomeres or whatever there should be, but that is not an argument. I think that is really Montagnier said 'approximately' and it is.

Q. It has also been suggested that to prove sexual transmission you need to find the agent, namely HIV, in the genital secretions. Putting that aside, have there been tests to determine whether or not HIV is found in genital secretions.

A. Many times. You can find HIV in saliva, you can find HIV in vaginal secretions and seminal fluid and semen, you can find it in the cells in those body fluids and you can also take those cells out and find it free in the non-cellular material. I couldn't say now where but I have seen, again, electron microscopic pictures of

semen with viral particles in them. It must be remembered that genital secretions and saliva and things like that are really made up of many components that are in blood for that matter, and plasma, and there is no doubt in my mind that viruses present often in very high levels in those body fluids.

Q. Now just one final topic, dendritic cells.

A. Yes.

Q. What can you tell us about those in the context of HIV.

A. I think the discussion about dendritic cells is in the context of, you know, what is the method by which HIV enters the body, and dendritic cells, for example, are present, if you like, right at mucosal surfaces, such as in the genital tract, and they're often the first part of the immune response that might see something new, be it HIV or be it any other sexually transmitted disease or whatever, and with those dendritic cells, if you like, sort of - the virus attaches to those or is moved by those, dendritic cells then to nearby lymphocytes which then start the whole replicative cycle. The dendritic cells are not the key target cell of HIV but the dendritic cells move the HIV to its target, to the target T cells in local lymph glands, or free in the mucosal surfaces.

Q. Are you aware of the studies that have been done in relation to the male circumcision and the impact that has on HIV.

A. Yes, I'm certainly aware of them. I don't know the detail of those studies other than to say that circumcision would appear - male circumcision has some benefit in reducing transmission. The theory might be that reducing the number of dendritic cells might affect transmission, but I haven't read those in detail.

*CROSS-EXAMINATION BY MR BORICK

Q. You've referred on a number of occasions to genetic sequences.

A. Yes.

Q. And, as I have listened to your evidence these are the -

it seems to me they seem to be the most important aspect of all this; you find the genetic sequence, you've isolated HIV.

A. No, although they are extremely important, finding the genetic sequence doesn't mean you've isolated HIV. Isolation or culture of HIV is a separate thing to finding the genetic sequence. Of course, in a virus that you isolate the genetic sequence is there, you can detect it, but they are two separate techniques if you like.

Q. I'm sorry, you've confused me. By genetic sequence what precisely do you mean.

A. Let me go back a step to what a virus is. It's a particle that contains the genetic sequence of that virus, and is surrounded by viral proteins and lipids and so on.

Q. And a piece of RNA or DNA.

A. That's right; contained within that virus.

Q. And it's not an antibody.

A. No, no, it's got nothing to do with antibodies; that is a viral particle, that's right. So that when you do isolation or culture the virus, you culture the viral particle and you can then do tests to determine if the genetic sequence is there and that's the one you're looking for, that viral proteins are there, such as p24, or the various other things that occur in virus isolations as I've mentioned earlier.

Q. You culture the viral particle but how do you remove all of the cellular fragments.

A. For what purpose do you mean?

Q. To find out that you're looking exactly at the virus. As I understand it, by virus isolation, culturing it, you're attempting to isolate the virus.

A. Right, right.

Q. How do you get rid of the cellular debris.

A. When you say you're isolating the virus, it doesn't mean you're isolating it from absolutely everything else that is around it that might be present in that culture

medium. What you are doing is finding the virus from a clinical sample that has come out through that culture system, so that if you then want to do - if you set up a virus culture with a clinical sample and the cells, and you want to see if the virus is being produced, okay, you then look for evidence that the virus is there in that fluid and you can do that either by looking at the viral proteins that are being produced, the p24. You can look at it to see if the genetic material of the virus is there. Should you so desire you could even do EM - electromicroscopy - although that is not at all a normal thing to do with viral isolation.

Q. Can we leave that out for a moment and stick to the culturing.

A. Yes; so the actual practical method of doing the culture is you take the fluid from the culture, you think you have a virus there, and you might have seen the cytopathic effect and so on, and then you take that fluid and you do certain tests on that fluid to see whether the virus is there, the genetic material, the proteins, whatever. It doesn't undergo a great purification step. That's not actually required for that. We don't do that for any form of virus isolation, be it measles, Rubella, influenza. It's not required.

Q. You've read the evidence of the Perth group.

A. Yes, I have read the evidence.

Q. Is it your understanding that the real difference between you and the Perth group is this question of isolation. Their position is you have to isolate the virus and you have to use a purified virus from the very beginning, whereas, as I understand you, you're saying 'No, that's not necessary'.

A. Look, I've got a number of differences from what the Perth group say, one of which is isolation and what they say is necessary to this term of purification and so on. From my perspective, and I think this is the common perspective, there are tried and true methods of virus isolation and those methods were developed from the

original work done in 1983 by Montagnier's group and then Gallo's group and all the others, so that now - and all that follows a process that we do for virus isolation of any description for any virus, and the way that that is all done, I think is perfectly appropriate and correct in identifying HIV.

CONTINUED

Dwyer

Q. In those tried and true methods, can you refer me to any paper that explains exactly how you remove all the cellular debris so that you are looking at the virus itself and there can't be any mistake about it.

A. There is not a need to remove all the cellular debris, anyway, to see whether the virus is present or not. I mean, if you want to take a virus for use and research experiments and so on, you will take that fluid from a culture and you will do certain things to it to sort of enhance the purity of it, if you like. So you will get rid of perhaps dead cells and other things and you can do that in a range of - often it is simply some centrifugation or putting it through a certain sort of filter. Then you take that more purified fluid and use it for your experiments, so that is one thing. The other way of sort of getting over this concern about cellular material being present is to make a molecular clone of the virus. So you take this material and you take out the genetic material and you go through a series of processes where you just work with the genetic material, take just the genome out and put that into a system with plasmas and bacteria and so on to produce a whole virion in infected cells. So, if you like, that gets rid of any cellular debris or material that you might be concerned about is complicating your assays.

Q. Yesterday you heard Dr Dax talking about what happened in 1985 in relation to virus isolation and she said that the trouble was that in the cellular preparations there were a lot of other proteins and the virus is not isolated. Do you remember that evidence.

A. I remember that sort of discussion, yes.

Q. Isn't that what I am just putting to you now; that the problem with saying you have got a virus is if you have got cellular proteins already mixed in there, you can't say it is a virus.

A. Sure you can. There may be cellular protein - you can say that there is a virus there and there are cellular proteins there and there are dead cells and living cells

and all sort of things, but you can certainly say there is a virus there.

Q. Is p24 a HIV protein.

A. This is a HIV p24 protein.

Q. Can it exist in cellular debris.

A. Free of the virus.

Q. Can it exist in cellular debris.

A. It can exist in cellular debris.

Q. So when you are getting p24, how do you know that it is coming from the virus and not from the cellular debris.

A. It is coming from the virus to get into the cellular debris, if you like.

Q. How do you know that.

A. Because the only thing that produces the HIV p24 is HIV. It is not produced by other cells.

Q. That is not right, is it, because p24 is found elsewhere. It is found in breast cancer and cervical cancer.

A. I'm not aware of p24 being found in breast cancer. I'm aware of HIV-like sequences being found in breast cancer and breast cancer tissue. That's a different thing.

Q. I will get some more exact information on that. The questions I will be asking you are a lot of questions I have posed to other witnesses, so you will have a fair idea of what is coming, but I want to clarify what is meant by not only 'genetic sequencing' but 'genetic variability'. As I understand it, Professor French was quoting 'The immune activated is affected by genetic factors in the hosts so it varies from individual to individual. It would, therefore, be more correct to say that AIDS is caused by factors in addition to HIV'. You may have read this.

A. Yes.

Q. And the factors he was talking about were genetic factors.

A. Yes.

Q. And he handed a paper over to the Perth group to have a look at, and I haven't had time to get instructions on

on it, but first of all, with the genetic factors he is referring to, they are something quite different to genetic sequence, is that right, or am I wrong.

A. No, that's correct. When he talks about genetic variability, each human, each host, has their own genetic make-up, we all do, and that genetic variability of the host influences the likelihood of us being infected with certain things or having certain genetic diseases, like cystic fibrosis or something like that, and it very much influences the way we react to certain infections such as malaria or HIV and a whole range of other things, influenza, but that's the host variability and the host immune make-up and so. It is all encoded in our genetic material. The virus' genetic variability refers solely to the viral RNA or DNA. That is two quite separate things.

Q. When you are talking of DNA or viral RNA, are they the two things you are talking about.

A. When I talking about viral RNA or DNA genetic material or genetic variable, I'm talking about just the viral material. So it has got nothing to do with the host genetic variability.

HIS HONOUR

Q. To get it into something that I perhaps understand, the host genetic variability, for example, in someone who suffers from diabetes, research has shown that if your father or mother suffer from diabetes, the children are more likely to suffer from diabetes. There are other factors as well that enforce that.

A. That's right. Exactly, exactly.

Q. So that's what you are talking about when you are talking about 'host'.

A. Host variability is the human and how they may or may not develop certain problems or react to certain infections. The viral variability is how the virus switches and mutates and so on.

XXN

Q. We better make sure of what we are talking about when we

use the word 'host'. What is the host.

A. Theoretically the host is the cell the virus infects, okay; so the individual cell that that virus goes into. It is really the lymphocyte but the lymphocyte is part of us, the host. When the virus infects somebody, it doesn't infect you as a person, it infects certain cells in your body.

