Tuesday, 17 May 2011

(9.30 am)

THE CHAIRMAN: Good morning.

MS DUNLOP: Sir, we have Professor Andrew Lever with us this morning.

PROFESSOR ANDREW LEVER (sworn)

Questions by MS DUNLOP

MS DUNLOP: Professor Lever, we normally begin by looking at a witness' curriculum vitae and that's how I propose to start with you, if I may. We have your curriculum vitae in our database, it's PEN0120234.

You have listed for us, on the first page, your qualifications. We see that you took a BSc at the University of Wales, 1975, and then you were at Cambridge. Should that be 1978 or ...?

A. No, it's 1998.

Q. It is 1998. So that's where you go back and you convert it into an MA?

A. It's something that you get if you teach for a number of years at Cambridge.

Q. I see, thank you. And you took your main medical qualification in Wales as well, and then The Royal Colleges of Physicians of London and Edinburgh. We can see listed there. Your MD at Cambridge, 2001.

You have also listed for us your previous positions,

your house jobs, and then on to the next page, working up, including a position in Boston at Harvard. On to the following page we see your current position at Cambridge, where you started off as a lecturer, and then you became a reader in infectious diseases and then professor in infectious diseases from 2000 onwards. Grants and studentships, and then on the following page, page 4, you show your current post under clinical duties and you are still seeing patients.

A. Yes.

Q. And that's at Addenbrookes, is it?

A. Correct, yes.

Q. Do you mainly see patients with HIV or is it a wider remit than that?

A. No, it is much wider than that. I see patients with problems in general in internal medicine in infectious diseases, amongst whom are some patients with HIV.

Q. We see research interests, structural and molecular biology of HIV replication. Rotavirus RNA encapsidation and replication. Is rotavirus another classification like retrovirus and lentivirus or is it a particular virus?

A. It's a particular virus which is very different from HIV. It's the cause of diarrhoeal disease in children, and it causes about half a million deaths in the

developing world every year, but everybody here has already had rotavirus.

Q. If we scroll down to the bottom of that page, we can see mentioned a number of journals. You have in the past been editor in chief of the Journal of Infection and you were founding editor of a journal called Retrovirology. I take it that continues?

A. It does.

Q. Yes. And we can see also other journals relating to genetics, International Journal of Infectious Diseases and Travel Medicine. Then on to the next page, invited reviews and book chapters. We can see even by looking at the first page, that you have written on a number of different viruses, Hepatitis B, non-A non-B. Hepatitis delta virus. And if we look on to the next page, we start to see, I think, your interest in genetics coming through. Is it possible for you to tell us in a few simple sentences how gene therapy for HIV infection might work?

A. So, HIV, because it's a virus that inserts itself into the DNA of the cell, effectively becomes like a gene within that cell and the cell treats that virus as though it's a gene and hence becomes a producer of the genetic material, RNA, which then codes for the proteins of the virus. There have been a number of different

suggested ways forward for gene therapy but the two most popular would be that one delivers a gene to a precursor of the cells that HIV infects, which would prevent HIV getting in, or if it got in, would neutralise it. Or you try and deliver a gene to cells which are already infected, which would then inhibit the virus within that cell.

Q. Right. We can certainly see that the genetics of HIV and HIV infection feature in your research, although not exclusively. We see, for example, if we scroll on, articles about septicemia. Then if we carry on to page 11, you have listed for us refereed papers. Again, obviously across a wide spectrum of different interests. And covering also drug treatment for various different diseases, including interferon and post viral fatigue syndrome.

Moving on through the articles, even a reference to the use of thalidomide. I think one of our other witnesses has mentioned that thalidomide still has use in the medical profession. How is it used today?

A. Thalidomide is a very powerful inhibitor of a certain part of the immune system, particularly a part which relates to inflammation caused by a specific protein called TNF Alpha.

In some conditions, initially leprosy, where the

immune system after many years of not really recognising the leprosy bacteria, suddenly seems to wake up and produce an extremely florid immune response against the leprosy bacteria, which in itself is so dramatic, it can be life-threatening, then it's sometimes necessary to try and calm this reaction down so that the immune system doesn't cause too much damage to the host as well as clear the bacteria, and thalidomide was found to be useful there.

The case in this particular instance concerned a patient that we had who had tuberculous infection of the brain, and the inflammation around the foci of tuberculosis in the brain was so florid that the inflammation was damaging the nerves that went to the eye and she was progressively losing her sight, and as a rather long shot, we treated her with thalidomide. It was the first time it had ever been used, and the inflammation settled down and her sight stopped deteriorating and some three years later, she was left with a cleared infection and no inflammation.

Q. I suppose, as an infectious diseases physician, you are studying the pathogens themselves, you are studying the human response, so our immune systems and how they cope with these challenges, and also the different treatments.

A. Yes, indeed.
Q. And that's a crude oversimplification obviously but all these different aspects must feature in the job of an infectious diseases physician?
A. It's a very good summary.
Q. Perhaps I could also take you on to page 19. I see an article there, number 115, mentioning progressive multifocal leukoencephalopathy, which is, I understand, one of the many ways in which HIV can manifest itself or one of the many difficulties that HIV can lead to in a patient. Is that right?
A. Progressive multifocal leukoencephalopathy is one of the conditions which affects the brain in people with advanced HIV, with AIDS in fact, and it's caused by a virus that just goes by the initials JC virus, and this particular individual had a rather unusual neurological condition associated with this, which resembled Parkinson's disease. When the person was treated for their HIV and the immune system was restored, which is the best way to reverse the progressive multifocal leukoencephalopathy, then the Parkinson's also resolved.
Q. When a patient has AIDS and something else is wrong with them, has the medical profession come to see almost everything that develops in a patient with AIDS as

connected to their having the virus, or does it sometimes happen that people get ill and there isn't a connection?

A. I think that's something that has changed very significantly over time in that, when HIV was recognised as causing AIDS, the concept was that it was a relatively limited effect just on the immune system and would therefore predispose the individual to infections, and as it turned out, infection-related cancers. Then a number of additional medical conditions became apparent in patients with HIV infection, such as degeneration of the kidney, and HIV-associated brain disease, and it was realised that by mechanisms which weren't always completely obvious, HIV was affecting other systems directly, and that when treatment for HIV came along and the virus load was successfully suppressed, these conditions would reverse.

That was a phase in which everything was potentially put down as attributable to HIV infection. More recently, I think, there is a more balanced feeling that a lot of what goes wrong in someone who is HIV-infected is HIV-related but that HIV-infected people get diabetes and get other conditions, so there is, I think, a more ready acceptance, particularly in the fact that the HIV population is now becoming an aging population, that the

diseases which affect aging populations without HIV are affecting people with HIV.

Q. For those who have HIV but in whom the virus is being successfully controlled by drugs, that group of people, is there still an excess mortality?

A. Yes, although the risk of an infection by an unusual organism which wouldn't cause disease in people with a normal immune system, the so-called opportunistic infections, has gone down, almost effectively to zero, perhaps not quite. Then there is still an increased risk of some of the HIV-associated tumours, the malignancies. They have not been quite as well controlled. So HIV-associated lymphoma, for example, is much less common in treated individuals but it has not been eradicated down to the same level as have opportunistic infections such as pneumocystis, for example.

Q. Thank you, Professor Lever. With that introduction, can we turn to the report which you have provided for the Inquiry, please? That is [PEN0150517].

On the first page you fleshed out a little more fully how you became interested in and became involved in the world of infectious diseases. I think I simply wanted to ask you about the second paragraph, roughly what timeframe this is, when you describe the

immuno-globulin episode, patients who had been treated with intra-muscular immunoglobulin and the discovery that they were developing abnormal liver tests. Roughly when was that?

A. My research period at the Clinical Research Centre in Harrow was late 1982 or beginning of 1983, for a period of approximately two years, 1983/1984, roughly.

Q. You say that following that experience, your interest in infections was ignited and you went to the Royal Free and then you went to the United States. Is that the laboratory at Harvard, that we saw mentioned in your CV?

A. Yes, that's correct.

Q. When you were in Wales, when you were studying and doing some of your earlier jobs, did you work with Professor Bloom?

A. I knew Professor Bloom but I was a medical student and a very junior doctor at the time, so our paths didn't cross very much.

Q. Then we see from the last paragraph on that page what happened when you returned from America. You have already told us that you are clinically active.

Can we then move to the next page, please? You have given us a very little bit of introduction about viruses generally and HIV in particular. You mention retroviruses in the very first line, and I think for our

general understanding it would be good if you could give an explanation about what is specific about a retrovirus?

A. So most living organisms have genetic material which is made of a substance called DNA in humans and other animals. This is the chemical substance that composes the double helix which most people will be familiar with. DNA is an extremely good storage of genetic information. It's very easy to replicate very accurately so we can pass on our genes very accurately to our offspring.

In the normal cell, the DNA provides the hard disk, if you like, from which the information is transcribed into a substance called RNA or ribonucleic acid. This is almost identical to DNA except there is a minor difference on the sugar which is part of the chain. RNA is a much less stable molecule than DNA, which is probably why DNA evolved to become our genetic storage, because it is so stable. But the RNA that is produced from the DNA within the cell carries a code on it which, when it is trafficked out of the nucleus of the cell into the cytoplasm of the cell can be read by small organelles in the cell called ribosomes, and that code will tell the ribosome which amino acids to put together in what order to produce proteins, and it's proteins

which make up most of the structural components of our cells and which do various functional things like enzymes; Factor VIII is a protein for example. So a gene would code for something like Factor VIII. It would be converted from a DNA into an RNA copy. That RNA would be trafficked out into the cytoplasm and the ribosome would make a protein called Factor VIII, which would then be exported.

For many years it was believed that this direction of information flow, as it was called, DNA to RNA to protein, was the only one that existed. We know that there are viruses which have a DNA form of the genetic material, as we do -- herpes viruses, for example, have DNA as their genetic material. But we also know that there is quite a large number of viruses which don't have DNA, which have a substance called RNA. So they never use DNA. They are just a piece of RNA and that directly goes on to the ribosomes and is translated to make proteins. It's a slight short cut if you like. These viruses comprise many of the common pathogens. The fact that you have a RNA virus which is coding for something which becomes a protein, still maintains the same directionality of the DNA to RNA to protein, although you have missed out the DNA step.

When retroviruses were first identified, it appeared

that within the virus particle the genetic material was made of RNA. When the virus got into the cell, there was a lot of evidence which eventually was believed -- and it took a long time to be believed -- that that RNA was converted, if you like, backwards into a DNA molecule and that DNA molecule was then inserted into the DNA of the cell so it looked like one of the cell's own genes.

Because of that apparent reversal of the flow of genetic information from RNA back to DNA, this family of viruses were called retroviruses because they had turned the direction backwards. They are also sometimes known as reversy(?) viruses, which is perhaps slightly more graphical, but reversy viruses include Hepatitis B, which also goes through an RNA intermediate.

The term "retro" comes from that original observation that the flow of genetic information went back. Of course, when the DNA is made, the flow of genetic information goes in the normal direction again because that DNA is made into an RNA copy and into protein, which then produces the virus.

Q. Would it be correct to see that incorporation into the host DNA as then leading to a malfunctioning?

A. No, the DNA is very small. It's about 10,000 of the individual nucleotides, which make up DNA, which is very

tiny compared to the 30 million or so that we have. And it almost always inserts in places which don't disrupt the normal functioning of the DNA. So it's a very small insertion, and although it does commonly insert for reasons we don't quite understand in areas where there are other cellular genes, there is only one documented example in 30 years of that integration disrupting a human gene.

Q. You say in the second paragraph that in 1977 the Japanese had identified a retrovirus, which was later called HTLV-I, as the causative agent of an unusual leukaemia, and then the virus itself was later isolated in the laboratory of Robert Gallo in 1981. If the virus was isolated by Gallo, does that mean Gallo cultured it?

A. That's correct, yes.

Q. Right. So if he was the first person to culture it, how had the Japanese identified it?

A. If my memory serves me correctly, they had seen it and it had the morphological appearances of a retrovirus.

Q. Did the name HTLV then come from Gallo?

A. It came from Gallo, yes.

Q. Then you say in the third paragraph that:

"The concept of a pathogenic retrovirus as a possible disease-causing agent in humans was very prominent and topical."

And that's just because of the recent work that had been done on HTLV-I?

A. Up until that time it was known that viruses from the retrovirus family infected many species, including a large number of mammalian species: cats, horses, goats, sheep. And to some extent, I think, it had been rather surprising to those people who studied viruses, that there hadn't been a human equivalent found.

So when a human retrovirus was identified, it was a slightly revelatory moment for those people who had been expecting it, but it was very much a revelation also for those people who hadn't known what retroviruses were and realised that there was now a new class of virus which was capable of infecting humans and causing disease.

Q. So there wasn't a bright line between people studying viruses in animals and people studying viruses in humans? There was obviously a bit of cross-over, was there?

A. Yes, there is. Not as much as perhaps there should be but, yes, veterinary pathologists had known about retroviruses for many years and there are a number of people who would work in both fields, who would probably be able to make the connection. But people who worked exclusively on human disease, of which there are plenty

pathogens to study, would probably have not necessarily kept up with the literature in the animal field.

Q. You also tell us that the discovery and usage of certain cell lines for isolating viruses and the discovery of growth factors for human cells were all essential prerequisites for retrovirus isolation. Is that just that it is much easier to study something if you can make a supply of it in your laboratory? Is that the point?