HIS HONOUR

Q. Therefore, called the host.

A. Called the host.

XXN

Q. We are not saying that the person themselves, you, me or whoever, we are not the host. It is ourselves.

A. It is ourselves that are the host.

Q. How does the virus select the cell.

A. The virus selects its host cell -

Q. That's what I meant.

A. - by an interaction between proteins and the virus on the outside of the virus and proteins or receptors on the host cell. So, for example, with HIV, it binds first to something called the CD4 molecule, which is a differentiate molecule on the lymphocyte. It actually does use some other receptors as well to actually get in. Every virus infects its host cells through some sort of receptor; in other words, some sort of unique binding. So that's why the influenza virus only infects the lungs, because it only binds to particular receptors on the lung cells and it doesn't infect anywhere else. Other certain viruses will only affect the liver cells because that's where the binding occur. HIV affects CD4 positive lymphocytes, which happen to be the linchpin of the immune system, if you like, which is why it has such a profound immune effect. HIV does affect other cells, that's true, and they have often similar receptors on them.

Q. HIV selects as its host the CD4 lymphocyte cells.

A. Yes. Selecting gives it a kind of higher thought process. The virus binds to anything that has that

particular receptor, okay. It happens to be, in the case of HIV, the CD4 positive T cell lymphocyte and it is complicated but it does need some other co-receptors as well. It doesn't bind to many other cells in the body because they don't have that receptor.

Q. Somehow or other, if you are walking around the town and you haven't got HIV and if you get it, you get it through unprotected sexual course, so we are told.

A. Yes.

Q. What are one of the other ways in which you can get it.

A. There are various ways that the transmission of HIV occurs. It can occur through the blood, so the sharing of infected blood, which might include things like transfusion or needle sharing amongst injecting drug users or even needle stick accidents, provided there is HIV infected blood in that material. It can be transmitted by close contact, ie sexual contact, because the virus is present in sexual fluids and it can be transmitted that way, and often there is some minor blood transmission in that process as well. It can also be transmitted from mother to child, which is called horizontal transmission - no, vertical transmission, sorry - where the virus is passed on to the baby via the mother usually at the time of delivery, and that's probably mostly via blood contact and sharing at the time of delivery. So they are really the main methods.

Q. I think what I would like to do in a moment is for you to imagine there is a jury sitting over there. We are not talking to a highly intelligent judge as we are at the moment. Just imagine that. We are talking to 12 ordinary people about this and we have told them that a virus exists and you grow it in a cell culture and it gets into your body and then you can pass it on to another person by the means you have just said.

A. Yes.

Q. And then this virus, it goes into its home, its host if you like, the CD4 cells, so we know where it goes.

A. Yes.

Q. And it has to do that because it lives inside a cell. It gets its life from there, so to speak; that's right.

A. Yes.

Q. From what I understand - and we are back to the genetic factors - different people have different cells; is that so.

A. Yes. Well, they have the same cells but a different genetic make-up, yes.

Q. It seems from what we have heard from another witness that this genetic factor which host cell you have gone into can determine whether you will become infected by the virus, is that so.

A. That's so occasionally.

Q. Do we really know for sure that Professor French is right about that, that these genetic factors will affect it.

OBJECTION: MS MCDONALD OBJECTS

MS MCDONALD: That was not Professor French's evidence. Professor French's evidence was much more limited. It related to two different propositions.

HIS HONOUR: Mr Borick, I think you ought to take the witness to the evidence you refer to first.

XXN

Q. For the benefit of all people sitting here, what this other expert said was: 'The immune activation is affected by genetic factors in the host', so it varies from individual to individual. Perhaps could you tell the members of the jury what is meant, firstly, by 'immune activation'.

A. Could you just please repeat that comment?

Q. Yes. Would you like to read the whole paragraph in its context.

HIS HONOUR: It might be better. What page of the evidence is it?

MR BORICK: The first page of the second French report.

HIS HONOUR: P59.

Q. Would you read the first paragraph.

A. So my interpretation of this is - and I think we have known this for quite some time - that the way people behave or progress with HIV infection, and the progression is measured by the decline in their T cells or so on, or their clinical illness, is influenced by other factors. There is no doubt about that. It is influenced by other diseases they might have, it is influenced by their own genetic host make-up and so on and how people respond to HIV does vary from person to person. That is why we have people with HIV infection who die within a year or two of the infection if untreated and others who might progress for 20 years without becoming ill and any range in between, and what causes a person to progress with HIV is a very complex interaction of their own host genetic make-up and how they might respond to things and also the virus itself, how virulent that virus strain might be or how non-virulent the strain might be. You can't take away the fact that once infected with HIV you are virtually always infected with HIV and that if untreated you will die of the complications of that infection. The speed that that happens will depend on the interplay between the host genetics and the virus itself and also any interventions you might put in place, such as antiretroviral therapy.

Q. 'Immune activation', what does that mean.

A. 'Immune activation' really is the body's response to a pathogen. So when anything -

Q. Pathogens. You see, the jury don't know that. 'Pathogens' means -

A. Any organism that invades somebody will cause an immune response generally and that is the immune activation. It is how your body responds to the virus or the bacteria or the parasites.

HIS HONOUR

Q. Can you relate that perhaps to the common cold.

A. So when you are exposed to the virus of the common cold you may get a runny nose, you might get sick, feel unwell, headache, a fever. Another person might get the same virus infection in the family or something like that and just get a runny nose. Another person may, in fact, get virtually nothing, and sometimes someone might even get quite ill with that. So it is the same virus infecting everybody but how the people deal with that virus varies from person to person.

Q. So if you tested each one of those four people -

A. They all have the common cold virus present and they all have evidence of the immune response to the common cold but how their own body kind of manages it varies from person to person.

Q. And once you have been exposed to a particular virus, if you are tested at any time throughout your life for that particular virus, would it be shown in the tests that you had been exposed to that virus.

A. Not necessarily, no. So with some viruses and some infection, once you have an antibody detected against that virus in the blood, that antibody might be present for life. So that is why we test pregnant woman to see if they have had rubella, because if they have had it as a child we know that they are immune and, therefore, the baby is safe, but other things like Hepatitis B where we might have, for example, a vaccine or even the ordinary infection, you might lose antibodies after 10 years or so. Other things like the common cold, you may, in fact, lose your antibodies before next winter, so it varies tremendously from pathogen to pathogen, and there are even some pathogens where you don't make any detectable antibody response, so it various from pathogen to pathogen.

CONTINUED

With HIV, once infected, then the antibodies are present, it would appear from all the evidence, for life. There may be the occasional ones where it goes away, but you are essentially positive for life. And the reasons for that may partly be or may well be due to the fact that the virus is still growing in the person at various times all the way along.

XXN

Q. Is there a general acceptance of any theory as to why HIV behaves differently to other retroviruses.

A. HIV has some of the features of other retroviruses and has differences with other retroviruses. Again this is something you see in any family of viruses. You will see some cause certain disease and others cause completely different disease, yet genetically they are related. Electromicroscopically they might look similar so there's nothing surprising that HIV itself behaves differently clinically in the laboratory at the basic science level to other retroviruses such as HTLV1 or 2, or HIV 2 for that matter. Then there's a whole range of other retroviruses in other animal species that sort of are in the same family but behave differently.

Q. In your answer to his Honour he asked you about the common cold someone gets; is it a virus.

A. There's a number of viruses that cause the common cold but a particular virus, rhinovirus, is a common cause.

Q. And some people have severe symptoms which we all know about and some people get symptoms. Everybody gets symptoms when you get a cold.

A. No, not at all, people may not get symptoms. You can take many viral infections, even something more obvious clinically say like chicken pox where the clinical disease of chicken pox is very obvious, but if you look at everybody who is exposed and infected with chicken pox, they may not all get chicken pox, many of them may be asymptomatic, not have any disease or a mild disease. It's a continuum if you like.

Q. It's obvious that's what's happening with HIV too

because we know that lots and lots of people are positive HIV but don't know it, have no symptoms.

A. No, I would argue that a little bit because in people with HIV, the clinical course of HIV is pretty well eventually the same in everybody. When somebody is infected with HIV, most of them, 60% will get acutely ill, glandular fever-like illness, the sort of seroconversion illness, so they do get ill at that time, at least 60%, and those that didn't get that will then become asymptomatic. If you like, clinically they are not terribly unwell and then as time develops over the next decade or so they start to get the various manifestations of a weakened immune system that has been weakened by the HIV killing the T-cells or making them impaired in one way or another and then they start to develop the various clinical features of HIV. In my clinical experience and the published literature, all people progress down that pathway, and death is the ultimate outcome due to some manifestation of the impaired immunity from HIV. Not to say that at any given time point the person might be asymptomatic, and a person may be asymptomatic for years, but still the whole clinical illness, the whole course of the clinical disease is pretty straightforward.

Q. So the fact that it behaves differently within the host cell is explained by genetic factors.

A. How that whole clinical illness evolves over the life of the person will be influenced by the host genetic factors as you mentioned. Some people seem to go very badly with HIV and progress quickly and others go for a long period of time, long-term survivors or non-progressors, if you like, of HIV. That may be due to host factors, but it may also be due to the virus itself, some strains of the virus that are particularly virulent and others that appear to be less virulent. In fact, a very celebrated group so-called Sydney Blood Bank cohort in Sydney, which is really one of the most important HIV events where those people had a deficient

virus, they still actually ended up progressing into HIV. There are other things that interfere with that whole clinical picture that are not host genetic factors but are host factors, other things like the general health. If you happen to live in Central Africa and have other illnesses like high rates of genital herpes or high rates of malaria or high rates of tuberculosis, whatever it might be, those other illnesses themselves might also enhance the speed of the progress of the clinical disease.

HIS HONOUR

Q. Because those other illnesses affect the immune system.

A. Yes, or switch on the virus and the people are weaker anyway, they may be malnourished, all of those sorts of things, so the spectrum of clinical disease with HIV is well understood and there are many factors of the viral host and societal level, if you like, that interplay with that.

XXN

Q. In that answer and in an earlier answer you were indicating that the progression of HIV in the host cell is influenced by disease that the individual may have.