A. These viruses at the time proved very difficult to grow and isolate, partly because of the state of advancement of science and things like tissue culture at the time.

For example, if you were trying to isolate HIV, you could only do that by triggering the cells you were trying to grow the virus into multiplying very fast. And the sort of cells that you needed which would do that without dying -- because cells, if you stimulate them too much, will die. The sort of cells which you need to do that which would survive that sort of stimulation had been developed in Gallo's lab, amongst others, but Gallo's lab in particular. And the sort of factors that you needed to trigger those cells to divide for a long period and safely, were also developed.

When I say "developed", they were identified, because these are naturally occurring substances which

we have in our own bodies, which trigger our own lymphocytes to grow and divide in response to an immune stimulation when we need to make an immune response. But actually isolating significant quantities of these proteins to do that had been a very important breakthrough in being able to grow the virus in the laboratory.

Q. From the fourth paragraph you seemed to be suggesting that it was even possible for people, I suppose, thinking laterally, to say in the early 1980s when AIDS was emerging, that this might be another retrovirus. The very far-seeing virologists of the time might have been thinking to themselves this is a little bit like HTLV-I, might they?

A. I think some people might have made that connection. I think partly it relates to the perception at the time that, having just identified one retrovirus and shown that we were able to identify a retrovirus, people were looking for the next retrovirus.

Since there was an association with blood, there was possibly an association with sexual transmission, then a retrovirus, in rather simple terms, might fit the bill. Again, it's not something that every virologist or everybody studying human infectious diseases would have immediately alighted upon --

Q. I must ask you about HTLV-II: where does it fit into the story?

A. HTLV-II was, as you might have guessed, was identified soon after HTLV-I and has very similar characteristics and a very similar structure, but as yet it appears to be associated with almost no disease in humans. It's relatively rare, rarer than HTLV-I. There is a hint it's associated occasionally with a rather rare form of leukaemia, but mostly it seems to be non-pathogenic, or not harmful.

If I might just expand on that a little bit, we assume that HTLV-I and HTLV-II have been in the human race for many thousands or probably hundreds of thousands of years, and again, in the same way as HIV, we know there are relatives of HTLV-I and HTLV-II in the primate populations -- in monkeys, in primates in Africa, in orangutans and such like. And by looking at those, one can look at the genetic sequence and calculate roughly when the common ancestor of HTLV-I and the monkey virus may have diverged, and this goes back many thousands of years.

In general terms, if a mammalian species has been in contact with a virus for a very long time, they both become rather adapted to each other in that, the people who are very susceptible to the virus causing them to

have severe disease or death, will actually die out quite quickly and Darwinian natural selection will promote the survival of those people who have a better immune system or some sort of better form of defence against it.

At the same time, if a virus kills its host -- and viruses can only replicate inside hosts -- they can survive but they can't replicate outside hosts in the environment, unlike bacteria. Then for the virus' own survival, it's not a good strategy to be highly lethal. So over time the virus will become less pathogenic, less able to cause disease, and the mammalian species will become more resistant to it. One therefore assumes that one reason why HTLV-I is such a benign disease is that we have been associated with it for many, many thousands of years, and hence it doesn't harm us very much and we can tolerate it very well.

Q. If HTLV-III had been left to follow its own natural course, that might have been a pattern that would have developed with it too, or do you think it's different?

A. No, I think you are exactly right. It's speculative because it's an experiment that will never be done, but if one takes analogies from other infections where that has been done -- I suppose the best example is myxomatosis in rabbits.

When rabbits were accidentally introduced into Australia and caused such a devastating problem there, a virus called myxomatosis was introduced from South America, which was highly lethal to rabbits, and the idea was that the virus would help lower the rabbit population and within around five years the virus had clearly become less dangerous, less pathogenic. It had mutated and the rabbits that had survived had become more resistant to the virus so that the mortality rate had dropped from about 95 per cent down to about 50 per cent. That occurred probably within about five or six generations. So left to its own devices in the human race over the course of a minimum of five to ten generations, one might expect that humans who are resistant to HIV would emerge at the cost of the loss of a very large number of human lives.

There is already some circumstantial evidence that this may be happening, in that we and other people are seeing individuals from Africa who are in their early teens, their early adolescence, so they will not have had any sexual exposure, and yet they are HIV positive and yet are well. And they undoubtedly, as far as we can ascertain, once one has taken out factors like possible abuse, but they almost certainly were infected vertically from their mother and appear to have survived

infancy and childhood as infected with HIV and are still relatively healthy some 12 or 13 years later, which isn't what would have been predicted. So there may already be people who are slightly genetically protected. And, if I might go on some more.

Q. Please do.

A. We know, for example, that in the Caucasian population in western Europe, around 1 per cent of the population carry a mutation in one of the proteins on the surface of their lymphocytes, a protein called CCR5. That's an essential receptor for HIV to get into cells, particularly monocytes and macrophages. So those individuals, if they are exposed to the type of HIV which infects the macrophage population, cannot get infected. Sexually transmitted HIV is almost exclusively, or probably exclusively performed by viruses which do prefer to go into this cell population called macrophages. So these individuals are effectively protected against HIV infection by the sexual route. And they are the explanation for some of the people who are repeatedly exposed to HIV but don't get infected. So that's 1 per cent of the Caucasian population. This genetic -- it is not an abnormality, it's a genetic variant -- does not exist in Africa and that says that it hasn't arisen in response to HIV, it

is just part of the very broad variation that we find in a stable population like the human race, where we are all slightly genetically different.

Q. The 1 per cent of Caucasians who don't get AIDS, they don't become infected with the virus, HIV, at all?

A. They don't become infected.

Q. What are they called? Do they have a name, that group of people?

A. They don't have a generic name. The mutation in the receptor is called the delta 32 mutation on CCR5, which means that the protein on the surface of the cells has a mutation which truncates, it makes it shorter. So it's not long enough for the virus to latch on to. These individuals appear to be otherwise quite healthy, although there is some evidence they may be slightly more prone to a rather rare form of virus meningitis.

But the fact that they are very healthy goes back to something else earlier, which is that targeting this particular protein has been one of the suggested strategies for gene therapy, to see if one can lower that on the surface of cells. One of the currently available anti-retroviral drugs actually targets this protein and if you like, coats it or stops it working so that the virus can't get into the cell.

Q. Right. The reason I asked you about what they were

called is because I have heard the term long-term serial non-convertors, but that's obviously a different group of people. That's people who have the virus but don't become ill, is it?

A. I'm not sure that there is one term which describes individuals. I think if there is a term which says there are long-term non-converters, those would be people who aren't infected. There are also groups of people who do get infected and appear to control the virus extremely well, and they are called long-term non-progressors or elite progressors. So they are infected but for a variety of reasons, not all of which we understand, they seem to maintain a normal immune system and appear to suppress the virus for many years.

Q. These characteristics that you are describing, that, albeit in a very small number of people, make them much less vulnerable, are these passed on genetically to our children?

A. Well, because you get a gene for each protein from each of your parents, the people who have this have to have inherited two abnormal genes, both of which have the mutation in. So they will have received one from their mother and one from their father. So they will only pass on one copy to their children unless their partner also happens to be passing on a copy.

There is evidence that if you inherit just one copy of the gene so that you have a lower number of these receptors on the surface of your cell, then you also, although you get infected, have a slower progression of disease to the point where you develop AIDS.

Q. Just to follow the train of thought about how virus and host adapt to each other -- and you have covered this. Can we go on to the next page, please. You have covered this at the top of the next page, when you discuss zoonoses.

A. Yes.

Q. So viruses spreading from animals into humans. You refer to HIV being a zoonoses from chimpanzees. Has the same thing happened in the chimp population? In other words, is the virus less damaging to chimpanzees now because it has been in chimps for longer?

A. Until relatively recently -- and chimps are not the only primate or monkey species that is infected with a virus similar to HIV. These are called SIVs, by the way, simian immunodeficiency viruses. There are simian immunodeficiency viruses infecting many, if not most monkeys. So there is one that infects the sooty mangabey, one that infect the rhesus macaque and such like. And in those populations they appear to be carrying the virus without sustaining any disease. It

was thought, until relatively recently, that the chimpanzee population also were able to carry their SIV without sustaining disease but more recently, some detailed studies in equatorial Africa have shown that SIV-infected chimpanzees actually do have a reduced lifespan compared to non-SIV infected chimpanzees. It's difficult to be absolutely certain what they die of but the evidence is pretty compelling that SIV is not completely benign in the chimpanzee population, although it would appear to be more benign than HIV is in the human population.

With wild populations, it's very difficult to ascertain these things. For example, the cat equivalent of this, feline immunodeficiency virus, which causes an AIDS-like disease in cats, and affects some 20 per cent of domestic cats in this country, infects almost 90 per cent or so of wild lions in Africa. And until recently it was thought to be benign but now it's apparent that FIV infected lions also die young, but if you are an FIV-infected lion and you are less fit, you are much more likely to die of something else, like another lion, than FIV infection.

Q. We have skipped over the concept of lentiviruses, which you tell us in this introductory section. Because HIV is a lentivirus, this puts it in a different virus group

from HTLV-I. "Lentivirus" I understand to be a descriptive term, because it's slow. You say that they are organisms which cause disease after a long incubation period. But is there also something physically different about lentiviruses?

A. The two pathogenic groups of human retroviruses, the HTLVs and the lentiviruses resemble each other genetically but they are clearly different. They have the same sorts of proteins but they are very different in sequence and they also have proteins which are unique to each of their families.

So HTLV-I falls into the family of retroviruses called delta retroviruses, which are all recognisably identical, like HTLV-I, HTLV-II and STLV. HIV falls into the family of lentiviruses, which include feline immunodeficiency virus, which I mentioned, Maedi-Visna, which infects sheep, equine infectious anaemia, which infects horses.

So it's a functional classification. In the case of lentiviruses it's a historical descriptive classification and in the case of HIV a rather inaccurate one.

Q. Right. You have talked about nomenclature. Is it correct to deduce from what you have just described that HIV shouldn't actually have been put in the family of

HTLV in the first place? That was a misnaming? It didn't --

A. It was --

Q. -- belong with HTLV-I and 2?

A. Yes, it was quite a serious mistake in nomenclature and I think it was driven -- everyone thinks it was driven by Robert Gallo, having discovered HTLV-I and HTLV-II and finding something which was genetically similar but not the same and, himself actually not being someone who had a long history of being steeped in virology, assuming that they were all very similar and from the same family. And there may have been a certain possessiveness about this as well.

Q. In this taxonomy of the viruses in the area I should also ask about HIV-1 and HIV-2. What's the difference between those two?

A. So HIV-1 is far and away the most predominant of the HIVs. It causes probably more than 98 per cent of the human infections and it's very closely related to the virus that I mentioned before in chimpanzees. So it's a cross species transmission from chimpanzees.

HIV-2, although, if you just looked at the map of the virus, you would say was very, very similar to HIV-1, is actually quite different, if you look at the individual nucleotides in the sequences of amino acids

in its proteins, and that is very closely related to a virus found in the monkey species called the sooty mangabey. So the evidence is that HIV-2 crossed into humans from the sooty mangabey, whereas HIV-1 crossed into humans from the chimpanzee. Both of these, almost certainly -- as I think it's well understood now -- came into the human race, as far as we can tell, through the bush meat trade, where wild monkeys are caught and slaughtered and butchered and sold for food, and since both viruses are blood-borne and in fact in the monkey population they're transmitted predominantly by blood -- by fighting, by biting and scratching -- then it's relatively easy to think of how a virus may have been transmitted from fresh meat into someone who was handling that.

Q. Right. You have given us on page 3 an interesting table. It's a timeline, rather than a table. We can blow it up a little bit. But it shows various emerging infections since 1980, not all of them viruses. We can see E. coli 157 featuring in there as well. Is this a complete record of emerging infections or is it just the most significant ones?

A. It's certainly the most significant ones. I don't think it's absolutely complete.

Q. I think in fact you have it in colour in your report and

we, I am afraid, only have it in black and white, but we can certainly see some other ones that we recognise from our general knowledge: H5N1 featuring in there and BSE, which I think we all understand is not really a virus at all; toxic shock syndrome, which is a bacterial infection?

A. It is.

Q. Right. Can we move on to the next page, please, and begin looking at the history of matters as they are more directly relevant to our Inquiry.

You have given us on page 4, if we can have that, a heading, "The emergence of AIDS". I think we need to go a little bit higher up, back on to the previous page, please.

Thank you.

Under a heading, "The emergence of AIDS", you have documented some of the early events and I think we are all familiar with the publication of the MMWR in June 1981. We have also heard that the attention of Dr Evatt was drawn to this new phenomenon by requests coming in for a particular drug, pentamidine and I understand pentamidine to be an antibiotic. Is that right?

A. Yes, it is. Yes.

Q. But for some reason it's a very tightly controlled

antibiotic. Is that correct?

A. It is. It's used for a very restricted range of infections and it's given by injection, and it has potentially some very unpleasant side effects.

Q. Right.

A. It can also be given by inhalation but for severe disease it's given by injection.

Q. In America it was only available to physicians through the CDC, the Centres for Disease Control, as we understand it. Is it similarly controlled in this country? Is it difficult to obtain?

A. No, not now. It's readily available in most hospital pharmacies.

Q. But then it might have been?

A. For that sort of medication in this country, because it would have been used so infrequently, and because all of these medications have a shelf life, it would have been uneconomical for everyone to be storing this. So its availability was probably restricted largely on economic grounds rather than because it was restricted in usage.