A. Other disease; it may well be, not always but can well be.

Q. AIDS is a syndrome.

A. AIDS is a clinical description, that's right.

Q. Explain that to the jury.

A. What the definition of AIDS is is somebody who has a positive HIV antibody test and who has clinical evidence of an impaired immune system, be it a certain type of infection, a certain type of cancer or malignancy, a certain type of brain dysfunction or dementia and assorted other less important ones, so an AIDS-defining illness is someone who is HIV specific antibody positive who has one of these specific features. Not to say that other diseases can occur independently of being HIV antibody positive; of course they can. You can have tuberculosis, you can have shingles or all sorts of

other diseases and not have HIV, but if you are HIV antibody positive, then you have AIDS.

HIS HONOUR

Q. Does it matter which one occurs first. Say you have got somebody who has never had any sexual contact, they happen to have gone through their lives to the age of 30 and they have never had a sexual contact, for one reason or another, and they develop tuberculosis. Then they have sexual contact after they develop tuberculosis, and as a result of that sexual contact they become HIV positive, or what we call HIV positive. They have got tuberculosis, they are HIV positive. Is that AIDS.

A. I'm not sure the answer to that to tell the truth. It's a very unusual scenario.

Q. Sometimes unusual scenarios help us to understand.

A. Yes. I think if someone had tuberculosis and they didn't have HIV, and then at some later time point develops an HIV antibody test after a sexual contact, I probably wouldn't call them AIDS, no, but I would be very concerned that they would in fact, once they have got HIV, be at risk of developing more severe tuberculosis than somebody else. Look, I'm really not sure what the answer to that would be. I wouldn't traditionally call that AIDS. Really AIDS is where you are antibody positive, then you get something else and really you are getting that other thing because your immune system is impaired, which is different.

Q. I understand that. One might ask the question if you are dealing with, say, a population in Africa, how do you know which one came first.

A. Overall in Africa we know that tuberculosis has been around for hundreds and hundreds of years and HIV has probably been around for a matter of some decades, maybe a little bit longer, depending on the theories. So in that situation tuberculosis preceded AIDS as a human disease.

Q. No, I meant if you have got somebody in Africa -

A. The key is you look at the other markers of HIV

infection, so if you had somebody who had an antibody test and they had tuberculosis, and you thought well, what did come first, if you looked at things like their viral load perhaps, or CD4 T-cell count, if you saw their CD4 T-cell count was very low, that would make me think clinically they have had the HIV infection for a long period of time and this tuberculosis manifestation is because their immune system is impaired.

Q. Is age a factor in making those kinds of assessments. Say you have got a 25-year-old with positive HIV and tuberculosis, is that a factor.

A. Yes, that's true because often someone who has acquired HIV sexually in Africa may well have other sexually transmitted diseases or other problems as well. So if I saw other things in a patient like that, that had severe genital herpes or they had shingles or they had thrush in the mouth or various things like that, that would also be a helpful indication that they had the HIV for a long period of time, and the tuberculosis has come later. It is complicated because tuberculosis is a difficult example here because what can happen is that TB is very common in Africa so people may well be exposed to tuberculosis in childhood or as a young adolescent or what have you and be infected with tubercle bacillis in their lungs and they might get HIV and become immunosuppressed and that allows that to break out, and then they present very ill with severe TB. You could argue the TB infection occurred in childhood well before their AIDS, but the sort of clinical manifestations of the tuberculosis in HIV are often much worse than that, not always, but much worse than they are in otherwise healthy people.

XXN

Q. Would you agree with Professor French in his last sentence 'It would therefore be more correct to state that AIDS is caused by factors in addition to HIV'. I read that as I think he accepted that means HIV is necessary, but it's not sufficient to cause AIDS. Do

you agree with him.

OBJECTION: MS MCDONALD OBJECTS

MS MCDONALD: That's not Professor French's evidence.

MR BORICK: I withdraw the question.

QUESTION WITHDRAWN

XXN

Q. Do you agree with the statement made by Professor French 'It would therefore be more correct to state that AIDS is caused by factors in addition to HIV'.

A. I think my interpretation is that it is absolutely necessary to have HIV to get AIDS. There are factors though that influence the severity of AIDS and the rapidity of clinical presentation and the types of presentation and there are lots of factors that contribute to that, as we have discussed, the host, the virus, the environment.

Q. I am referring to the use of the word 'caused'.

A. No, HIV is a cause of AIDS.

Q. 'AIDS is caused by factors in addition to HIV'. That's what he said. Reading that and interpreting that as you want to now, do you agree with him.

A. I'm not sure that I quite agree with the way it's expressed. I know I am hedging my bets here, but -

Q. Have a think about it over lunch. I just want to ask you a couple of other questions and you can have a think about that and see if you want to pick a horse if you like. AIDS illnesses, like tuberculosis, have been around for basically ever.

A. Yes.

Q. There are 30 of them at least, but they have been around for a very long time.

A. Yes.

Q. When were all these diseases first grouped together and described as AIDS.

A. All of that discussion happened really as people worked on what the clinical presentations of AIDS were. The first descriptions came from North America where very unusual infections were recognised, things like PCP or

Kaposi's sarcoma, otherwise extremely rare. They do occur in profoundly immunosuppressed people in North America but they basically occurred in a much more frequent manner than had ever been seen so then they were all occurring in the same sort of community group at that stage, gay men practising particularly high risk behaviours, so then they started to think how do you work out what these people have got, which diseases are important as representing the immune suppression of AIDS or in fact which diseases might be part of the general that people might get anyway. So they started to come up with lists of clinical syndromes that are otherwise pretty rare but seem to be far more common in this group than in the rest of the communities, and then, as the disease was found in other parts of the world, people then tried to build up their own sort of lists of disease that are associated with AIDS so, for example, in Thailand there's a particular fungal infection that is very uncommon in Thailand except in people that have HIV infection. Africa was also the same; they tried to develop lists of disease seen to be more common in certain groups of antibody positive people than in the general community, but certainly a lot of those diseases occur in both HIV negative and positive people.

Q. But AIDS as a word or syndrome, did it come into existence before 1983, before Montagnier found it in 1983.

A. The term AIDS, no; the term AIDS came well after that. There had been other descriptions of gay-related immune deficiency and so on. People were starting to recognise in certain big cities of the world that there are young men sort of getting unusual infections, and there were acronyms used and so on, most of which fell aside, and then the term AIDS was accused for Acquired Immune Deficiency Syndrome. There are other forms of immune deficiency of course where people might get unusual infection, particularly in the people who have had a transplant, or there's very rare congenital things, the

boy in the bubble type diseases, and they get an immune deficiency, but it was the obvious acquisition of this immunity, sexually and so on. That's why it got the name 'acquired immune deficiency'; you weren't born with immune deficiency, you caught it from somebody, and that's what was so novel about it, and that's where the term Acquired Immune Deficiency Syndrome came from.

Q. You spoke about virus classification earlier. What genus is HIV now classified as.

A. HIV is classified as a lenti virus, and it's within the retroviro family.

ADJOURNED 1.05 P.M.

RESUMING 2.20 P.M.

MS MCDONALD: If there is any way possible it would be very good if we could finish this witness by 3 o'clock. I know we may not be able to but if it is for the sake of five minutes - I will just flag that will enable him to get the flight he is booked on.

MR BORICK: Can have the arrangement of written questions?

HIS HONOUR: If you have got written questions you want to submit to the witness. Ms McDonald, do you have any objection to that course?

MS MCDONALD: No, as long as it is within limits, it is reasonable.

MR BORICK: I'll agree to the 3 o'clock, then clearly I will need to put some questions in writing.

HIS HONOUR: Mr Borick, you can do that.

XXN

Q. Take a disease, you think that that disease is caused by a virus; all right.

A. Yes.

Q. How do you go about proving that a particular virus caused the disease.

A. So the question is really whether if you have a disease, whether a virus is causing that disease -

Q. The way I expressed it was you suspect that this is caused by a virus.

A. Yes. I guess, the first analysis is really of what the clinical disease is: is it a disease that seems to be a communicable disease, for starters, and if it is a communicable disease, what sort of transmission is occurring? Because that gives you an idea of what sorts of things to look at. When a disease appears - for example, say SARS - it is very quickly apparent that it is communicable and it is mainly being spread by the respiratory method, so, therefore, you look for pathogens that kind of fall into respiratory spread. So you look to see what type of communicability there is with the disease. Then you look to see what the disease

actually is: is it an acute illness? Is it something that presents and then the person recovers, or is it something where they might get sick a little bit but it is not until a long period later that they get really ill or get some other complication, or is it a disease where many people don't seem to have any clinical manifestations and others do? All of those sorts of things guide you on groups of diseases or groups of organisms that we already know about that might cause similar illnesses. In the context of something like HIV, what really started was the description of people becoming ill with very unusual infections and that they appeared to have a common epidemiological link - they were gay - for example, in the early cases of San Francisco, Los Angeles and New York, where gay men who were practising this risky behaviour were getting these illnesses. Then you start to look for pathogens that are associated with sexual transmission because that's what the clinical and epidemiological evidence was suggesting. Then you start to look at what sort of pathogens might be spread that way and how you might look for them. It was very quickly done, that it wasn't one of the viruses that we knew about or bacteria for that matter, such as herpes virus or Cyto-Megalo virus or Epstein-Barr virus but it was something else. Then it is a question of working out what is it? Something else. Then one takes a broad brush approach at trying to identify what this cause might be. With the discovery of every agent there's usually a series of bits and pieces of evidence, when put together, start to make a coherent story. Things that don't fit that coherent story tend to be rejected and people look to add to that story to make it a reliable story that this particular agent is causing that disease. In the context of HIV, we have the clinical picture that they are immunosuppressed, that it was communicable, so then, when looking in the lab, people knew there were diseases, such as retroviruses, that cause

immunodeficiency or it might be perhaps spread that way, although that was controversial and people started to look for these novel agents, these novel - in this case - viruses. Then people tried to look at the tissue of infected patients, maybe look under the microscope, see what sort of damage there was. It was apparent with HIV that the lymph nodes - sorry, the characteristic with the people with this syndrome, their lymph nodes were very abnormal, so whatever it was that was targetting the lymph nodes were not targetting the brain or the liver or something like that. People took lymph nodes and tried to see what was in them. For example, in trying to culture it they would take the lymph node and grind it up and put it into a whole range of cell lines that might be used to culture a virus - a whole range of them. It turned out that, in fact, as the French group found, that the virus could grow in lymphocytes and then it was found they could grow in lymphocyte-like cell lines. Then people got some evidence of retroviruses there because there was reverse transcriptase, there was some preliminary electron microscopy data to suggest that it was a retrovirus or retrovirus-like agent there and it wasn't other things. Then, having established that in a couple of people, as the French group did, the next step was to see whether this could be done in lots of different places and, sure enough, it was, it was done in the United States, it was done in Australia, it was done in the United Kingdom and everywhere. At that same time the clinical and epidemiologic features are also being worked on by the researchers and experts in those sorts of areas and it became apparent that it wasn't just the disease, as initially thought, of gay men but that it could be spread sexually between men and women, or that it could be in the blood supply, and that made sense because we knew it was a virus that could infect lymphocytes, so the blood supply then became another area of looking and so on. I don't want to go into the whole sort of

discovery of HIV but it is putting together a lot of small bits of evidence from the lab, from the public health, from clinical, from the epidemiologic, that started to develop a story and that is exactly the process that happens with any other pathogen. One of the big differences, though, I guess, with HIV, compared to the newer things, like SARS or Avian flu, is that we didn't have all of the technology then that we had now - mind you the technology in the 1980s was way better than what was available in the 1950s. Like with everything in science, as things get better, it is easier to gather the evidence and it is easier to gather different types of evidence to come up with a story of a virus being associated with this illness.

HIS HONOUR

Q. When you see criticisms of 1983 or 1985 work, you have to consider those criticisms, the time when they were written or made, and have regard to what has occurred since -

A. Of course.

Q. - in making any assessment of those criticisms.

A. Of course, one has to consider how the work was done in 1983-85. Of course we would do it differently now but that's the way it was done then and the reason, I think, as I said before, that we continue to go back and refer to that original work is that as all the other evidence has come in, what they said then has held up, whereas all the other sort of pathogens and causes of AIDS - be it drugs or lifestyle or popping-uppers or whatever it was - all of those sorts of things have fallen away and so we don't really talk about those any more. It is entirely appropriate to have a discussion about what was the cause of, for example, AIDS then, just like we do with anything new but as the evidence comes in, the other ones fall away. I think this whole discussion about what is the cause of AIDS is now a 20-year-old discussion. It has gone, finished, and we have moved on.

Q. If you go back 50 years from 1983, to say 1933, no-one would have even dreamt of what you are talking about now - different sciences and different techniques in 1933.

A. Yes, the technology in 1933 would have been completely different to what it is now.

Q. That is to be expected.

A. That is to be expected.

Q. That's the way things happen. What was regarded as absolute truth in 1933 is regarded as rubbish in 1983. For example, use of heroin; heroin was commonly used in 1933, in 1983 it is a crime. Things like that happen, don't they.

A. Things change, you're quite correct that things change. The principal of organism and discovery of disease have actually been going for centuries. It is more of the technology to confirm or disprove a theory is improved. The ancient Greeks had some sensible theories and some nonsensical theories about disease transmission. As we went on, with time, more and more theories developed, Professor Koch, and those things came through. Now we have the technology to prove or disprove those theories. With infectious diseases, take 1933, influenza was first isolated from a human in 1934, that was the first time the technology was available but people knew in 1918 in a pandemic how the virus was transmitted, what the disease was, they knew it was a virus, they couldn't demonstrate it because they didn't have the technology, they couldn't culture the virus but, of course, the theory of influenza being the cause of that disease was proven when they cultured the virus and as more technology comes through, that is really the story with HIV.

Q. I have to go quickly with you today - 50 years from now how can you be sure that the theory of HIV causes AIDS which you are proposing now is not regarded as rubbish.

A. Of course I could not predict what would be happening in

50 years from now. What I can suggest, on the way the AIDS debate has developed, and the way other infectious disease theories have developed, this is really fitting, the typical theory of an infectious agent causing a clinical disease.

Q. Going back to the virus culturing. In order to prove that a virus causes the disease, you have to start with a virus culture.

A. Yes.

Q. Don't you have to start with a pure culture preparation.

A. No. In a sense, no virus culture from a clinical sample is a pure thing. What you're taking is material from a patient which contains all sorts of junk - cells, serum, proteins, bits and pieces, as well as the organism and you put that into the culture of cells and you see what virus comes out or if a virus comes out. If you want to go on, perhaps, and analyse that virus further, to understand what it is, what it does and so on, then you may want more pure preparation, but the actual process of isolating a virus from a clinical sample is in fact quite a messy procedure, truth be known.

CONTINUED

Q. But by a 'pure preparation' I mean at least ensure that it's free of anything that will confuse the issue, bearing in mind that you are looking for proteins and nucleic acid. Do you agree.

A. I don't think you need a virus culture. I'm not quite sure really - discussions gone a couple of days about what 'pure' actually means but to detect the genetic material of a virus it doesn't have to be pure in that there is nothing else there except just that viral protein.

Q. I'm accepting that but I'm saying, but you've got to get rid of anything that can confuse the issue. For example, what are endogenous retroviruses.

A. Endogenous retroviruses are components of retroviral viruses, are part of our genetic make up.

Q. That are in cells.

A. That's right.

Q. And in broad terms, coming from within us.

A. That's right.

Q. You want to be sure that you are not getting a reaction from an endogenous retrovirus, don't you.

A. You would want to be sure of that. There are very few endogenous retroviruses that are present in man, or animal, for that matter, that can actually be cultured, most of them are just small amounts of genetic material and incomplete viruses. There are very few endogenous retro-culture. One way around this of course, and in fact Montagnier's group did this in 1983, that they take the patient sample which they add to the donor cells to grow the virus but they also look at the donor cells by themselves and they go through exactly the same sort of process to make sure, to see, and nothing comes out of those cultures, it only comes out of the cultures where clinical material from a person with the disease occurs.

Q. You referred to 'Montagnier' then, did Montagnier's experiments have proper controls.

A. Montagnier's experiments had controls, they had - it depends on what you mean by 'proper controls'. I think

they had controls that were entirely appropriate for the experiment, yes, they are not the controls that we would run nowadays.

Q. What is the difference between the controls that he had and the controls you would now require.

A. It's a bit hard to have controls for something that wasn't known to exist until they did the work. They didn't know HIV was there so they took the patient's sample and they took the donor cells that they use for the cultures and they left some donor cells without the clinical material and added the clinical material to the other. So in fact that's the ideal control and that's the principal behind controls for any cultures or laboratory tests, you know, negative controls as we heard with antibody testing. So that control is entirely appropriate. If we are doing virus cultures now routinely in the laboratory there are different sorts of controls we use, mainly because we are wanting to ensure that what we are producing for patient management is as good as it can be. Just like with the antibody tests, you might have negative controls and positive controls.

Q. Better move on. Have you read Mrs Papadopulos's description of Montagnier's experiments.

A. I have read some of the material that's been submitted here, yes, that relates to her opinion of what -

Q. Has she correctly described the experiments undertaken by Montagnier.

A. I would have to read them again to see but - I'd have to read them to see but my gut feeling is no, that she hasn't because she has misinterpreted what he has done and what he says.

Q. Have you read it.

A. I would want to read them again before I comment on them.

Q. That is better than saying she has misinterpreted at this stage; do you agree.

A. No, I think she has misinterpreted the story of HIV, she

bases that on her interpretation of what Montagnier said about the '83 work and I think it is misinterpreted, but I'm very happy to read it again.

Q. Your specific comments on 1, her description of his experiments, has she got that the right, and 2, what do you have to say about her criticisms of his experiments. Would you do that. Not now.

A. Certainly. Yes, I would be happy to.

Q. You won't be getting on that plane if you did that now.

HIS HONOUR: Might I say it might assist me, Ms McDonald, if Dr Dwyer's further evidence can be given orally rather than in written form. Mr Borick has flagged the question now, Dr Dwyer has got some homework to do, but if some arrangement can be made either by way of video link or Dr Dwyer coming back. I must say I find it much easier to understand this evidence when it's being given orally than trying to interpret written material.

MR BORICK: Could I suggest we break at 5 to 3, then we can talk and see what we can work out. I'd just like to get as much evidence as I can.

HIS HONOUR: Yes, I just flag that, that's all.

XXN

Q. You have read Montagnier - obviously read Montagnier's paper.

A. I have and I have spoken to him about it, yes.

Q. What evidence in that paper convinced you that Montagnier proved the existence of HIV.

A. That's not the interpretation he put at the end of the paper but what he did really suggest was that they have found evidence of a novel retrovirus that may be associated with the clinical syndrome as it then stood, he didn't say that that was the cause of AIDS. I just have to check the last paragraph of his paper but I think he discussed - in fact I think I have it.

Q. You are checking his paper now, are you.

A. His last paragraph - the statement is 'The role of this virus - which I have identified - in the aetiology of

AIDS remains to be determined.' So I don't think they said at the time 'This is the cause of AIDS' but this was evidence, the first evidence that a novel retrovirus might be associated with this clinical syndrome and that is then where all the further work continued to prove - to continue to support that hypothesis.

Q. The question then was 'What evidence in the Montagnier paper convinced you that Montagnier proved the existence of HIV'. We are not talking about AIDS now.

A. The evidence that this paper shows, to my mind, is that they identified something coming from clinical samples from sick people that was a novel retrovirus, that appeared to be different from other retroviruses that had been discovered and that this wasn't present in normal cells and that therefore this is what needed to be confirmed and further examined as to whether this really was the cause of HIV, or AIDS. HIV infection is really the correct term, and then others, including the Americans, much to their chagrin who were a bit slower about it, they confirmed the same findings, as did everybody else.