Q. The presenting problem, which led to this particular antibiotic being requested, we understand to be a particular form of pneumonia. You explain to us that that form has been renamed and it's now called pneumocystis jirovecii, as I understand it?

A. Jirovecii.
Q. Right. It is due to a fungal infection in the lungs. Is that correct?
A. It was originally thought to be a protozoan infection. Protozoans are single-cell organisms like amoebae. Most people will, I hope, know what an amoeba is. In fact, it is unusual because something like pentamidine would be predicted to be very effective against an amoeba-like organism, but advances in the molecular biology of identifying organisms where one looks at, again, the organelle I mentioned before, the ribosome. If you look at the genetic sequence of that, you can reclassify organisms by how closely they are related to each other, and pneumocystis on its ribosomes is clearly in the fungal family rather than in the protozoal family.
Q. The significance of the illness in these individuals we have understood, I think, to be that this would be a pathogen that a healthy immune system would be able to deal with. Is that right?
A. Yes. Many people are exposed to pneumocystis, often in childhood, and seem to suffer no ill effects whatsoever. It has always been associated, certainly in adults, with conditions where the immune system is impaired in some form.
Q. Right. So it wasn't the pneumocystis in itself that was

unusual, it was the fact that it was making people very ill that was worthy of note?

A. And the fact it was there at all, yes.

Q. Right. You say that at the time some people thought cytomegalovirus or Hepatitis B might be responsible for what was happening in these particular homosexual men. By this point not just PCP but also Kaposi's sarcoma. When we are talking about pneumocystis, is it correct to continue to call it PCP, if you are talking about that era? What does it get called now? Does it still get called PCP or does it get called PJ for short?

A. The lingua franca is PCP and the justification is that the "C" is the cystis part.

Q. Okay. So if we just continue to write "PCP", we will be fine?

A. Everyone will understand what PCP is.

Q. Good. You chart developments between 1981 and 1982, more specifically June 1981 to June 1982, and the number of cases had gone from five really in June 1981 to 355 in June 1982, which, on any view, looks like a very significant rise. Is an epidemiologist going to pay particular attention to something like that?

A. I'm sorry, was that a question?

Q. I just wondered, it looks a remarkable rise. I mean, 355 in the population of the United States is not as an

absolute number very significant but I take it it's the scale of the increase that would be drawing attention?

A. I think the fact that they have a very good reporting system there actually brought it to prominence because the cases, although they were locally clustered, were geographically scattered on the two sides of the USA. So it might have been less obvious unless the state sponsored reporting system, the CDC, had not put them all together.

If one doesn't have an obvious single focus, which would be the case for something like SARS -- when SARS broke out there was clearly a very good geographical focus and reporting was very good -- then it may have been less obvious that there was a single infectious cause because something was appearing at very large geographical distances.

Q. Yes. Can we, when we are thinking about all the information that was coming out around about this time, stick with an analogy of a jigsaw? It's rather a tired analogy but I think it's one that we all understand. So if we can think of it in terms of a jigsaw, you mention in the paragraph where you have shown 8.8, 8.9, the fact that intravenous drug users were being affected. Did that represent a new piece of the jigsaw?

A. Yes, it did. Until that time then there were plausible

arguments that what was being seen, which was effectively confined to the gay, homosexual population, might have had a number of causes and, as mentioned there, people initially started looking for things they could find, which was why cytomegalovirus and Hepatitis B came up, and the fact that these populations were almost uniformly positive for these viruses, whereas the general population has a much lower instance overall, made them potential candidates. But there was also an uncovering of information about the gay lifestyle at the time, about sexual promiscuity and about drug abuse, which also distinguished that population to some extent, certainly in the level of it, from most other populations. So there was room for a lot of speculation as to what might be triggering the immunodeficiency.

The intravenous drug users were another part of the jigsaw, in that, for example, the speculation that abnormal exposure of pathogens in the rectum, in the gut, as opposed to by heterosexual transmission, somehow made these things more pathogenic because the intravenous drug users as a population were not characterised by indulging in homosexual practices. So that narrowed down, if you like, the potential causes and pointed to the fact that there was something which

was probably in common with the two.

So, yes, it was an additional piece of the jigsaw.

Q. Right. Did it point away from things like amyl nitrate? You mentioned drug abuse among the homosexual population, and I take that to be not intravenous drug abuse but tablets, I suppose. Is that correct?

A. Yes, I think amyl nitrate would have still probably been the potential contributorial cause while the intravenous drug users were included because it would be difficult to be certain that they were completely absolved from usage of agents like that as well.

Q. Right. And also the fact -- and this is mentioned in the same paragraph -- that people were coming through who were heterosexual, I suppose might take you away from the idea that this is something that's peculiar to people of homosexual orientation?

A. Indeed, yes.

Q. Around about this time, June 1982, another phenomenon -- you haven't specifically recorded it and I don't imagine it's a big piece of the jigsaw at all -- which seems to have been discussed is diffuse undifferentiated non-Hodgkin's lymphoma, that that was starting to come through as well as a manifestation. Is that something that we should see as analogous to the Kaposi's sarcoma, by which I mean another odd malignancy?

A. The emergence of unusual malignancies I think are part of the jigsaw. I suppose, if I can talk around that a little bit, because if one is thinking that this is an infection, one has to think: does it have the characteristics of an infection? In terms of there being clusters within certain populations, that is in favour of it and obviously, as I'm sure you will come onto, there is the common factor about blood products. Other than that -- and this is not in any way meant to be a defence -- HIV doesn't behave like what most people think of as an infection.

Everyone recognises an infection like flu or measles or whatever. It tends to be a relatively short-term event with a high fever and people tend to get over it and it's rather easily recognisable. We know that there are chronic infections like hepatitis, which can cause disease, but they are normally also associated with target organ damage like liver disease and the immune system being activated to do things to try and clear it. I think one of the mysteries of this particular time was that this appeared to be a degeneration of the immune system. It was almost like a degenerative disease, things were failing, and there was no obvious evidence before testing came along that the body was doing anything about it. So I can expand on that later, if

you like, but although there were pieces of jigsaw hinting at infection, there are also pieces which are saying this is very unusual as an infection.

Q. This may be a really crude nutshell but we have all these different diseases emerging, some of them quite unusual, it is quite an intellectual leap to see that the cause of all of that may itself be a disease, another disease.

A. Well, yes and no, but if one looks at analogies -- so, for example, people who have been put on very powerful drugs to suppress the immune system -- then that would also be associated with acquiring a variety of different infections because your immune system can no longer cope with things which the normal immune system can cope with. And the other analogy would be people who have advanced cancer, where again the immune system is suppressed for whatever reason and they also, certainly when the malignancy is sufficiently advanced, would be prone to infections they wouldn't otherwise be prone to. So both those scenarios, where the immune system was failing, would have been suitable analogies for this.

Q. So someone really thinking about this phenomenon, particularly in the United States, in looking at the different infections or malignancies that are being suffered by particular groups, would be saying to

themselves, "Is there a common element causing the suppression of the immune system?"

A. That would have been the logical thing to be looking for: what's going wrong with the immune system?

Q. If we could go down, we can see it at the bottom of the screen. You mention something that we refer to in our preliminary report. That is the reporting of AIDS in Denmark in gay men in the summer of 1982, and you say that a case was also described in Italy. I don't think we picked that up, that there was someone around about that time in Italy who also had AIDS, was there?

A. Yes. I would have to go back to the original reference for that but I remember reading it.

Q. That's fine. It's all something we can add in. Was that also someone who was homosexual?

A. I can't remember.

Q. Right. Okay.

THE CHAIRMAN: Ms Dunlop, before you move on.

Professor, a few moments ago you were asked the question:

"So someone really thinking about this phenomenon, particularly in the United States, they would be saying to themselves, 'Is there a common element?'"

And you say:

"That would have been the logical thing to be

looking for."

The answer is very general. Is there a particular constituency of experts one should have in mind here or would it be all medical people or what?

A. I would think everybody looking after patients who are suffering these would be trying to work out what was going on and particularly as they were clustered, they would be looking for the common factor.

THE CHAIRMAN: Yes.

A. So individual physicians and also those people whose job it was to study the epidemiology, such as those at the CDC. So it should have been a general phenomenon, that people were looking for common causation.

THE CHAIRMAN: There is always a concern that in some areas there would be particular specialists who would be likely to have a focus that would inform them that wouldn't be general, but on this occasion you are content that it should have included all those with an interest in this area of work?

A. Mostly the people who saw the initial cases were seeing a lot of the initial cases or at least several, and it would have been an unusual phenomenon for anyone to have seen one of these and certainly very unusual for them to see two or three. So everybody should have been alerted.

THE CHAIRMAN: Thank you.

MS DUNLOP: Yes. Just at this point, Professor Lever, I wanted to ask you about people from Haiti. Some of the reading that we do is rather out of date because we are so steeped in the 1980s, but I have certainly seen references to that never having been satisfactorily explained. Is that still the case, or is there now an understanding of why there appeared to be a concentration in Haiti?

A. I don't think it has been documented -- it's rather difficult to document it in retrospect anyway. I don't think anyone has a very clear idea about how that arrived but there are speculations about immigration from Africa and contact with people of Afro-Caribbean background, but I don't think there is anything specifically unusual or any specific route that has been documented for that particular phenomenon.

Q. I wonder if I could take you to an article that we have looked at on a number of occasions by Dr Bruce Evatt. It's [PEN0150265]. I imagine this is something you have seen before. It's entitled "The tragic history of AIDS in the haemophilia population, 1982 to 1984."

We have been discussing those who in the early 1980s were trying to work out what was going on and Dr Evatt was certainly one of them. I don't know, was he the

leading detective around that time?

A. He is not somebody that I knew a great deal about in fact but he clearly was very prominent in the CDC.

Q. Right. He published this article really quite recently. I don't know, do you happen to know what led to this being written and published in 2006?

A. I have no idea why it was published then.

Q. On the first page of the text he has a heading, "The epidemic begins". And this is an example of a reference to the idea that the original outbreak in homosexuals might be something to do with sexual practice, because at the end of that paragraph, towards the bottom of the page, we can see the sentence:

"Leading scientists focused on non-infectious causes such as antibodies to sperm or a reaction of the immune system to chemicals such as inhaled amyl nitrates that homosexuals use to maintain prolonged erections."

By what time do you think these had really faded from the picture as theories? We have looked at some of the other data that emerged about other groups of people who were becoming ill with AIDS. Do you think these theories began to fade quite rapidly?

A. I think theories like that will always have some degree of credibility until you find the infectious agent, and certainly once Montagnier and Barre Sinousi had

identified something, which I think most of us believed at the time, even though there were a little bit tentative and probably they had the publication slowed down a little bit by competitors elsewhere, and certainly by the time Gallo had published, there was only a small fraction of individuals who still clung on to a theory of anything other than infection.

Up until that time I think it's a gradation. There was a gradual acceptance that it couldn't just be put down to immunological-based theories and that the epidemiology looked more and more like an infectious agent. I'm not sure there was a clear defined cut-off point between the initial thoughts that it didn't look infectious and then the ultimate revelation that this was infectious.

Q. He goes on to say that:

"The course the investigation began to change in 1982."

Then he mentions the pentamidine angle. Then on to the next page he says that:

"In early 1982 [he] had a call reporting a haemophilic patient who, treated with Factor VIII concentrates, had died of PCP."

Indeed, it's quite interesting to note that the doctor treating that patient had wondered if the

clotting factor itself had been contaminated with pneumocystis carinii, but Dr Evatt looked to have been slightly dismissive of that particular possibility.

Then he goes on to refer the reports of the immune disorder in patients from Haiti and IV drug abusers, and then really just the thinking I have been putting to you, about anal intercourse or use of amyl nitrites not being common practices for haemophilic patients or IV drug abusers:

"The author reasoned that these four groups had very little in common except for one thing, the risk for blood-borne diseases."

I suppose it all comes to seem simple in retrospect?

A. It does.

Q. And perhaps there is a danger in reading something like this, that it appears simpler than it really was. Do you think that's a risk?

A. Yes. I don't think people dismissed the idea of there being an infectious cause, and there were lots of people who thought it was an infectious cause from the word go and a lot of people who didn't. I think the issue about it is that, as I mentioned before, it didn't really have the physiological appearance of an infection. I think things like infections cause rashes and high fevers and things, which actually -- those are very powerful social

signals. The fact that you get a rash with measles is probably only there to tell the rest of the population that you are infectious and should be kept away from. The fact you get a very high fever in some diseases doesn't actually do you very much good but it tells other people that you are ill. That's how mothers know their babies are ill because they feel hot.

So we have a lot of inbuilt signals which we have evolved to recognise as things which are infectious. If it doesn't tick all those boxes then you have to find other reasons why it's an infection, and there were other reasons admittedly but it didn't quite look like a normal infection.

Q. Certainly the geographical spread must have been difficult to fit with the infectious picture, all these different people all over the United States?

A. I think that contributed, yes. I guess it wouldn't be unprecedented because some infections can spread very rapidly, but the fact there was no continuity in the explosion of a cluster in one particular area made it slightly unusual as well.

Q. Yes. The rest of that page is concerned with documenting what happened in 1982. Can we go back to the previous page, 2296?

I'm sorry, I had forgotten. This is a missing page.

We should go to the other reference. It's [PEN0161183], which has the full article in it.

Right. Can we go to the second page of text, please? Thank you.

Dr Evatt is documenting what happened throughout 1982. He refers, on the right-hand side at the top, to the MMWR reporting the three patients with haemophilia, suggesting the probability of blood-borne infection as a cause of AIDS. I think in fact the text refers to it being "possible" rather than "probable", but we have looked at that certainly. He says that:

"In July, we reasoned that the time had come to shift US investigations towards a blood-borne and sexually transmitted infection as a cause of AIDS."

In fact, from Douglas Starr's book on blood, we know that Dr Evatt did a tour around the United States, trying to spread the message, indeed at his own expense. We can also see that a meeting took place on 27 July 1982. He says:

"To present the evidence of a possible transmission by a blood-borne agent."

We can see that under the heading, "Confronting existing wisdom". If we read on, it doesn't seem to have been a particularly successful event. He says, reading from the middle of the last paragraph:

"Rather than expressing alarm at a possible blood-borne infection and suggesting ways to reduce a blood-borne risk, the audience expressed an almost universal reluctance to act."

Even to the extent of there being reservations about taking steps to limit certain individuals as blood donors.

If we read on, we can see a quote on the top of the next page:

"Three haemophilia patients with the syndrome did not mean that they ..."

That's the companies, the blood industry:

"... should spend millions of dollars changing recruitment and screening practices."

All that really seems to have been achieved at that particular meeting is summed up in the short paragraph in the left-hand side column, firstly the use of the name "AIDS" and then secondly an encouragement to continue studies of haemophilic patients.

We can read the rest of that page for ourselves. We see a reference to some of those who considered that immediate action to reduce exposure to concentrates was warranted, perhaps chief among them, to us, is Dr Oscar Ratnoff because we have heard quite a bit of him and his practice in Cleveland, Ohio. What I want to

ask you about particularly is that paragraph beginning "finally", where Dr Evatt mentions the development of AIDS in a 20-month old infant and he describes that as an unequivocal transfusion case.

Again we are, I think, now familiar with this story. This is a child who had had a number of platelet transfusions, I think to do with rhesus sensitisation. After the child became ill, the donors of the platelets were investigated and it was discovered that one of them had become ill with AIDS.

I would like to show you the particular MMWR which reported this case, if I could. It's [SGH0085105]. Can we go to the top? It's December 10, 1982. Firstly what happened in this edition is that there was an update on the three people whose cases had been reported in the July. We can see from the fourth line that all three had died:

"In the intervening four months, four additional heterosexual Haemophilia A patients have developed one or more opportunistic infections accompanied by in vitro evidence of cellular immune deficiency."

This piece goes on to write up the four additional cases and one highly suspect further case.

What's interesting against the information you have been giving us about how doctors investigate the

possibility of a new infection is to see how all-encompassing the enquiries seemed to have been. So questions had been asked about the patients' sexual activities, drug usage, travel and residence. And they seem to have drawn a blank with that particular line of questioning because it didn't reveal that the individuals had been in contact with each other, with homosexuals, with illicit drug abusers or with Haitian immigrants. But what they did have in common was that they had all received Factor VIII concentrates.

Can we read on through this, please, having looked at page 1, page 2 and 3, you go on to discuss the individual cases. We can just see that, if we look quickly, including a ten-year old child and a seven-year old child who was the suspect case. Then on to page 4. another insight into the thinking of those who were investigating here. These individuals have had no known common medications, occupations, habits, types of pets or any uniform antecedent history of personal or family illnesses with immunological relevance. It looks to have been a pretty thorough investigation of all possible common elements, doesn't it? Even thinking could it be something to do with their pets?

Obviously --

A. Those would be standard questions in an infectious

disease history, asking about pets.

Q. Okay. So still very much thinking about the products used in the treatment of haemophilia and then going on to discuss the 20-month old infant. If we can scroll down, we can see what had happened there.

This child, in the first month of life, had received blood products, including whole blood, packed red blood cells and platelets from 19 donors and then became ill.

Then can we go on to the next page, please? This is charting the illness of the child. The discovery about one of the 19 donors having had AIDS. Indeed he has gone on to die in August 1982.

Then can we go down through the editorial note, please? Particularly that passage at the bottom of the page:

"If the platelet transfusion contained an aetiological agent for AIDS, one must assume that the agent can be present in the blood of a donor before onset of symptomatic illness and that the incubation period for such illness can be relatively long."

On to the next page, please. The concluding comment is that:

"This report and continuing reports of AIDS among persons with Haemophilia A (7) raised serious questions about the possibly transmission of AIDS through blood

and blood products."

Professor, we have discussed this case with a number of witnesses and I simply wanted to ascertain from you, as a professor of infectious diseases, how important you think this event was?

A. I think it's very compelling data for an infection. That's my perspective as someone who is looking for an infection in everything, admittedly, but I think it's compelling. In the interests of complete balance, I would have to say it's not conclusive. I perhaps could give an example of when Hepatitis B was identified as being transmitted sexually and particularly by homosexuality, and up until that time it had been extraordinarily unclear how so many males had been getting Hepatitis B in certain countries, and then when the revelation of homosexual transmission came out, it was apparent that they had been concealing the fact that they had been homosexual for many years.

So as I say, my perspective on this is that this points very much to an infectious cause but one has to think that there are alternative points of view there, and that taking a history from somebody, classically their smoking history, is notoriously inaccurate.

Q. Right. So having asked you to give us your own words, I'm now going to suggest something to you: this case of

a child in whom AIDS could be linked with a donor, could that be seen as a step change in the thinking?

A. Again, I think it's compelling but not absolutely conclusive because this was a very young child and we don't know anything else about the genetic background of the child or its own particular susceptibility to illness, and a percentage of apparently normal children are born with a genetic abnormality which would make them more prone to an infection. So there are alternative explanations for this. Again, it's another piece, as you say, of the jigsaw, which is more and more suggestive of an infectious agent and a transmission by blood products. But it doesn't close the door.

Q. Yes. I suppose, as lawyers, we are very familiar in lots of different contexts with a phenomenon where a number of different things have happened and any one of them can be explained individually, but the totality of the picture is more than the sum of the parts really and might it be that we are within that kind of situation?

A. I think that's a reasonable analogy, yes.

Q. Now --

THE CHAIRMAN: Ms Dunlop, time.

MS DUNLOP: I had my eye on the clock. I just wanted to go back to the article and warn everyone. Can we just go

back to the article because I'm right in the middle of asking about this particular case.

Can we just bring it up again -- thank you -- to see what Dr Evatt said about that. Can we go on to the next page, please? He said that:

"We were now convinced ..."

Just at the end of that section. So that was where I wanted to get to, sir, before stopping for a break, just to finish the case of the infant, if we could.

THE CHAIRMAN: Just before we do break, you have used two expressions in recent answers that are quite important, I think. You talk about the evidence not being "absolutely conclusive" and the examples "not closing the door" on the range of possibilities that have to be considered. Ms Dunlop has drawn your attention to the practice of lawyers in putting together various strands of information to reach conclusions.

Lawyers would normally specify the standard of proof that they were applying, normally a balance of probabilities, professor. When you talk about absolute certainty, what standard of proof are you applying?

A. I'm familiar with the concept of balance of probability from previous exposure to the legal profession. The absolute proof is the identification of the agent and total association of that with the disease. Until that

moment there is, in my mind, a shadow of doubt but I would be pushed in the direction of saying a balance of probabilities exists before that.

THE CHAIRMAN: Yes. Is this some version of Koch's Postulates that you have just applied or is that your own?

MS DUNLOP: That's where we are going next.

THE CHAIRMAN: That's where you are going next?

It is time for a break then.

(11.09 am)

(Short break)

(11.33 am)

MS DUNLOP: Professor Lever, just before we stopped, we were looking at Dr Evatt's article and I think, as a useful way in to Koch's Postulates, we can look at what he says. Can we go back to the article, please, [PEN0161183]? It's page 2298, so over the page, please.

He describes the next big meeting that they held, after the meeting in July 1982. We understand that there was a big gathering on 4 January 1983 and we know it was a difficult day, but if we go a little bit further down, we can see that one of the things that was said at that meeting seems to have been:

"Show us the agents ... Subject it to Koch's Postulates."

We have thought about Koch's Postulates over the past four weeks and I have warned you that this was coming. So you presumably have been thinking about Koch's Postulates as well. We have looked at a particular line, which I'm going to come back to later today. But a particular line:

"There is no conclusive evidence that AIDS is transmitted by blood products."

What role do you think Koch's Postulates should have had in all this investigation and theorising as to what was going on?

A. You would hope a professor of infectious diseases would know what Koch's Postulates were.

Q. That's why I'm asking you?

A. Perhaps just to put it in context, Koch's Postulates had such a level of authority in terms of identifying infectious diseases, largely because of Koch himself, who identified both tuberculosis and anthrax, and again, to put it in context, at the time tuberculosis was responsible for a third of deaths in young people. So discovering the agent that caused that was clearly a fantastic leap forward. So he is held in some level of awe by most people who deal with infection because he did that and then set down some very basic rules for identifying whether a particular infectious agent was

the cause of a disease, and I unashamedly have notes on what those Koch's Postulates are.

The first was that it should be found in abundance in every case of the disease and not in healthy individuals. The second was that it must be isolated from the diseased organism and grown in pure culture. The third was -- initially "must" but then changed to "should" -- cause disease when introduced into healthy organisms, humans. And fourthly, it should be re-isolated from those diseased organisms and be identical to the original agent.

So Koch himself abandoned postulate number 1 very early on because there were cases of healthy carriers of things like cholera, who were excreting it but had no disease, and yet it was clearly able to cause disease in other individuals, and those postulates served people very well when they were dealing with bacteria, which can be grown in pure culture mostly. Some it's still very difficult.

But they have major limitations when you move outside of the veterinary field because experimentally introducing an infection into an organism to prove it's the cause of disease is not something that one can do outside of the non-human field.

So they are valuable as a guide but they are not the

final definition of whether something is an infection. And in fact, there is a relatively more recent and slightly more lengthy and fractionally more woolly version of a molecular form of Koch's Postulates which look at the level of genetic material of a particular infectious agent within somebody who has an infection.

In very basic terms, the level of the amount of infectious agent should correlate with the amount of infectious material and should be reduced by successful treatment or eradication, and should then be found again in another individual who has the infection.

So Koch's Postulates are bandied around rather loosely and they apply well to things like bacteria, and to some extent to parasitic organisms, but for viruses they are much more difficult to apply because viruses only grow within living cells and if one doesn't have the appropriate cells in culture in which that virus can grow, or one cannot keep the appropriate cells alive, one cannot fulfil the second of Koch's original postulates.

Q. Right. I think we have perhaps struggled to get a sense of how significant they would be when a doctor was faced with a new disease and this is thinking about the early 1980s. I mean, you wouldn't find them on the wall of the laboratory. Or would it be something that every

infectious diseases physician in the early 1980s would have had in his or her mind?

A. Every medical student would have been exposed to them as part of the historical background to infection and for their value within a certain range of infections, but there were already infections in the human race, including non-A non-B hepatitis, which certainly hadn't fulfilled Koch's Postulates and yet were accepted to be an infectious agent.

Q. Right. Can you just tell us a little bit about the advent of viruses, we have heard it said that Koch wasn't really applying his mind to viruses. Was there a concept of the virus at that time, or is that a 20th Century concept?

A. It's more of a 20th Century concept and it originated in the idea of a filterable agent. Viruses are much smaller, ten to 100 times smaller than bacteria, and it was known that you could sterilise certain infectious innocula by putting them through a very fine filter which would retain things like bacteria or fungi, and what came through would no longer transmit the disease but there was a category of agents, which were called filterable agents, which were not retained by this filter and were thought therefore to be smaller but their nature was not understood.

Q. Right. When we met you in our preparation for the Inquiry to give us an idea of how small a virus is, you did suggest to us that if the virus was the size of a cookie, the human body would be about the size of Britain.

A. A tennis ball is quite a good analogy.

Q. Right, so the virus is the tennis ball and the human being is Britain?

A. The United Kingdom.

Q. The United Kingdom. Right.

THE CHAIRMAN: Can I ask one question?

If we look at the 1980s and consider the emerging information, would a person, a skilled person, looking at the emerging data, have appreciated that Koch's Postulates were perhaps already not directly applicable to what was happening?

A. I think so. I don't think that anybody who was very conversant with infectious diseases would have made the request in this article.

THE CHAIRMAN: If we think more particularly about someone who already accepted that had non-A non-B hepatitis was transmitted by an infectious agent, could he think in terms of Koch's Postulates or could he, with proper, I suppose, values, think that Koch's Postulates provided an appropriate set of criteria for application?

A. If Koch's Postulates are fulfilled, then there is no question about it.

THE CHAIRMAN: Indeed.

A. But I think, my Lord, it comes back down to your own phrase of the balance of probabilities, in that if most of them were fulfilled, one would believe that it was more likely than not an infectious agent.

THE CHAIRMAN: We know that some clinicians at that time took that approach but others didn't.

A. That's correct.

THE CHAIRMAN: Yes. I think there are some areas in which I'm going to have to take decisions rather than try to get you to take them for me, professor, but it is quite difficult.

If one thinks of Dr Aledort, for example, who is well-known as an opponent of Dr Evatt's views in this, he was clearly an extremely prominent, highly respected clinician, very wide experience of the treatment of haemophilia patients, and yet resisted, I think one can say, the notion of an infectious agent longer than most. Do you have any observations that you could make on his position?