HIS HONOUR

Q. What paper are you referring to.

A. This is the very original transcription from the Journal Science, with Montagnier's group called 'The Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Deficiency Syndrome'. It's the classic paper that everyone has been referring to.

EXHIBIT #A17 PAPER ENTITLED 'ISOLATION OF A T-LYMPHOTROPIC RETROVIRUS FROM A PATIENT AT RISK FOR ACQUIRED IMMUNE DEFICIENCY SYNDROME' PUBLISHED IN VOLUME 220 OF SCIENCE TENDERED BY MR BORICK. ADMITTED.

HIS HONOUR

Q. I assume it was in '83 was it.

A. 20 May '83.

XXN

Q. Are you aware of the interview that took place between

Montagnier and the French journalist Djamel in 1997.
A. I have heard that there was that interview, yes.
Q. Have you ever read that.
A. Not fully.
Q. Are you aware that Montagnier said in that interview that 'The analysis of the proteins of the virus demands mass-production in purification, it is necessary to do that', then he went on to say that he did not purify it. Are you aware of that.
A. Yes, I've seen that discussion. I mean what it means, this was the preliminary evidence that something was growing in culture that was new, a new virus. The next step of course is an enormous process to determine what the viral proteins were or the structure would be, what the genetic structure would be, all of the sorts of normal things that we do when investigating a new pathogen. Of course to do all the work with developing, for example antibody tests, or studies of the protein you would need to make larger cultures to grow enough to undertake that sort of work. He might have done - and he did continue to do it over the next -
Q. You accept that that's the first time, after 1983, that he admitted that he had not purified the virus.
A. I've got no idea if he has said that on any other occasion.
Q. It's a significant fact, don't you think.
A. No I don't think so because I'm not quite sure what was meant by the journalist and Montagnier when talking about purifying. If they want to go on and do further studies with the virus, yes like everybody else they would be purifying large amounts of virus and extracting protein and genetic material, doing the analyses and so on. He may not have purified that particular virus as described in his paper but that's because it wasn't required for the scientific evidence he was producing.
Q. Keep your answers - just from the point of view of time because there are a couple of topics. You said in your response to the report that 'In general virus isolation

and ... viral genetic material via NAT are the gold standard tests for confirming infection'. In that answer what did you mean by 'gold standard'.

A. Gold standard relates to the idea that when you introduce a new test to diagnose an infection you want to know how good that test is. Ideally you would like to compare it to something that you already know is a very good test, but unfortunately when you're discovering something for the very first time then you've obviously got nothing to compare it with. As time goes on and you start to develop all sorts of different tests then you try to measure their relative ability against each other to best diagnose the infection.

Q. Sorry to interrupt but would accept that neither Montagnier nor Gallo had gold standard.

A. Well there was no gold standard to use in those days, no.

Q. So you accept that proposition.

A. That Montagnier didn't have a gold standard to test?

Q. That's right. You accept that.

A. Yes, I accept it because it makes no sense.

Q. The same for Gallo.

A. Well the same for Gallo.

HIS HONOUR

Q. You said 'it makes no sense'. What do you mean by that.

A. Well it makes no sense because what Montagnier's paper does is describe the new virus, he doesn't describe a diagnostic test, okay, so he has got nothing to sort of compare it with. If he then, as he did and others did, went on to make a diagnostic tests well that's when the argument and discussion about should we have a gold standard, how do we know whether your test is better than the American or Australian test, whatever. That's when you start to wish you had something to which you could compare the new testing. His paper is not a description of a diagnostic test for AIDS, it is a description of a possible new virus causing a clinical

disease.

Q. Is his discovery of that virus - that is what is now known as the HIV virus - and the methodology that he used different from the discovery of other viruses, given the differences in -

A. No, I don't think - what he did was in fact based on, to some degree on work that Gallo had done before work on discovery of other retroviruses. So in fact the scientist who is a senior author on the paper she went to Gallo's lab to learn how Gallo detected HTLV; different virus but same family. So the principles he followed were entirely reasonable with the current evidence of the time and also were entirely consistent with the way we might go about discovering new viruses for other things that are not immunosuppressants but might be causing immune suppression, or something like that.

XXN

Q. You have spoken about the nucleic acid test or the NAT, which is now being used, the genomic sequence. In effect we are talking about the viral load, aren't we.

A. No, the viral load is a type of nucleic acid test but a nucleic acid test is not just the viral load. The first nucleic acid test - well, nucleic acid tests aren't designed to pick up either DNA or RNA. It so happens that you can quantify them to give a viral load.

Q. What sort of testing is nucleic acid testing; is that known as PCR.

A. PCR is one of the NAT technologies.

Q. Can you isolate it for quantitative assessment.

A. You can.

Q. You realise that the man that discovered it, Malla, said you can't.

A. I have never heard him say that you can't quantify material using PCR.

Q. If you do quantify you would expect to be getting pretty good results which are mathematically sensible.

A. Well, I'm not quite sure what you mean by that question.

Q. I'll show you what I mean. Look at annexure 5 to Dr Turner's affidavit. Have you got that.

A. Yes.

Q. It will save time if you read it because I want you to comment on it.

A. Yes.

Q. Obviously you need to look at the figures.

A. Yes, I know this paper.

Q. Do you agree with Dr Turner's conclusion about it that it in effect demonstrates the concept of using HIV viral load is just, on those figures it's incomprehensible.

A. I think he has completely misinterpreted the data in this. What this data is telling me is that there are three different laboratory types of quantitation that are being used, all of those assays need to detect the specific part of the HIV genome. Some of the original material that was produced by companies only actually picked up the North American strain of HIV and completely missed the African strains of HIV. So some, and in fact the company that produced the RTPCR assay, which is Roche, in fact had to re-alter their product to make sure that it picked up all genetic variations of HIV and they now do and those assays are now used. Our own lab has done exactly, and published, the same sorts of experiments and it's quite well recognised that unless your PCR primers, which are what start the reaction, are to highly conserve parts of the genome you will miss certain strains of HIV. That is quite well-known and understood.

Q. Thank you for your answer. We have finished with that for the moment. I want to just turn to your laboratory techniques. You are just an ordinary doctor and someone comes in and you test for HIV and you send them off to a laboratory. You would get, in Australia, some ELISA tests, maybe a Western Blot, that's what would happen.

A. Yes. Well, if it's positive, yes.

Q. What would you expect to appear in the report from the laboratory. You're the doctor, after the report, what

would you expect.

A. Well if I sent a person off for a blood test for HIV antibodies I expect to get one of three things back. I expect to get a test result back that says 'HIV antibody testing negative', and then perhaps some comment about 'retest if you are worried or if, you know, in 10 months time' or something like that. If the test is positive I expect to see 'HIV antibody test positive' and I expect to see 'positive by enzyme immuno assay', and the Western Blot, 'positive by Western Blot' or 'reactive by Western Blot'. And the third thing you can get is when the result is perhaps indeterminate, which is a very small proportion but a proportion. So you either get - I'm expecting to get back either, a negative result, so to speak, a positive result, or an indeterminate result.

Q. You mentioned with the Western Blot you might just get reference back - what's the word I want.

A. Reactive.

Q. Reactive. That's not possible, is it, it's either positive or it's not.

A. No, no, they can be indeterminate; I said the result can be positive, it can be negative, it can be fully reactive, which would be consistent with being positive, or it can be indeterminate because the required bands that we called the Australian algorithm yesterday, are not there.

CONTINUED

Q. Would you expect on the form for the name of the individual who conducted each of the tests to be there.

A. There are certain requirements by law as to what has to be written on a request -

Q. Tell me what they are.

A. Well, I would expect that on the request form it would be a NATA approved laboratory, that the patient details are there that identifies either the patient's name, initials, date of birth, the laboratory number so the lab can trace exactly which one it is, and the name of the ordering doctor who ordered the test and also the name of the person who runs the laboratory from where that result is generated. I'm not sure of the exact legal requirements as to what is on the form but that is certainly what is on our form in our lab and from what I see from most of the other laboratories.

Q. You as the doctor, would you need to know who conducted each of the tests.

A. I need to know who is responsible for conducting the tests. I need to know that that laboratory is headed by a pathologist and is running NATA approved laboratory. I certainly don't need to know the name of the technician or the scientist who actually performed the test but I would expect, if I wanted to - in fact, I can expect - to go back to that laboratory and if I so asked, I could ask what was the person's name who did that test and that would be traceable.

Q. You would get the answer and if you wanted to go back and see the western blot result, you would expect to be able to see that.

A. We store our western blots for a defined period of time. There are formal requirements for the storage of clinical samples in laboratories, like you have to store the serum for a year or something like that. Most laboratories will store their western blot. It depends on whatever the formal requirements are but within reason you will usually be able to go back and see the western blot.

Q. In your laboratory, what is the time limit.

A. For storing western blot, I'm not sure, but I know that we keep the original serum from the patient for a year.

Q. That would be one of the things I would like you to elaborate on, as to exactly what laboratories should produce.

A. Okay.

HIS HONOUR: Mr Borick, how much longer do you think you will be with the witness in an oral cross-examination?

MR BORICK: About an hour and a half.

HIS HONOUR: Ms McDonald, I would prefer to do it by way of the witness returning.

MS MCDONALD: Yes. I heard what your Honour said about that before. We will arrange something.

HIS HONOUR: Doctor, you have got a little bit of homework to do. If you wouldn't mind doing that before you are next cross-examined. Thank you for your time.

WITNESS STANDS DOWN

+THE WITNESS WITHDREW

MS MCDONALD CALLS

+DAVID LLEWELYN GORDON SWORN

MS MCDONALD: I just want to check, before I question this witness, I have been assuming that for the purpose of the leave to appeal your Honour will have the trial transcript as well. For example, there was evidence from this witness about Mr Farenzee's clinical status at various trials.

HIS HONOUR: I will have to go back to the trial transcript to look at it, but the answer is yes.

MS MCDONALD: I can certainly identify the parts I am going to look at.