A. I think, if I was making observations, it would be speculation. But it would include the possibility that his understanding and knowledge of infections was not as

great as others, and also one would have to bear in mind the implications of accepting that it was an infectious agent.

THE CHAIRMAN: I think that second point is one that we have not missed, yes.

MS DUNLOP: I think I need to come back to it, sir.

THE CHAIRMAN: Yes.

MS DUNLOP: Just on that page, Professor Lever, do you see on the right-hand side and the right-hand column, there is reference to recommendations from the National Haemophilia Foundation. They find some echo in the United Kingdom as well around about that time.

There is mention of the NHS issuing a number of important recommendations:

"... including postponing elective surgery and using cryoprecipitate in newborns and patients without previous clotting factor exposure."

What's the thinking behind giving cryoprecipitate to patients without previous clotting factor exposure? That seems to be very similar to the sort of ideas that were around about NANB hepatitis. Was that a legitimate basis on which to issue recommendations?

A. The implications behind that are that an infectious agent which is transmitted is a possibility.

Q. Right. But what would be the thinking behind continuing

to give similar amounts of concentrates to patients who had already had concentrates? Is that some sort of suspicion that, like NANB hepatitis, they will be infected anyway, they will be infected already? I think that's what that's designed to meet?

A. Yes. There are several issues about infections and (inaudible) in particular, which possibly is not immediately clear. One is that the history of exposure to infections is that one more often than not clears the infection and is then immune to the infection. I come back to measles or mumps or rubella. If we get it once and if we are exposed to it again 90 years later, our immune system still remembers and doesn't allow us to get infected a second time.

With some chronic infections which were known about at the time, like Hepatitis B, it was also the case that, although a proportion of people were known to be rather poor at clearing the virus, the majority of healthy individuals did appear to be able to clear it and develop immunity so they couldn't be reinfected. There are people who don't clear Hepatitis B and become the chronic carriers.

But the concept in exposure to infectious agents is still, in many cases, that exposure somehow gives you some level of protection, even if it doesn't just

protect you from being infected a second time by a completely new virus. It's clear in hepatitis, and indeed to some extent in HIV, that if you have a good immune response, then you do better because your immune system is fighting the agent. So there would be a perception that having been exposed to something, it was not going to harm you to be exposed to it again because either your immune system would have developed sufficient immunity to protect you completely or you had some immunity which would somehow help to suppress the second exposure.

The difference -- and one of the unique issues about HIV -- is that prior exposure to one HIV gives you no protection against a second HIV or a third or a fourth.

That, in infectious diseases, is a new concept.

Q. Right. You see, it's just that, because this is a bit of a recurrent theme, the idea of particular protection for patients without previous exposure, you end up wondering whether that turned out to be a misconception because, if you look at the statistics for different countries about people with haemophilia, it is always the people with severe haemophilia who show the highest infection rate.

So that to me, as a layperson, suggests a much more straightforward relationship, that the more they have,

the higher the chance they were going to get HIV. Do you think enough attention was paid to reducing across the board the amount of exposure to concentrates?

A. There are two issues there. One is your chance of getting infected at all. And the more often you are exposed, the more likely you are to get infected and that's very well documented from a number of studies with HIV. So if you are a mother who breast feeds your child, there is about a one in seven chance of passing the virus on, for example. And so, where hygienic bottle feeding is available, that's a preference.

So being exposed multiple times to something which might be infectious is more likely to get you infected.

The other things about HIV is that it's a very imperfect virus in terms of what's technically called the particle to infectivity ratio, but what that means is how many virus particles there are and how many of them actually work.

HIV has a notoriously high particle to infectivity ratio. Estimates being that certainly less than 1 in 1,000, possibly less than one in 10,000 and possibly even less than one in 100,000 viruses are actually functional and infectious.

So even though you might be exposed to a million viruses, you might only be exposed to ten which could do

you any harm and that means, the more exposures you get, the more likely you are to get exposed to one which actually infects you successfully.

So that's the chance of infection.

The second issue relates to what I said previously, in that HIV is not able, or our immune system is not able to produce a sterilising or protective immunity to stop a subsequent infection.

HIV has proven to be so far impossible to develop a vaccine against because it is hugely variable. Every time it replicates it mutates at least once and probably five or ten times.

Without being too technical, the virus, as I said, is made up of RNA and there are about 10,000 individual nucleotides making up the RNA of the virus. We know that the enzyme that copies it makes a mistake about once every 10,000 bases, so it makes a mistake every time it replicates. Within an infected individual, even when they are well, they are producing around 10 to the 11th, which is 100 billion viruses every day, and they are mutating at the rate I mentioned, which means that in one infected person, every single one of the 10,000 nucleotides is being mutated at least once every day. So the variability of that virus is enormous. It also explains why so few of the viruses are infectious to

some extent because many of those mutations will be lethal for the virus. They will interfere with some important protein that the virus needs.

The second issue which makes HIV so variable is that it can undergo a process of what's called recombination. And again, I apologise for getting slightly technical but within each virus particle the virus carries two copies of its genes. When it's replicating its genes, it can take pieces from either copy to make up the final product. If they are both the same, that doesn't make any difference because what comes out is a bit of each which add together to make the same, but if you have a cell infected with two different viruses, then -- I say possibility -- factually what happens sometimes is that the virus picks one of each of those to go inside a virus particle. Then, when the recombination occurs, the resulting virus is a mixture of the genetic sequence of the two apparent viruses it came from and this also makes the virus extremely variable. It's probably more important in variability than the fact that the enzyme makes mistakes.

This means that if you are infected once with HIV, you have a family of viruses which develop from that infection and certainly by sexual transmission, you probably only get infected by a small number, a handful

of viruses. But you get a family that derive from that handful and rapidly become very large. If you are repeatedly exposed, you are going to be exposed to different variants, and because those variants can recombine, then the resulting diversity of viruses that you can get is going to be even larger.

So multiple exposures is a bad thing for increasing the diversity of the virus that your immune system has to encounter, and again this would be something which would not have been obviously predictable from other infections that we knew about.

Q. Just to pick up a couple of things to see if I have understood you, professor. The enzyme making the mistake, that leads to a mutation?

A. It does.

Q. Right. The person's body does manufacture antibodies, it is just that they are antibodies to an old edition of the virus and the virus has moved on?

A. Largely, yes.

Q. Yes. The phenomenon you have just described about multiple exposures, and I suppose a sort of almost infinite amount of mutation and combination and so on which is going on, does that make the person more ill?

A. It means that the variety of viruses that the person will harbour is going to be larger and therefore the

risk of the virus mutating to evade the immune defences, and if the person is on treatment, evade therapeutic drugs, is higher. So they will not be more ill, but they would potentially get iller more quickly. So the time period between infection and AIDS may be shorter.

Q. In retrospect, would it then have been a good thing to try to reduce everyone's exposure to concentrates, including those people who had the most severe haemophilia and who were taking concentrates perhaps three times a week?

A. In retrospect, that's absolutely correct.

Q. Yes. Just so that we can finish looking at Dr Evatt's article because it is quite a useful chronology of what happened, he goes on to describe at the bottom of that page a development in March 1983, whereby Hyland licensed a form of clotting Factor VIII, that had been heated in lyophilised form, which we understand to be freeze-dried, and marketed as a product with reduced risk for Hepatitis B:

"Unfortunately, clinical studies soon demonstrated that the Hepatitis risk was not eliminated and patients and physicians considered the process ineffective."

Just to let you have a look at that paragraph, Professor Lever, do you think that the sort of reservations that physicians had, particularly in

relation to what had happened with the Hyland product, were reasonable?

A. I think they were understandable; in that different viruses have very different susceptibilities to inactivation procedures. Hepatitis B is particularly tough, difficult to inactivate. It turns out that HIV is actually very easy to inactivate. It's very susceptible. Smallpox is an another example. It survives very comfortably outside the body in blankets and things and it can survive drying outside the body. So there is a complete spectrum of susceptibilities to inactivation in the virus families.

Q. One of the theories that's evident from the Internet is that AIDS, at least in some people, has a non-viral pathogenesis and one point that's made is: how could a virus survive freeze-drying? I asked another witness about this and apparently there is no difficulty in the concept of a virus surviving freeze-drying. So it doesn't need, for example, a lot of moisture in order to survive?

A. It turns out that HIV would be more susceptible but a number of viruses are designed to survive. If you imagine something like an enterovirus, which infects us and gives us diarrhoea, gastroenteritis, that virus has to survive in the environment, perhaps in fresh water or

salt water or on vegetables. So that when you eat it, it is still intact. It hasn't replicated but it is intact. It then has to go down into the stomach and survive an extraordinarily acidic environment, which is actually designed to try and protect us against infections. It then has to go through the small bowel and survive an extraordinarily alkaline environment with lots of enzymes which are designed to break down proteins of which it is made. So some of these things are very tough indeed.

Q. Looking back on what's described here about the initial experience with the heated product -- a Hemofil product, I think it was called -- when it was discovered that in fact the hepatitis had not been inactivated and that, I suppose, turned people away from this as being a possible answer to the problem. I mean that really does seem in retrospect to have been very unfortunate because as it turned out -- and there is a study from the Netherlands -- albeit it did continue to transmit hepatitis, it was actually HIV-safe, as I understand it.

Just to finish looking at Dr Evatt's article, he goes on to talk about what happened in the Institute Pasteur. You have mentioned this in your report as well, about the isolation of the virus by Barre-Sinoussi and Montagnier. In retrospect, it looks

as though not enough attention was paid to the French discovery. You have alluded to this already this morning and said that for some people -- I think yourself included -- it seemed very significant at the time but perhaps not to the mainstream. Would that be correct or is that not the right way to see it?

A. I think the fact that they identified a virus in somebody who was clearly a person who had all the characteristics of AIDS, and it was the first plausible one which looked like a category of virus which would be a possible candidate, was very persuasive.

The scientific community -- more then than now but certainly then -- was very US-dominated, and it's difficult to say this without sounding as though either one has a chip on one's shoulder or that one is anti-American, and I'm neither of those, I hope, but there was a sense that certainly amongst the American community, unless it had been discovered in America, it wasn't real. That, as a rather trivial example, occurred with SARS, when the Canadians isolated the SARS virus first and the Americans isolated and published it about a week later and the comment in their article was that they were pleased that the Canadian sequence agreed with theirs.

So there is that sort of mentality, that unless it

had been done in the US, it wasn't real. There were also, and are also, very high profile people like Robert Gallo, who felt that they should be the person to discover this and would have a vested interest in making sure they were the first. Having discovered HTLV-I and HTLV-II, and HHV-6 and HHV-7 by the way. So they felt that they were the people who should do it. So there was, it's thought, resistance to having the French data published and so that was purportedly delayed by reviewers, whom one suspects, were American, and then there was a degree of scepticism about whether this was a real virus.

If there is any mitigation about this, the Montagnier-Barre-Sinoussi team were not a group with a long track record of discovering viruses, unlike the Gallo group, which had. So one might have been forgiven a small degree of reasonable doubt, if you like, about whether or not what they had found was real.

As we know subsequently, there have been lots of false dawns about viruses as causes of diseases, most recently the retrovirus XMRV apparently being associated with prostate cancer and chronic fatigue syndrome, which excited a lot of publications and turns out to be highly unlikely. So these false dawn publications, particularly perhaps from groups who didn't have a track

record, would naturally excite more scepticism than a report from a laboratory with a well established record, which had been proven by others.

So there was that sort of atmosphere about it. However, I think objectively at the time, many people, myself included, felt that this was a significant finding.

Q. Right. I suppose if one is not going to fall into the post hoc fallacy, there is still a bit missing because it could just be that this new virus has been found in someone who has AIDS and it is an incidental finding. The first one wasn't in doubt -- that a new virus had been found in a patient with AIDS?

A. They had found a virus, certainly.

Q. I suppose to be fair to Dr Gallo, he did contribute the other part about a year later, where he demonstrated the transmission. Is that right? Perhaps you should explain to us what bit of the jigsaw he supplied.

A. It's quite a convoluted story. He also identified a virus and also showed a lot of evidence that people who had AIDS-like syndromes had antibodies against this virus.

So that was more compelling circumstantial evidence that the virus was associated with the disease, rather than just finding the virus in somebody with the

illness, which, as you correctly say, it could have been a passenger and it could have been a virus to which the real AIDS virus had made this person more susceptible.

Q. Right.

A. So he contributed a lot from that point of view. Their identification of the virus turned out to be, as I'm sure people have said before, flawed in that it turned out to be the same virus that the French had led them to compare. So it's not clear that they actually did identify the physical virus itself.

Q. Yes. As Dr Evatt goes on to say, the story after that is a shorter one, talking about the year between the middle of 1983 and the middle of 1984, and the development both of testing and also of heat-treated products.

Although even there we can see that that wasn't entirely straightforward because if we look at the bottom of the left-hand column, we can see that there was a concern about inhibitor formation.

But he goes on to say, at the very end, that the AIDS epidemic in the haemophilic patients thus suddenly ceased. That's about ten lines up from the end:

"... and subsequent studies of birth cohorts demonstrated that no haemophilic patients born in the USA in 1985 and later were infected with LAV, later to

be renamed HIV."

But in that period, 1981 to 1984, more than 50 per cent of the population of haemophilic patients in the USA had already become infected.