HIS HONOUR: Yes. Mr Borick, that is appropriate, is it not?

MR BORICK: Yes. That is why we asked your Honour to do it.

HIS HONOUR: Yes.

+EXAMINATION BY MS MCDONALD

Q. Have you provided the court with a curriculum vitae.

A. Yes.

EXHIBIT #P71 CURRICULUM VITAE OF PROFESSOR D.L. GORDON TENDERED BY MS MCDONALD. ADMITTED.

Q. I just want to ask you about one particular position that you have held until very recently in relation to what that position involved. In your CV you have described being the Chair of the Clinical Drug Trials Committee, Flinders Medical Centre and the Flinders University from 1998 up until the present. What does that position involve.

A. The Clinical Drug Trials Committee reviews submissions from investigators who are planning to conduct any type of clinical study on patients from the Flinders Medical Centre or affiliated institutions. So, if you like, it is the first part of the process of the ethical review of the clinical study. So as Chair of that, I oversee the running of the committee and chair the committee meetings where we discuss the nature of the clinical

trial, if there is any concerns that we have about that particular clinical trial, any alterations to the clinical trial protocol that are required, basically to ensure also the safety of the clinical trial and that it is a statistically valid trial and it is likely to give clinically useful results.

Q. What sort of clinical trials.

A. These are clinical trials in all areas of medicine. So, they, for example, might be clinical trials of a new treatment for heart failure, clinical trials of the new anti-clotting drug to prevent clotting after surgery. A number of trials relate to new drugs for cancer treatment. So it is really the entire range of clinical trials.

Q. During your time as Chair on that committee, have you had to consider clinical drug trials in relation to HIV and anti-retroviral medication.

A. Yes, I may be involved in those trials so in that situation I would step out of the room.

Q. So your involvement with those sort of trials, that is with the antiretroviral medication trial -

A. Might be as an investigator or clinical investigator. People who are on the clinical committees who have their own trials involved step out so that the trial is assessed in their absence.

Q. How many clinical drug trials have you been involved in in relation to antiretroviral medication or any sort of HIV medication.

A. Probably about three or four over a number of years.

Q. Can you give us an idea of what those have involved.

A. Generally they involve comparing a new HIV drug with an existing therapy. In the very early days when people were trying to evaluate HIV drugs, they were compared with a placebo but once those drugs were shown to be effective, and this would be the usual practice in medicine, the potential advance in therapy would be compared with what was the existing therapy at the time. So, far example, if you knew that a drug such as AZT was

effective and saved lives, then you couldn't go back and compare the new treatment, say two new drugs, with no drugs at all because that would be unethical. That would apply to most of the trials I oversee, comparing the new therapy with what was the best existing therapy and it is not appropriate to withhold effective therapy in someone in giving a placebo, and that would apply to HIV and it would apply to people with high blood pressure. People with cancer, you couldn't withhold existing therapy with that. So that would be the standard way in which advances in therapy are achieved or evaluated.

Q. You provided two reports for these court proceedings, one dated 10 July 2006 and a second supplementary report dated 31 July 2007.

A. That's correct.

EXHIBIT #P72 REPORT OF 10/7/2006 TENDERED BY MS MCDONALD. ADMITTED.

EXHIBIT #P73 REPORT OF 31/7/2007 TENDERED BY MS MCDONALD. ADMITTED.

Q. Do you have your two statements in front of you.

A. Yes.

Q. I will just have you talk to the two statements.

A. Sure. I will start with 10 July.

Q. I might just take you to certain parts, if that is all right, just in terms of time.

A. Sure.

Q. In the second paragraph of that first statement 10 July you make a fairly strong statement about the Perth group in that you say that 'the group has no credibility at all amongst scientific or medical groups with expertise in the field and their conspiracy theories are akin to UFO supporters'. Before you became involved, were you aware of Ms Papadopulos-Eleopulos and the so-called Perth group.

A. I had known her and the group in Perth who had been

purporting to support this theory.

Q. Their reputation amongst the medical and scientific community.

A. I don't think they have any reputation or credibility amongst the scientific community.

Q. Had you heard of any AIDS denialists before this.

A. I think the best known AIDS denialist was Peter Duesberg from California and he was the - I guess he was sort of the leader of the AIDS denialists in the mid 80s. He didn't suggest that HIV didn't exist, he was perfectly comfortable with the idea that HIV exists but he proposed that HIV was an accidental passenger, if you like, in people who had HIV and he proposed at the time various other therapies related to behavioural factors in people in relation to sexual behaviour and other hypotheses as to what AIDS might be due to. So certainly he strongly publicised those views at the time and published those views at the time.

Q. So even amongst this small groups of AIDS dissidents, those who suggest that HIV has not been proved to exist are a minority.

A. I think the Perth group is unique. As far as I'm aware, the Perth group is unique in that suggestion and, as I said, Duesberg has never suggested that HIV didn't exist, as far as I'm aware. He debated whether HIV was associated with AIDS or not but certainly didn't dispute its existence.

Q. I want to turn then to the next page of your report of 10 July. There is a heading 'Epidemiological'. Is it your view, as someone who has worked in this field for many years, that epidemiology has a role to play in identifying viruses in training a horse.

A. Absolutely. I think it is the key part of finding and confirming an association between a pathogens or some outside external agents, for example, smoking and lung cancer. The epidemiological data is very critical. As Dr Dwyer said right at the very beginning, there was clear evidence epidemiologically that this disease was

occurring in a particular group of people. So epidemiological association is fundamental to concluding that there is an association between a disease and a particular pathogens, and that, in fact, was accepted by Koch in the original, Koch postulates, that the distribution of the disease had to have a relationship to the distribution of the pathogens.

Q. And you set out some examples there of the sort of epidemiology that we have in relation to HIV.

A. Yes, that's correct.

Q. Can I go over the page. There are two headings on that page 'Isolation' and 'Pathogens'. Do we take it from that paragraph that in your view the virus has been isolated.

A. I don't think there is any question of that at all.

Q. You have just sat through the evidence of Dr Dwyer. Did you agree with his evidence.

A. Absolutely. I have heard from a number of witnesses here. It is clear that the HIV virus has been isolated.

Q. Then, in para.3, you talk about transmission.

A. Yes.

Q. And you give some examples of where it has been known for the virus to have been transmitted.

A. That's right. When one is trying to attribute a disease to a particular agent, one of Koch's original postulants was that the isolated pathogen could transmit the disease to a susceptible host and then the host would eventually develop that disease. Now obviously for something like HIV, it is not something that you could do deliberately but there have been a number of accidental instances where this has been confirmed. For example, there have been laboratory workers who have been dealing with concentrated cultures of the HIV virus and have suffered a needle stick injury and they have subsequently been infected with the same virus. There has been mention previously about the Florida dentist case. I don't know how much detail you have gone into that previously.

MR BORICK: There was lots about it.

A. The Florida dentist, in the early 90s I think it was, I think 1991 or 1990 it was recognised - there was a group of patients or one patient particularly called Kimberly Bergalis, I think, and she was found to be HIV positive and had no known risk factors and she eventually made a link with the dental treatments she had had. Subsequent to that, the dentist was found to be HIV positive, and around about 1,100 of his patients were tested for HIV and I think approximately 10 of those patients were found to be HIV positive. So they naturally looked to see whether those patients had other risk factors for HIV. Four of them had likely other risk factors for HIV, so they were not attributed necessarily to that case. There was one indeterminate one where it was unclear whether they had other risk factors or not and five others that had no other known risk factors for HIV. Subsequent to that, viruses from a number of those groups were sequenced and there was a very strong sequence link between six of the 10 patients between their HIV virus strains and the denialist's HIV virus strains.

Q. Do you know if they subsequently traced what happened to those various players in that scenario.

A. Certainly in the mid 90s, the dentist had died, Kimberly had died and several others had died and I'm not sure of the current status of the remaining ones but I would be surprised if too many of those patients were still alive because this was in a time where the effect of the antiretroviral treatment which we have today was not available.

CONTINUED

I think there's other instances. I think someone, might have been Professor Cooper, alluded to a similar instance of a Sydney surgeon where he was using local anaesthetic, a plastic surgeon. He operated on a series of patients one morning. He probably introduced some blood from the first patient into a local anaesthetic vial. The first patient happened to be HIV positive and then the subsequent patients that were operated on that morning, can't remember the number, but a number of them became HIV positive.

Q. I think we heard during the evidence of Professor Cooper that that was a matter that was extremely thoroughly investigated.

A. Yes.

Q. Because it involved the Medical Conduct Board.

A. These are not isolated examples. There are many instances of direct linking epidemiologically and virologically between patients who have contact with another HIV person.

Q. This is probably dovetailing with the subject of sexual transmission, but have you produced to the court a very recent article published in January of this year in relation to clusters of the virus.

A. Yes, this is another example which was well documented. It's a rather unusual -

Q. Before you start telling us about it, I will tender it so his Honour can have it in front of him and I will ask you some questions.

EXHIBIT #P74 EPIDEMIOLOGIC INVESTIGATION OF A CLUSTER OF WORKPLACE HIV INFECTIONS IN THE ADULT FILM INDUSTRY: LOS ANGELES, CALIFORNIA 2004 BY TAYLOR AND OTHERS TENDERED BY MS MCDONALD. ADMITTED.

Q. When was this article published.

A. It was just published previously in Clinical Infectious Diseases in 2003.

Q. Just tell us about what happened in relation to this.

A. This was a study of adult film sex workers, I guess, in

the pornographic film industry. The practice in this industry is to perform regular PCR tests for HIV at monthly intervals to try and detect the presence of HIV and obviously then to prevent risks of transmission to other actors or performers or whatever you like to call them.

HIS HONOUR

Q. I think 'performers' is probably a more apt word because they are not acting.

A. That's true. These people have well defined sexual interactions with a number of people. Because they have that, and they also have well defined PCR tests done every month, it's possible to determine with a fairly high degree of accuracy when they became positive for HIV who subsequently had contacts with them and who subsequently became positive, so it's almost a prospective analysis, if you like, when all of that information is available. In this case there was one male performer who tested negative on 12 February 2004 and 17 March and then on 9 April, just a few weeks later, he tested positive. In between that time he had had a film shoot in Brazil, I think it was, where it's likely he acquired HIV. When this performer was found to be PCR positive, the contacts that he had had in the intervening time were tested for HIV, and there were 13 female partners. All of them had tested negative for the virus in all their previous tests and after the performer had been in contact them, three of them became HIV positive and there was 100% viral identity between them. This is just another one of many instances documenting the transmission of HIV.

XN

Q. What do you mean by 100% viral identity.

A. The sequence is identical.

Q. If we go to p.303 there is a diagram.

A. Very complicated diagram.

Q. Are you able to assist us at all as to what that is intended to represent.

A. Basically the index patient is the one right in the middle. It's showing you the negative result for PCR. It says negative 2/12 and negative 3/17 and positive 4/09. This is the US so it's the other way round. 4/09 means 9 April, 3/17 means 17 March. Then the arrows refer to the sexual contacts and subsequent sexual contacts and they show - I have not counted them up - I think it's 13 contacts around there, and three positive ones shown. One of them is on the right hand, almost 3 o'clock from the index where they had a negative PCR on 20th of the 3rd and positive on 13th of the 4th.

Q. The other two squares we see are the other two.

A. I'm trying to find the other two positive ones. One is above at about 11 o'clock where they had a negative PCR on the 14th and a positive PCR test on 7/5, 7 May, so about five weeks later. I can't see the third one there. These sorts of diagrams are done to illustrate the sexual contacts and potential secondary sexual contacts.

Q. One of the criticisms that's been made of the sorts of tests that have been used to look at this question of sexual transmission is that double blind studies have not occurred.

A. I'm not sure what you mean by 'double blind studies' in relation to sexual transmission.

Q. In relation to transmission; I added the word 'sexual'.

A. I'm not sure I follow your question.

Q. I will come back to that. Can I just move back to your report that I was asking you about. At p.4 you have a big paragraph in the middle beginning 'The HIV antibody cut-off between negative and positive is set deliberately low'. You see that.

A. Yes.

Q. In that paragraph you make some comments about the antibody testing.

A. Yes.

Q. You are aware that there's been evidence in this court about how reliable those tests actually are.

A. Yes.

Q. And there's been talk about false positives and false negatives. You have obviously had extensive clinical experience over the years in that you would regularly organise for your patients to have antibody tests conducted.

A. Yes.

Q. In your experience how common has it been to see a false positive test result.

A. I suppose there's two, I see two types of false positives, if you like. We sometimes see people who have a very low probability of having the disease, for example, routine pregnancies, so the likelihood of them having HIV just by chance is very, very low. So a small number of those people have weak reactivity in the HIV ELISA test. They are virtually always false positives. They are people that have no risk factors for HIV, they have no progression to HIV. If you follow them up by doing the same test six months later, they may or may not have weak reactivity, so we call those biological false positives. This is well recognised phenomena in all serological tests.

Q. Going back to your answer, you indicated that a small number have a weak positive, or a weak reaction I should say, to the ELISA test.

A. That's correct.

Q. What about the Western blot.

A. Those patients would usually have a negative Western blot result or occasionally they would have an indeterminate Western blot result. I don't recall seeing anyone like that who has a clear-cut positive result or has had detectable virus present.

Q. So it's your evidence in that very small group who may give a weak reactive result to the ELISA they can then be excluded as being HIV positive on a subsequent test.

A. Yes. We see exactly the same thing with hepatitis C testing.

Q. Were you about to talk about a second category.

A. The second category is positive results or what people consider likely to be a true positive result, and patients who have true positive results generally have very high reactivity. The reactivity can be expressed as a sort of ratio called the sample to cut-off, but basically the cut-off is 1, so the people that have low reactivities often have ratios of 1.5 or 1.8 or 2 or something like that. People who have true positive results usually have very strong reactivity, so their cut-off might be 20 or 30 or 40 or 50 so there's really two different types of positives that you get in the HIV test. There's these weak positives which we expect a proportion of weak positives to occur, they occur in the low risk patients, and them there's clear-cut positives which occur in patients who we may already be almost certain that they have got HIV. For example, if they had PCP infection, we would know that almost always would mean that that person is going to have HIV, so these people have high reactivities. They may already have some of the manifestations of HIV infection. It's very easy to sort out those usually.

Q. We know from your evidence in the trial that you were Mr Parenzee's doctor for a period of time.

A. That's correct.

Q. In terms of how reactive his initial testing was, do you have that with you.

A. He had a highly reactive HIV test. His sample cut-off I think was about 34. His sample cut-off was 35.48 with a normal range of less than 1, so he fits into the second category. These have very strongly reacting tests.

Q. When you say the cut-off is 1, what do you mean by that.

A. That's the cut-off defining a positive from a negative.

Q. Mr Parenzee also was reactive to the Western blot.

A. Yes.

Q. During the time you treated Mr Parenzee did you speak to him whether he was taking his medication, wasn't taking his medication, how consistent he was being about appointments and so forth.

A. Yes. My recollection is when he was first seen he had quite advanced HIV infection as indicated by his CD4 count and he had a very high viral load and he had an extremely good response to therapy. I think he was started on traditional therapy that was available at that time, and then he was well maintained on therapy I think for around about the following 12 months, I would have to check some records, but he then did miss some appointments and there were gaps when I didn't see him. He hadn't had repeat prescriptions so I assume he may have been intermittently on and off therapy. That would certainly be supported by some of the changes in the viral load. If you go off therapy your viral load will go up usually quite dramatically relatively soon after stopping.

Q. Those were the sorts of results that you gave us when you gave your evidence the last time.

A. I think in the original transcripts, yes.

Q. Having treated Mr Parenzee what do you say to the suggestion that it hasn't been proved that he has HIV.

A. That's very worrying. It's very worrying in this individual case and it's very worrying sort of internationally that this small group of AIDS denialists are sort of leading people to cease therapy or leading to interruption of policies that are required for controlling HIV. It's been most evident in South Africa where the history of control of HIV is the worst in all Africa, and it's turning on an individual case. There's very clear evidence, particularly from some recent trials, that to go on and off therapy is a very bad idea. There are two studies, one that was called the Smart study which I think was referred to by Professor Cooper. This study looked at whether it was possible essentially to stop and start HIV therapy. The reason for doing this was because that might reduce the cost and some of the side effects of HIV-related drugs. That was randomly identified based on criteria of continuous therapy, stopping and starting therapy. Once it stopped

and started, they had a high mortality, so the suggestion that - and publication of these ideas has the potential for a very deleterious effect, both with respect to potentially causing hundreds of thousands of additional deaths and in an individual case if Mr Parenzee took this line as a reason to stop HIV drugs, then that will virtually certainly increase his risk of dying from HIV.

Q. You mentioned a second study.

A. Sorry. There was another study called Staccato study; basically a similar sort of thing, and that study again looked at stopping and starting, as indicated by the name. In light of the interim analysis of the Staccato study and the data from the Smart study, it's clearly evident that this was not a way to go. It will sometimes happen in a clinical trial where it is so apparent that during the analysis of the trial it's found the wrong thing to do, that the study will be terminated because it's not safe or ethical to continue the study.

Q. It's also been suggested in this court that to prove sexual transmission you need to find the agent HIV in genital secretions. Putting aside whether that is necessary or not, are you aware of any studies in which HIV has been detected in genital secretions.

A. There are many instances where the virus has been detected in genital secretions. I think Dr Dwyer can refer to that. I don't think there's any dispute about that. In addition there's an association between the amount of virus in genital secretions and the risk of sexual transmission, and that's been well documented.

CONTINUED

Q. Taking you now to your second report, p.1, in the main paragraph on that front page, starting one sentence in you have written 'Acceptance of the defence 'experts' arguments would lead to the conclusion that no viruses or virus diseases (such as measles, mumps, polio hepatitis B and C, smallpox and many others) exist at all'. What did you mean by that.

A. I think what I am implying there is if you use this line of reasoning that the defence are proposing, then it wouldn't only apply to HIV, it would apply to every virus that exists and probably even extrapolated to other diseases. They could probably make the same sort of argument about cancer, in addition. Certainly, I don't see how their argument raised, to suggest that HIV doesn't exist, would not imply to every other viral infectious disease that exists. All the issues, such as the antibody testing and the virus isolation, that would equally apply to every single virus. That is impossible.

+CROSS-EXAMINATION BY MR BORICK

Q. You're registered in South Australia as a specialist, under the category 'general medicine'.

A. Yes, and a microbiologist.

Q. Are you registered under any categories; for example, immunology or infectious diseases.

A. No, the reason for that is that you can only be registered as a specialist in two fields from the Medical Board. I do a small amount of general medicine but my clinical practice is infectious diseases.

Q. Do you know why that is so.

A. Sorry, the Medical Board?

Q. Yes.

A. I'm not sure.

Q. Would you describe yourself as a virologist.

A. No, I am not a specialist virologist or a pure virologist.

Q. You have expressed yourself in very strong terms in relation to the issues relating to isolation of HIV -

you have basically said the Perth group are talking rubbish.

A. I think that's correct.

Q. Now I think about it, that's what you're telling his Honour, isn't it.

A. Well, I think that is basically correct.

HIS HONOUR

Q. You would prefer not to call it 'rubbish' but if you're forced to you would say it is rubbish.

A. It lacks all credibility.

XXN

Q. Is that expression of opinion based on your own research and study or is it based on your acceptance or views of other scientists who are virologists.

A. I think it is a little bit of both. It is predominantly the analysis of the scientific literature in looking at the unequivocal evidence for the presence of HIV but I have also looked after HIV patients. I have seen a number of them die. I have seen the effectiveness of HIV treatment and, in my mind, there is no question whatsoever that HIV exists and that HIV infection will result in AIDS.