Can we put that article to one side, please, and return to your report?

I wanted to go back to what was happening in the UK and if we look at 817 onwards, you refer to the meeting, which is actually a meeting at Heathrow Airport, in January 1983. You go on to say that a figure then described one or two cases of AIDS being documented in the UK is probably an underestimate. You personally saw two cases of what was, in retrospect, probably AIDS. The first documented case in the UK of which we are aware, is the one that was reported from the Brompton Hospital, actually reported, I think, in December 1981. Did you actually know of that case?

A. The first case I saw was a -- I'm not sure it was the same one but actually it was a patient who was transferred to us when I was working in Northwick Park, from the Brompton Hospital. Because at the time, when I was working on the immunoglobulin concentrates, I was working with Dr David Webster, who was an expert in what's called primary immune deficiency; in other words, immune deficiency that you are born with or you acquire

and there is no obvious external cause. That distinguishes it from secondary immune deficiency caused by drugs or cancers or HIV.

Because David Webster was an expert in immune deficiency and the treatment of people who had infections related to their defective immune system, this particular individual was transferred from the Brompton Hospital because they had a lung infection, which the people at Brompton couldn't understand and were unable to get on top of, and it was felt that Dr Webster's team might be able to provide some additional expertise and as I say, this is in retrospect almost certainly an AIDS case. It was a person who was widely travelled, homosexual and had an history of weight loss and an unexplained infection.

The other was somebody I saw transiently on a paediatric ward who had come relatively recently from either the Southern United States or the Caribbean, and I can't remember exactly, and had been admitted soon after arrival in Britain with an immune deficiency syndrome, which again, in retrospect had the characteristic of HIV. So it may have been that I was just in a place which might have seen more than average but I don't believe my experience was unique.

Q. So the second case will have been a child? Is that

likely to have been a vertical transmission then?

A. I think it probably was, yes.

Q. Right. I wanted to go on to ask you about Kaposi's sarcoma, which you discuss in the ensuing paragraph. You say:

"It was noted, inexplicably at the time, that the haemophilia population were not presenting with Kaposi's sarcoma, whereas this had been an early and ongoing feature of AIDS in gay men."

You now know the answer to that conundrum, which is that it was due to another virus. Is that correct?

A. Yes.

Q. You were explaining earlier about the nomenclature here, that HHV, human herpes virus -- there is a sequence of them. Is eight the final one at the moment or does it go beyond eight?

A. To my knowledge it's eight.

Q. Right. So this one -- I think you say HHV6?

A. I'm sorry, that's a typographical error.

Q. It should be eight?

A. Yes.

Q. It's eight on the diagram certainly. HHV8 was identified in 1994?

A. Yes.

Q. Where was that identified? Is that a Gallo discovery?

A. Gallo was involved in that as well, yes.
Q. You think that therefore the reason why people with haemophilia were not presenting with Kaposi's sarcoma was something to do with the technique for preparing the blood products. Is that correct?
A. I think there are probably two or three possibilities.
Q. Right.
A. One is that that virus may be very poorly transmitted by blood-borne routes, not totally zero but certainly less than HIV. So the amount of virus present in the blood may be far less than the many millions of copies of HIV that one finds.

It may be far more easily transmitted by the sexual route, and that would be also plausible because other herpes viruses are transmitted by mucus membrane contact. Classically, herpes simplex type 1, which causes the cold sore, is transmitted mouth to mouth or by saliva and Epstein Barr virus, glandular fever, is known as the kissing disease.

So it is quite likely that sexual transmission of KSHV is far more efficient than any other route. And the third possibility is that a product preparation technique may have been enough to inactivate what is a large and also relatively fragile complex virus.
Q. Or a combination of the above, I suppose?

A. Or a combination of the above.
Q. Yes. So blood to blood is not always the best way of transmitting a virus; for some viruses other ways are better?
A. Yes. So one can divide viruses up into categories in different ways. Simplistically one can call them -- I call them hit and run viruses: things like flu, measles et cetera, which infect an individual commonly by the air-borne route, cause a very florid infection and then have to pass on to a new susceptible individual quickly because that person becomes immune and clears them. And those viruses classically cause very severe, acute disease but once you have had it you are immune, you don't get it again, at least not that variant. Just out of anecdotal interest, those viruses probably didn't come into the human race until relatively recently, 5,000 or 6,000 years ago.

Then there are viruses which have been with us for a far longer period of time, including those of the herpes virus family, which persist within us for many years and then reactivate from time to time and take what opportunities they can to transmit, either, as in the cases of herpes simplex or glandular fever, by mouth contact or sexual transmission, and those usually have to hide away somewhere and usually cause much less

damage because they want to maintain their host alive for as long as possible so they can take the opportunities to transmit.

Those tend to be less robust viruses and are more commonly transmitted by either things like sexual contact or blood contact. The former group, the air-borne ones, would not be transmitted by blood contact.

Q. Right. Thank you.

You go on in your report, Professor Lever, to talk about guidelines in early 1983 and then about Dr Galbraith's recommendation.

I just wanted to ask you, Professor Lever, about your comment in relation to Dr Galbraith, that:

"From an individual whose approach to the situation is coloured by his infectious diseases background, this is an understandable and rational suggestion."

Sorry, I think we need to go on to the next page for that. How new to medicine is the specialism of infectious diseases?

A. It's very old, it went through a period of decline after many of the large infectious threats to society were controlled better by antibiotics. So in the 1960s and 1970s it was felt that it was not so important. There is a classic comment from the then Surgeon General of

the USA in the 1960s to say that infectious diseases is now a closed book. My purpose in putting that small figure into the report at the beginning was to point out that it's not and we are exposed to new infections all the time.

Every year since I have been a consultant, there has been at least one new infection which hadn't been predicted before. So they have come into prominence again because of HIV, but actually in the 1960s, 1970s and 1980s, they were less prominent, but historically it's probably one of the oldest if you go back to Hippocrates and his description of fever.

Q. Given that, I think what's interesting to us is what happens when a physician treating a chronic condition -- and obviously for these purposes, we are talking about haemophilia -- suddenly finds himself or herself confronted with what may be an infectious disease, is there a judgment call as to the period for which he or she continues to look after the patient before involving an infectious diseases physician?

A. The answer is there is a judgment call. I think there has been a cultural change in the last 20 or 30 years in medicine globally, certainly westernised medicine, in that between the founding of the National Health and the late 1960s, 1970s and 1980s, there was much more the

case of the general physician, the general surgeon, who would treat everything that came their way and there were fewer specialists, and the specialists were specialised in their own area and knew what they were doing and there was less of a proclivity to ask advice. This has changed very dramatically and now multidisciplinary teamworking is really the norm and one would have experts from all disciplines which were pertinent to one's own area. So in a haematology ward round these days, it would be unusual not to find someone who was an expert on infection, either from the microbiology laboratory or from the infectious diseases unit. But that's a relatively recent and obviously very desirable phenomenon.

So I think people would in the past probably have tried to manage, unless they really felt they were out of their depth.

Q. Do you think pride ever came into it?

A. I'm sure pride came into it.

Q. A sort of, "I can handle this, I don't need to ask for advice".

A. I couldn't possibly say that never happened. We are probably all guilty of that to some extent but I don't think in many cases it's a driving force. I think one also is coloured very much by one's own experience in

the field and again, I may as well come to this point as others: the experience that the doctors treating patients with haemophilia will have had will have been of non-A non-B hepatitis or Hepatitis C, with, effectively, a 100 per cent infection rate but a tolerable risk, in that the risk/benefit analysis of giving the person the clotting concentrate versus not giving the clotting concentrate versus what was the outcome of being infected with another chronic virus, or a chronic virus -- or Hepatitis B, come to that -- would be that the balance was in favour of continuing the clotting factor concentrate. So I think one is inevitably coloured by one's own experience and again HIV turns out to be tragically an extraordinarily unique virus.

Q. Yes. One of the things that I think we have struggled with actually, looking back to that time, the early 1980s -- and it's no doubt impossible even yet to be prescriptive about what should have happened -- is the extent to which there was enough interaction. I suppose the people who had something to bring to the debate will have been, as well as obviously the haemophilia clinicians, infectious diseases specialists. Virologists, would they have been a distinct group of people then?

A. Yes, I think Richard Tedder appears in some of these documents and he was a virologist.
Q. Epidemiologists?
A. Again, people from the Centre for Disease Control in the US and the CDSC in the UK. Epidemiologists would have been involved, yes.
Q. This is purely in retrospect but do you think, looking back, that those who were directly responsible for the patients, the haemophilia clinicians, were receptive enough to the information coming from those other disciplines?
A. That's a very difficult question because it's a qualitative answer.
Q. Yes.
A. They clearly heard what was being said because they had meetings which discussed what was being reported in MMWR, at CDSC, at every meeting that I have read the minutes of, then the issue of a blood-borne agent as being responsible for AIDS is raised. So they are aware of it.

Whether they were taking enough notice of it or perceiving the severity of the threat, in retrospect clearly they weren't. Should they have been taking it more seriously? In retrospect, they should. It's difficult to get into the mindset of the person at the

time in that meeting, when they had a lot of conflicting priorities, which I realise means I have ducked the question.

Q. No, it's quite all right, I understand, professor. It might make it slightly easier for you by saying that one haemophilia clinician has said of that time:

"We needed a bit less democracy and a bit more guidance from experts."

How do you respond to that?

A. I think even the experts -- and this includes Dr Galbraith, who, on the face of it, has given an enormously prescient comment -- but even his comment was based on flawed data because at the same time the general consensus was the number of -- well, actually it was soon after, when the antibody testing occurred. The evidence was not there that HIV was 100 per cent fatal, I say 100 per cent. People die of other things while they have HIV, but left to its own devices.

So he actually underestimated the risk when he was talking about this, whereas other people were underestimating it more dramatically. Perhaps you could rephrase the question again for me.

Q. It was, I suppose, quite a noteworthy comment from a haemophilia clinician of the time that:

"We needed a bit less democracy and a bit more

guidance from experts."

A. I don't think there would have been an expert there who could have justifiably said, "This is what's going to happen," as it turned out. And that doesn't mean, I don't think, that everything that happened was perfect by any means, but I think it was understandable that, never having been confronted by an infection which was 100 per cent fatal, infection by which gave you no protection against a second infection and which no individual who was infected ever cleared, all three of those things are unique. So nobody really could have confidently said, "This is what's going to happen with HIV".

Q. Yes. Far less gone on to say, "And this is what you must do".

A. Again, that would come down to what were the consequences of doing that. That would have been something rather simple such that there was an easy alternative, and the example I would give you is my own sad experience with the intravenous immunoglobulin, where patients were infected with what turned out to be Hepatitis C, but there was an alternative product available and so other people who hadn't been exposed to that were switched to the other product. If there had been an easy option, which people knew had been tried

already and was safe, then it would have been easier to do and then one could have said that more dictatorship would have been very helpful.

Q. One doesn't get the impression reading a lot of material from that time, or indeed reading more broadly, that doctors take kindly to dictatorship. So one might hypothesise that somebody who had come along and said, "This is how it looks and this is what you must do," would have been a good thing, but actually in practice would there not have been doctors who would have said, "I reserve the right to make up my own mind and deal with my own patients as I see fit"?

A. That has always been the case in medicine, until more recently, when things like financial constraints have been put on the medical profession, restricting what they can do and what they can't do. There has always been a sense, certainly up until recently, that medical practitioners are individual practitioners who do what they believe is the best for their patients.

Q. I suppose there is more guidance around nowadays, is there? Is NICE the main type of guidance that doctors have to assist them?

A. It's one of a raft of different forms of guidance from specialist bodies like The Royal Colleges for example, providing guidelines, specialist societies that provide

guidelines, and the British HIV Association, for example, publishes extremely respected guidelines worldwide on the diagnosis, management and treatment of HIV.

Q. How far back does that phenomenon go then? Does it go back into this era or not really?

A. They would have been relatively scarce at that time, apart from some well established conditions like, for example, treatment of tuberculosis, where it would have been accepted that you started with at least three drugs of a particular set of classes and everyone would have agreed that that was a sensible thing to do. But there was much less in the way of written guidelines, and, of course, they proliferated with the access to electronic information.

Q. Yes. Just to go back to Dr Galbraith and his recommendations, we know, because we have seen the documents, what happened to his suggestions. We know there was a paper which he prepared and sent to the DHSS in May, and then the meeting of the biological subcommittee of the Committee on Safety of Medicines was scheduled for 13 July 1983, and even in preparation for that there was a suggested agenda and, I think, actually, suggested decisions, suggested disposal, of his recommendations.

It's difficult to avoid the impression that there is a bit of a logical flaw in the thinking, however, because much of the decision not to act on his suggestions seems to relate to questions of supply and, given that the task for the committee was to decide on the safety of these products, at first sight it's difficult to see that whether a product is safe depends on whether there is an adequate supply of alternatives. Surely it's either safe or it isn't.

A. It's a risk/benefit analysis, in that it's not safe to run across the road blindfold but that depends on whether it's midnight or it's the M1. So something can be unsafe but not unsafe enough to warrant a drastic change in policy, something can be terribly unsafe, in which case it would warrant a drastic change in policy, and I think the argument comes down to what was the level of unsafeness, or the perceived level of unsafeness.