Q. In that answer, you moved a long way away from isolation of HIV which is what I asked you. Your views on isolation, are they based on your own studies and research - forget about all the other issues - or upon views expressed by others.

A. I haven't personally isolated HIV. My research group had an interest in the pathogenesis of HIV and in those experiments we utilised virus-infected cells.

Q. Have you self-published any papers on issues such as isolation of HIV.

A. Not specifically, with respect to techniques involved in isolation, certainly not. I have published a paper in which we utilised HIV that had been propagated in infected cells.

Q. The majority of your papers are on drugs trials, effectively.

A. No, that is not correct. If you look at my - the bulk of my papers - there is a mix of papers there. There is some clinical papers but a lot of the papers relate to studies of immunology, a particular area of immunology involved in recognition of self versus non-self, a system called the complement system and that's been one of my major areas of interest. Another area of interest is in how particular pathogens survive in the body, how do they escape the immune system.

Q. What, in your opinion, is the basic science which underpins the isolation of HIV diagnosis.

A. Do you mean the techniques of HIV isolation?

Q. The question was: the basic science which underpins HIV isolation and HIV diagnosis.

A. I am not quite sure what you're getting at but it is based on the general principle. If you go to the virus isolation first, it is based on the general principles of virus isolation, which is, as Dr Dwyer said, a sample is added to a cell line that is able to be infected with that particular virus and then the presence of that virus is detected by one of several methods - either a change in the appearance of those cells, death of those cells, release of a particular protein from the virus that can be detected or detection of the presence of the virus by detection of the genetic sequence of the virus.

Q. Define what you mean by the expression 'virus isolation'.

A. To me, virus isolation is detecting the presence of a virus in a cell line and it is distinct from virus purification. There seems to be a little bit of confusion about the two issues. Virus isolation involves - again as Dr Dwyer indicated - the addition of a sample to a virus cell line and detection of the virus in that cell line and I would call that virus isolation.

Q. What do you mean by the expression 'purification'.

A. Purification means a second step, in which a single component of a mixture is separated out from other components of a mixture.

Q. From all other components.
A. Depends on the extent of purification. Sometimes it is very hard - one can purify a protein from other proteins and it depends on how pure you require the protein to be, how many steps you might need to take to achieve that. Purification is quite different to virus isolation. A virus does not have to be purified to be isolated.
Q. What is the fundamental difference between the two, in your opinion - I just want to understand your position. You have said isolation is the presence of a virus in a cell line. What do you mean by a cell line.
A. Viruses are only able to grow inside cells. They require the machinery to replicate. They're quite different to a bacteria, which you can grow on an agar plate, because their metabolic requirement is relatively small. A virus requires the machinery to replicate so it can only infect the cell. In virology labs, there are cell lines which are immortalised cells of different types and these cell lines you can grow in a culture and you can passage the cells - you can split them in five and then continue to grow them and then you split them again. In essence, they are long-term cultures and that's the standard way in which viruses are cultured. That is a cell line and so the sample is then added to this cell line and then the presence of a virus is detected in one of the other ways. The virus in that case has been isolated -
Q. The cell line then has cellular debris in it.
A. Yes, it has the cell lines, it has got cells.
Q. Lots of things, besides the virus - lots of other proteins.
A. It has the proteins that are in the cell line, or in the media, that is required to grow the cells.
Q. So that's the difficulty, because there are lots and lots of proteins there and how do you know they come from the particular virus you're looking for.
A. It is no difficulty at all because what you're looking

for is the difference between a cell line that has the virus added and the cell line that doesn't have the virus added. It is fairly clear that they are different and if you find something in the cell line to which you have added a virus sample, or a virus that is in a sample, you compare it with what's in the cell line that has had nothing added to it.

Q. Where did you get the original virus from.

A. The original virus - that may be from a clinical sample. If you have chickenpox, you take a scraping from a skin legion and add that to the cell line and that grows the viruses. The other thing about viruses in cell lines is they can be passaged. They can usually be maintained and divided and passaged. The virus continued to grow.

Q. Before 1983, no-one had heard of HIV, had they; before Montagnier said he discovered it.

A. I assume it is hard to hear of something before it is discovered.

Q. Asking you again: when you are doing this test and you're comparing one virus and looking to see if it is elsewhere - you have just told us that - where did you get the virus from in the first place - that is HIV.

A. The HIV isolates are obtained from people who are infected with HIV and the controls, at that time, were people that did not have HIV.

Q. Yes, but the first appearance of HIV came from Montagnier. From then on, they were able to test what he had discovered against other cultures.

A. Montagnier and Gallo described a finding -

HIS HONOUR

Q. They could have called it gobbledygook, couldn't they.

A. They could have called it what they like.

Q. It just happens it was called HIV.

A. Yes.

XXN

Q. When you're looking for gobbledygook -

A. The original papers were an observation of a phenomena. They found, from the lymph nodes of patients who had

AIDS, they found this virus.

HIS HONOUR

Q. Which they called HIV.

A. What they thought was a virus. They didn't find the same virus in people who did not have the clinical syndrome of AIDS. At that stage they didn't know if this was the final cause of AIDS or not but that clearly became apparent.

XXN

Q. We're not talking about causation at the moment, we're talking about isolation of a virus. Somewhere along the line in all of this, in order to test between what is said to be an HIV virus, you had to find it first, you had to isolate it.

A. It has been isolated. We know that the virus is actually thousands of viruses and sub-viruses but these viruses have been isolated on thousands and thousands of occasions.

Q. What about at the beginning; who first isolated it.

A. Montagnier.

Q. Montagnier isolated the virus.

A. A virus, at the time, from the lymph nodes of patients who had AIDS.

Q. We know that, and did he call that virus HIV or did somebody else.

A. His initial terminology was human lymphadenopathy associated virus.

Q. That is the virus that became known as HIV - the one that he isolated.

A. That's correct. That virus, and many other viruses like it - many other viruses. That was not the sole instance of virus isolation, of course.

Q. Are you talking of HIV or lots of other viruses.

A. It is the same virus but they're a slightly different sequence in the virus. We know that not every HIV virus has exactly the same sequence. He isolated a strain of the HIV virus.

Q. When you're testing for this virus, you're still looking

for that virus to see if it is in the other dish, so to speak, aren't you - you're testing one against the other.

A. During virus isolation?

Q. Yes, and you want to know something causes the disease and you think it might be a virus; all right, just as you heard me ask the previous witness.

A. Yes.

Q. You have to isolate the virus - 'culture it' was the expression used - don't you.

A. The virus has been cultured, yes.

Q. When you're culturing it, you get its proteins and its RNA and you have to make sure that those proteins and RNA are unique to the virus, don't you.

A. That's correct.

Q. When was the first time that HIV, the nucleic acid and the RNA were isolated.

A. The virus was isolated by Montagnier and he published that in '83.

Q. You heard Professor Dwyer say that by 1985 it had not been isolated.

OBJECTION: MS MCDONALD OBJECTS

MS MCDONALD: That is not what he said.

MR BORICK: I'm sorry, Professor Dax.

QUESTION WITHDRAWN

XXN

Q. Professor Dax said in 1985 the virus had not been isolated.

OBJECTION: MS MCDONALD OBJECTS

MS MCDONALD: I object. That was not Professor Dax's evidence. My friend took Professor Dax to two different statements she made in two different contexts. One was about isolation, the other was about testing. If my learned friend is going to put a response to this witness, he should put it in context. The response he's relying on is in the context of tests at that time.

HIS HONOUR: That is right, if you're going to put it, you need to put the exact passage, put it in context.

MR BORICK: I haven't got the transcript here at the moment. In her report, she said that in 1983 Montagnier isolated the virus.

XXN

Q. Do you accept that, for the moment.

A. Yes.

Q. In her evidence, she said that in 1985 the virus had not been isolated -

OBJECTION: MS MCDONALD OBJECTS

MS MCDONALD: It is exactly the same question. My friend knows that answer was given in a certain context.

HIS HONOUR: Mr Borick, you have to take the witness to the actual passage of evidence. There's an objection and you're not summarising it. In those circumstances, if you want this witness to comment on that evidence, you need to take the witness to the actual evidence.

MS MCDONALD: My learned friend can have my transcript.

XXN

Q. P.856, I will put it in context. She was talking about antibody tests. 'An antibody test rests on identifying the interaction between an antigen and an antibody. There are many tests that use that principle and that is the principle behind HIV testing, whether it be antibody ELISA, and very few ELISAs are used in Australia any more, a microparticle immunoassay, a chemiluminescent or a Western blot, or a P24 antigen, where the capture is the antibody and it captures the antigen. The principle is the same for all of these antibody tests, it is a question of how you put those tests together, as to how they operate, what their performance is. At first, in 1985, the antigen was made from cellular preparations of HIV. So when the tests were put together and the antigen was put on the plate to capture the antibody in the blood, there were a lot of other proteins involved, cellular proteins, because the virus was not isolated at that time, it was made from these cultures'. That is what she said; all right.

A. I think it's an issue of the terminology. Isolation

means the growth of the virus. On the other hand, the word 'isolation' could also be used as indicative of partial purification. Some people may use isolation. I think that's what she's referring to. She's not saying that the virus had never been isolated. If you didn't have the virus, you wouldn't have been able to develop those tests. The terminology she's using, in that sense, is that it had not been isolated away from other cellular material completely. She's not talking about viral isolation.

Q. If you don't isolate it, you can't use it to test for anything; is that what you said.

A. Isolation, in the sense of virus isolation. Obviously you can't use a virus in a test unless the virus has been discovered, unless the virus has been cultured and the virus has been isolated, isolated in the sense of growing. Dr Dax, I think, is using isolation in the sense - what she's talking about is that for the early HIV tests, there were problems with cross-reactivity with cellular material because the virus had not been isolated away from the cellular material. She's not suggesting that the virus had not been isolated, with respect to virus isolation.

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