Q. Right. But how is whether we have an adequate supply of alternative treatments relevant to that?

A. I'm sure the haemophilia specialists, who know more about it than I do, would be able to tell you about the change in lifestyle and morbidity and mortality that the factor concentrates had given to the patients with haemophilia, and the extension of life expectancy over

a relative short period of time by their introduction is very dramatic. So that relates directly to the availability of the supply.

Q. Yes. So you would see the exercise before the committee in July 1983 as entirely a relative one, looking at relative safety and looking at a comparison between maintaining the treatment or withdrawing the treatment and leaving people to cope as best they could, going back, I suppose, several decades?

A. I think Dr Galbraith, quite correctly, expected it to be a discussion of safety from his point of view, which was the infection risk, but, because he is not somebody who is involved or was involved in the administration or management of individuals were haemophilia, it would come down to the relative safety of an infection of completely unknown severity at that time. Although people knew that those who got AIDS-like syndrome died, nobody knew how many people who got HIV went on to get AIDS. So it would have been a balance between the safety of that which was unknown against a known risk of committing the haemophilia population to having no factor concentrates.

Q. There seems to be a sort of awareness that Dr Galbraith personally was dismayed by the outcome of his letter and the meeting in July. Do you have any knowledge of that

or is that purely anecdotal?

A. It's anecdotal. I have no personal knowledge.

Q. Right. In the early 1980s, when doctors were considering what might be going to happen with AIDS, particularly in patients with haemophilia, do you think there was any sort of read-across from non-A non-B hepatitis? By that I mean that it certainly seems to have been established by the middle of 1982 that the products, whether commercial or National Health Service, all seemed to transmit non-A non-B hepatitis. Was that in any sense a precedent for what might be going to happen with AIDS?

A. I would be surprised if people had not looked on it that way because that was the experience of what may have been, or turned out to be, or probably was, in most people's minds a chronic virus infection which had been transmitted, and one is always heavily influenced by one's most recent experience, for example, if you like, the over reaction to influenza last year compared to the under reaction the year before. So one is very much influenced by the most recent event that occurred and there may have been a sensation of it's just another virus or it's possibly just another virus and the non-A non-B is something we have been able to cope with.

Q. Yes, I suppose the mistake part -- and you have

mentioned this several times -- is that the virus may be destined to have a very wide prevalence or to affect a large number of people, but the missing part is how many of those people are going to become very seriously ill. I suppose at this time that wasn't really at all clear. Is that correct?

A. That depends on being able to detect infection when there are no symptoms and that depends on the availability of a reliable test, either for an antibody response in the individual or for a direct detection of the virus itself. If you can do a survey of people, as happened later, and find that everybody who develops an immune response against a particular agent gets better, or everybody doesn't get better, or 50 per cent of people get better and 50 per cent don't, then you can make much better predictions as to what's going to happen.

Q. Right. You have referred to the sort of investigations which might at the time have been thought to be helpful. If someone at that time had imagined that they had a group of patients who were perhaps at risk of developing AIDS and decided to study the immunology in those patients, would that have been something that would have been understood as a helpful investigation?

A. To a large extent that was done, in that, with the

relatively limited sophistication of immunology at that stage, people were able to look at the different types of white cell, which are part of the body's defences, and in particular the lymphocytes and in particular the different classes of lymphocytes, and it was observed that the lymphocytes carrying a protein on the outside, called the CD4 molecule, which are normally present in a higher abundance in the circulation than those which carry a protein called the CD8 molecule, actually had been depleted or declined and that that correlated strongly with the development of infections related to immunodeficiency, and this was to some extent already recognised as being apparent in some cases of drug-induced immunodeficiency. So people had been able to identify that there was a phenomenon which would be interpretable as an immunological defect, even though they didn't have a specific test for the virus or for the antibodies against the virus.

Q. It seems from what you say in your report -- there is a paragraph numbered 8.25, although I think that reference is actually to 8.25 in the preliminary report?

A. All of those are.

Q. -- that really the preponderance of opinion by the first part of 1983 -- this is, I think, in truth May 1983 we are talking about -- was that a virus was

the most likely culprit and you have spoken a bit about a particular letter from the Haemophilia Society. I don't think we need to look at that; we are quite familiar with its terms. But this:

"AIDS has not been proven to result from transmission of a specific agent in blood products."

Do you think even at the time, Professor Lever, this was pitched in too reassuring a manner?

A. It's trying to put oneself back in time again. There were competing hypotheses as to what was causing the immunodeficiency, some of which had quite powerful advocates. I think, as I said before, the balance of opinion or the balance of evidence was in favour of an infectious agent at that stage. However, as one knows, the amount of distress and concern and worry, sometimes unnecessarily, that you can induce in people by raising the fear of an infectious agent in something like a blood product would be undesirable unless it was absolutely certainly the case, or as near certain as you could be that that was the case.

I think people would not necessarily have been very understanding had this turned out to be a false alarm and individuals had either bled or died by withdrawal of the clotting factors and then it having been found that there was not the threat which had been assumed.

Q. Can we think a bit more about what we have been calling the "antigen overload hypothesis" and that we understand to have been a competing theory? I think you mention this in the next section. You say:

"The theory about repeated infusion of foreign protein is raised. Lancet paper from Edinburgh published."

We have already talked about this. I think this had been around since the first reports really, or very shortly after the first reports. But would I be right in thinking that the antigen overload hypothesis would have had to explain what was going on in these very different groups of people: in homosexual men, in the child with the platelets transfusion and in people with haemophilia, and so it would have to explain all these events, and I suppose it might also be a bit puzzling why it was all happening now or around much the same time? Do you think these factors really pointed away from the antigen overload hypothesis?

A. I think all those points are exactly right. One could create a plausible argument. We know from immunology that you can become tolerant to something which otherwise would trigger an immune response and that also depends on which route you are exposed to it. For example, we eat proteins every day and we don't develop

antibodies to them. But if we injected those same proteins into the blood, we would produce a very, very florid immune response. So the route with which one encounters the same molecule can make a very, very large difference to how your immune system sees it because the immune system is set up to recognise not only what is you and what is not you, so it can fight the things which are not you, but whether what is not you is dangerous or whether it is not dangerous, and part of that is which way did it get in.

THE CHAIRMAN: I wonder -- sorry, finish first. I would like to come back to the question. Have you got more to add that point?

A. I have some more to add to that, if that's ...

THE CHAIRMAN: Yes, please.

A. So in individual cases one could argue that excessive exposure to proteins found in sperm, for example, through a route which is known not to be particularly robust, which is the gut, the lower gut, the anal canal, might trigger some sort of aberrant immune response. We can manipulate the immune system. We can desensitise people to bee stings, for example, by giving them more and more of a protein so that the immune system gets fooled into thinking it's okay and it doesn't have to make a response. So the idea that one could suppress

the immune system by delivering proteins by a route they didn't normally go in was a plausible thought.

But all the examples of that sort of tolerance or lack of immunity are very specific. When you tolerise somebody to bee stings, they are not tolerant to wasp stings, so giving a particular protein by a particular route might be expected to suppress your immune response to that protein but not to every protein. It would be difficult to put that together with tolerising your immune system to suddenly becoming unable to recognise multiple different infections.

Although you could argue that this is a previously unexperienced way of doing things, like putting a lot of foreign protein into the blood or exposure to a lot of foreign, at least non-self, protein by an abnormal route, there wouldn't be a good precedent for that causing a generalised reduction in your immune competence.

The biggest exposure to foreign proteins that humans ever get is pregnancy, where a mother has got a baby inside who is half father's proteins. The immune system does fantastic things to prevent the mother rejecting the baby. There is a level of suppression of the immune system there but even so the mother does not get AIDS. The mother is able to respond to everything other than

baby proteins and can fight infections adequately.

So the protein overload hypothesis, although it's plausible from the point of view of we won't know what this might do because we haven't done it before, there wasn't a good biological precedent for that.

THE CHAIRMAN: I wonder if I might just take up this point a little by looking at the context. The use of concentrates really only began to get into its stride in the United Kingdom in the middle 1970s, and that's possibly pushing it back a little for most people; it would be the middle to second half of the 1970s anyway. When the Edinburgh study was published, I think in 1983, looking back a year or two to the data, one had, perhaps for the first time, a history of exposure of haemophilia patients to concentrates as a significant element in the background facts and circumstances.

The other factor that I think one identifies in the literature around about that time is this distinction between AIDS-like conditions in haemophilia patients, characterised by PCP, and the wider range of adverse factors emerging in the homosexual population, Kaposi's sarcoma in particular.

So people looking at the data might have had a very particular focus in mind. Do you think that that could help explain the approach that was adopted? Might have

persuaded them of one possible answer, until, of course, the virus is eventually characterised?

A. Is the implication that the alternative hypothesis may pertain to different populations in different ways?

THE CHAIRMAN: Yes.

A. I think again that's plausible because of the difference in the phenotype, the appearance of the disease, because of these different manifestations and exposures.

So I would agree.

I would just go back to what I was saying before, in that within the proteins which were being administered, it is likely that there were contaminating proteins -- because it's never a perfectly pure protein production unless it is recombinant -- which had come off immune cells. If my recollection is correct, there were believed to be some distortions in the levels of the different types of lymphocytes just from exposure to lots of proteins, so again that would add a little bit of weight to this idea that a protein exposure overload was pertinent in the haemophilia population, together with the phenotypic differences seen in the different conditions.

THE CHAIRMAN: The context, I think, you are very well aware, is that I have to be extremely careful not to use hindsight to be critical of opinions expressed at the

time, and so I think it is important to explore the rational basis, as it were, on which particular hypotheses could have been advanced, especially when very short periods of time are involved in the emergence of new data that undermine the previous expressions. So that's why I'm worried about it.

MS DUNLOP: I suppose it's very complex reasoning, professor, because if the big picture is that different groups of people or different individuals are suffering collapse of their immune systems -- so gay men, this infant who has had a platelets transfusion, people with haemophilia, intravenous drug users, people from Haiti and so on -- I suppose you are building in an assumption right from the start if you think you are looking for one explanation. But perhaps as a matter of logic, the fact that the collapse of the immune system is happening in all these disparate groups maybe does suggest that there is one explanation rather than a different explanation for everybody, does it?

A. I think you could argue either way, in that you can become immune-suppressed in all sorts of different ways, as I mentioned before, if you are given drugs that suppress your immune system or you develop advanced diseases likes cancer. So those individuals also would potentially develop an AIDS-like syndrome.

We see the same susceptibilities today in people treated with some of the newer agents which are designed to knock the immune system down rather more specifically, to treat things like arthritis; they become susceptible to rather specific infections.

So I think one could argue it either way. There may have been a common thing or there may have been multiple ones. I suppose one of the more compelling things was the timing, in that all this was happening at the same time. So, to invoke multiple different causes as coincidentally hitting different groups of the human race within the space of a few years is more pointing in the direction of a commonality of origin.

Q. Yes. Actually, Drs Tedder and Barbara, both virologists, when they published on this, on viral infections transmitted by blood products, they comment that it's unlikely that there had been an illness, an AIDS-like illness in people with haemophilia, caused simply by antigen overload but unremarked in the years leading up to 1982/1983. I suppose it couldn't be impossible because it could be that it had taken the period from the introduction of concentrates until 1982 for it to become apparent but it still would have been quite a long time to have passed without noticing anything.

A. Although the parallel is, of course, with HIV itself, which can take 12 years from infection to causing visible manifestations of disease, which is again one reason why the iceberg was not apparent for many years.

So I think you could again argue that either way, that if it was a very slow attrition on the immune system, caused by repeated exposure to protein, then you might not expect to see it very soon after the early administration. The immune system does, as in desensitisation therapies, take quite a long while to learn things.

THE CHAIRMAN: Professor James is encouraging me to back off from one aspect of my hypothesis by pointing out that one shouldn't look at the use of concentrates in the United Kingdom as the test since it's quite clear they were used earlier in America and it was there that the phenomenon emerged. Perhaps that's the right focus rather than Britain. The period is rather longer than I think I was suggesting to you.

MS DUNLOP: I suppose, sticking with the idea that all of these things are happening at once, we are really back to the same exercise that we spoke about a short time ago of whether you are looking at the totality or whether you are saying can I explain away these

different phenomena in different ways.

So the child, the case in the infant, again you would have to postulate that this child, what, has either been born with an immune defect or has in some way suffered some sort of immunological damage by being transfused with platelets from 19 donors? Would that be the possibilities there?

A. Yes. To some extent a very, very young child, a new-born, months old, is not something to hang a whole case on because some 2 per cent of children are born with some oddity about them, some minor difference from the average. There are well documented cases of immune deficiency. One in 1 million boys is born with no antibodies. The bubble babies; that's slightly rarer but they do exist.

So one doesn't know the full background of that individual, at least not as I'm aware of through the literature.

Q. Right. The case was written up. We can perhaps check this over lunchtime but perhaps at least the first of the possibilities, that the child was born with some sort of congenital immune defect, might have been considered by those who wrote up the case. So perhaps that's something worth checking.

When you talk about the foreign proteins which

people with haemophilia were essentially taking in with the injections of concentrate -- I think we can perhaps encapsulate it by quoting from one of the haemophilia clinicians, who said in his evidence:

"We are not designed to accept proteins in that magnitude intravenously."

He had calculated that, for a severe haemophiliac, over a lifetime that person might take in a kilogramme of foreign proteins intravenously with his doses of concentrate. I think the question that strikes a layperson is: was that treatment ever a good idea?

A. I suspect that the doctors treating the haemophilia and the haemophilic patients would say it was because of the documented increase in longevity and improvement in quality of life, but one also has to say that, assuming that every protein we make ourselves is perfect is not true. So, for example, the cystic fibrosis protein that we all make and we are supposed to make properly, only about 2 per cent of it folds up properly. So we make all sorts of junk protein ourselves. So we are exposed to slightly more abnormal proteins of our own design, if you like, and if you are administering that much protein to prevent coagulation, the calculation must also be made as to how much protein that individual themselves would have made over that time. One suspects it would

be quite a large amount, perhaps not a kilogramme because it would have worked slightly better but the individual would have been exposed to something which was biologically very similar, admittedly released in smaller amounts. But Factor VIII is a naturally occurring protein, which we all make, so it's not something which is a foreign protein you would expect it to make an immune response to.

THE CHAIRMAN: I think there is also the difficulty that the kilogramme proceeds on the basis of a normal life expectancy, whereas, without the therapeutic products, life expectancy might have been very much shorter?

A. Yes.

THE CHAIRMAN: So there is the trade-off pretty well inherent in the risk that, without the proteins, you do not survive; with them you accumulate the dangerous levels that are identified?

A. Yes.

THE CHAIRMAN: Should we stop at that?

MS DUNLOP: Yes, I think that's --

THE CHAIRMAN: If you have got some good reason --

MS DUNLOP: It was just the figures. I'm sure Professor Lever is very aware of the figures but I think in the Annals of Internal Medicine article it's perhaps best expressed, [LIT0010047].

This is the calculation that's done at the bottom of that editorial. Do you see the sentence beginning, "Each lot ..."? If you took the upper end of that, each lot containing material pooled from 22,500 individual donations, the average patient needing five to ten separate lots every year, the authors say that:

"A Person with severe haemophilia using clotting factor concentrates is potentially exposed to tens of thousands of donors per year."

Actually, without too much difficulty, you could get hundreds of thousands of donors a year as a possibility. I think that's really why I put it to you that, expressed like that, I suppose one wonders as a layperson whether that wasn't perhaps going to lead to results which might not be favourable in a different direction. You are solving one problem but perhaps creating others?

A. I think, if you look at numbers, they are big numbers. I don't know the exact figures but our kidneys filter about a kilogramme of salt every day or something like that, so we do deal with lots of things. But the issue here is, what you are doing with this clotting factor is restoring a requirement for clotting factor, which presumably is the equivalent of what the person themselves would have made had they not been a sufferer

of haemophilia. You are not overdosing them with a protein; otherwise, they would clot far too much.

So the numbers look big but that must reflect a physiological requirement for that amount of protein.

Q. I suppose I had understood, though, that there were contaminant proteins, particularly in the low and intermediate purity products, which one couldn't get rid of and therefore had to take on board alongside the required protein?

A. No, I agree with you entirely there that what else is in there is obviously going to be multiplied equivalently because of the number of donor and so that is a reflection of what else might be in there is significant. The amount of clotting factor per se is presumably what the person requires.

Q. Yes. But I suppose, just to round this off then, we are back to risk/benefit, and the ingestion of that amount of additional material is perhaps best understood by us as having been seen as a price worth paying.

A. Because one assumes the amount of clotting factor being given was the minimum that was required to sustain normal clotting.

Q. Yes. Thank you, sir.

THE CHAIRMAN: Thank you very much.

(1.06 pm)

(The short adjournment)

(2.00 pm)

THE CHAIRMAN: Yes, Ms Dunlop?

MS DUNLOP: Professor Lever, we need to go back to your report, [PEN0150517] again, please. Could we go over on to the next page? That section, professor. The paragraph beginning:

"The period of May and June 1983 ..."

Just to flesh out what you say at the end, the fact that AIDS has been diagnosed in a UK patient with haemophilia, could we have [DHF0014349], please?

We have looked at this before in the hearings but the particular section that's of interest is obviously the middle one, the heading "Acquired Immune Deficiency Syndrome, Cardiff." This is a bulletin for the week ending 6 May 1983.

We have had some debate, Professor Lever, about how this should have been seen but it certainly looks as though, from the perspective of the Public Health Laboratory Service, who are producing this bulletin, this was seen as a case of AIDS in a patient with haemophilia.

I think it might be possible, looking at this now, to split hairs and say, "Well, should it have been?" But I think firstly, at the time it was seen as a report

of AIDS in a patient with haemophilia and indeed from subsequent notes, it looks as though this person actually did die.

I imagine that this is the episode that you had in mind when you referred to AIDS being diagnosed in a UK patient with haemophilia, this report from Wales?

A. That was the one.

Q. Yes. It's perhaps interesting that this is around the time when Dr Galbraith penned his letter. The date of it is actually 9 May. So although it's speculation, it would seem to be reasonable to imagine that it was in his mind when he wrote his letter?

A. Yes, it may very well have been.

Q. Yes. Can we go back to Professor Lever's report, please, that paragraph that begins:

"By July of 1983 ..."

You refer to there being no motivation in the UK or the US to withdraw concentrates. Then you go on to say that:

"There was informed discussion amongst the medical fraternity but mixed messages being presented to the public, with some comments designed to reassure appearing rather overly optimistic."

I just wondered, from where comes the desire to reassure? Is that something that at the time will have

been pretty fundamental to doctors?

A. I think it goes back to the issue I mentioned previously of not wishing to panic people unnecessarily. And until there is an absolute consensus there may have been a feeling that it was wiser not to be seen to be spreading alarm and despondency without solid data. And at that stage, although I say that the weight of evidence is in favour of a transmissible agent, we are still in the state where we don't know what proportion of people carrying that agent get the disease and we still have the precedent of the non-A non-B hepatitis to go on. So that may have been in people's minds as well.

Q. I think one of the things that we have wondered is whether there wasn't perhaps a middle way of communicating that doctors didn't know, or would that have been seen as unsatisfactory in that era as well?

A. I guess, like many professions, there is a slight reluctance, when you have a body of individuals who put a great deal of trust and faith in you to just say you haven't a clue. It may have been more of a prevalent culture at that stage that the medical fraternity felt they ought to know or to appear to know more universally than perhaps now, although I can think of individuals who are the same now.

Q. You can think of individuals who are the same now?

A. Yes.
Q. All right. In the sense of being very unwilling to confess ignorance?
A. Yes.
Q. Right. Just reading down through your comments there, you say there was a disparity in the message being given by the UK health departments and the Scottish Office. I'm not sure if that's a disparity between the two departments. Maybe it would be better if we looked at the preliminary report to get the context of that.

If we go to 8.47, please, that's in book page 201. I think this is this whole section about the autumn of 1983. Are you pointing up the fact that there was a slightly more focused message coming from those responsible for blood transfusion?
A. I think I'm just pointing out that there was clearly still a level of uncertainty but this translated into a mixed message coming out, which had people who were at the point of receiving the blood products getting both minutes. It would have been clear that people didn't know the answer and that there was confusion amongst the authorities. And I think it was an unfortunate correlation that those two messages came out at about the same time. I don't think it would have helped people's understanding of the sort of problems that were

being looked at at the time. I think the modern-day phrase is "joined-up thinking", but it was not very good.

Q. We did put to someone, one of the consultants in the Blood Transfusion Service, the proposition that, as you say, it doesn't really look like joined-up thinking to have people responsible for the treatment of patients with haemophilia saying reassuring things at the same time as the blood transfusionists were saying, "Can AIDS be transmitted by transfusion of blood and blood products? Almost certainly, yes."

That really is slightly paradoxical?

A. There was a previous comment, I think, in my report where the issue of the risk to the people working in the Protein Fractionation Centre had been raised as well at the same time as there being a hypothesis that it wasn't an infectious agent, it was stated that possible carriers were being screened as though the implicit assumption was that there was an infectious agent. I think the same applies there.

Q. Then you take us through what is this section of the report, about what happened in the autumn of 1983, and then you go on to comment -- and I think we need to go back to your report, please -- that this period gives the appearance of some lack of coherence and

organisation and there was also delay in providing information to potential blood donors in the form of leaflets. So is the lack of coherence and organisation just what we have been saying about there not being joined-up thinking between, say, those who are responsible for the collection of blood and those who are responsible for treatment with blood and blood products?

A. That was relating to the persistence of different theories as to the causation.

Q. Yes. It is interesting, though, Professor Lever, to find that the proposition that the explanation is something other than an infectious agent appears to be being believed most strongly by those in the group of haemophilia clinicians, whereas people who are thinking this is an infectious agent tend to be more infectious diseases specialists or people responsible for collecting donated blood, for example. Is there a degree of emotional input in what people want to believe, do you think?

A. I know there must be. It is very difficult not to have your opinion about what might be the consequence of a particular theory influencing your belief in what the causation was. So I think it would be very human to want to be as persuaded as possible that what would be

a very radical course of action for you was as solidly proven as possible.

Q. Yes. You refer in that second sentence to there being delay in providing information to potential blood donors in the form of leaflets. I wonder, looking back, when do you think moves should have made to provide information to potential blood donors, taking, as we know, that it was really the summer of 1983 when leaflets began to be published and distributed, although somewhat patchy, I think, across Scotland?

A. I think that was the issue, that there was an inconsistency in distribution as far as I can tell, in that some areas were getting leaflets and some weren't, and that reflected again, as far as I can tell, different individuals, different perceptions of what the real risk was.

That was not just the perception of the risk but also the perception of the effect the information might have on potential donors. The issue of suggesting that people who might be at risk of HIV because of their lifestyle withdrawing from donor status would potentially have led to difficult situations in the actual blood donation centre, where somebody would read the advice then get up and walk out, or would read the advice and decide they didn't want to be observed as

standing up and getting out and go ahead and give their blood anyway. And in the absence of a screening test, then that would be almost counter-productive.

So I can see there are well-worked arguments as to how information, when the information available was incomplete, was not actually better than some information. But I still think there should have been a uniformity about the distribution of information.

Q. Yes.

A. With the caveats as to what was known and what wasn't known.

Q. Right. You go on to describe some serious viral infections of the 1960s and 1970s but you say that high mortality tended to be associated with what were, I suppose, highly visible viruses. You know, people were ill almost immediately and you could almost see the outbreak with your eyes, but this was very different, I think.

A. It goes back to the concept I mentioned of the hit and run virus that kills people and then goes on to somebody else, whereas viruses which survive a long time inside you tend not to; the exception being viruses which have recently crossed species and moved into a new species, as had this one, where the mortality tends to be higher, whether or not it's an accute hit and run or whether

it's a chronic infection but once again, HIV presented a uniquely terrible phenotype.

Q. Can we go back to getting a little bit more information about the effect that the virus has on different individuals. You have told us about long-term non-progressors or elite non-progressors, if that's correct. If we move on to people who do become ill, what now would be regarded as really the maximum length of time between seroconversion and someone becoming ill?

A. If we put aside the elite and the long-term non-progressors, it's difficult to actually say what that data is now because of the widespread access to anti-retroviral therapy but at that stage, the overall average was five to ten years, I suppose, for an adult, and shorter for a vertically transmitted infection.

But that distribution covers an enormous range of different factors.

Q. I don't want to get drawn into discussing this in any detail, not least, professor, because we didn't ask you to address it in your report, but it did strike us, when we got the statistics from the different hospitals, that there is a very much better survival from the children's hospital. So the children with haemophilia who acquired HIV, the majority of them are still alive, which is very far from so with the adult centres. Do younger people

tend to do better?

A. The virus is something that kills cells of the immune system, in particular the lymphocytes, which I mentioned, the CD4+ lymphocytes, and in fact it was the data from the patients with haemophilia that showed us that young people do do better because the disease effectively arises when your lymphocyte population is exhausted. Put in a rather prosaic way. Younger people have a much larger reserve of lymphocytes and bone marrow to keep them going longer. So the older you are when you acquire HIV, untreated, the shorter would be your time from seroconversion to developing immunodeficiency.

Q. Do younger people have a greater capacity to regenerate lymphocytes as well?

A. Yes.

Q. Can I ask you something else which has, I think, led to a difference of view and we need you, I think, to settle the debate. It's paragraph 8.207 in the preliminary report, which is page 246 and is I think page 61 [LIT0012479] in court book.

Both in paragraph 207 and paragraph 211 there is mention of the amount of product which patients individually had. 8.207, there is a quote from an article that the authors of a particular piece had

tentatively suggested that there was a relationship between the amount of Factor VIII transfused and time to seroconversion:

"Were that so, it would emphasise the association found previously with the amount of the contaminated batch used by these 18 which was larger than that used by the other 14 patients who remain seronegative."

That's the first reference. Then could we go on to the following page, to 8.211. There is an extract, a quote, from another article that says:

"In relation to the 14 patients who were transfused with a particular contaminated batch of product, they received significantly lower doses of this batch of Factor VIII and therefore may have received no virus or only very low doses, which were unable to establish infection."

I think this links back to something you were saying this morning about the mechanism of infection. In very broad terms, is the explanation for the fact that there were 32 patients who were given the contaminated batch and 18 of them acquired the virus and 14 didn't, likely to be dose-related, is it?

A. The ones who were infected had batches with live virus in, or enough live viruses to cause infection and the ones who didn't get infected were fortunate enough to

get batches in which there was virus but it was non-infectious.

Q. Could this all have been attributable to one donation?

A. Yes.

Q. And what about the proposition that the implicated viral strain appeared to be particularly virulent. That's obviously a comment of its time but looking at that now, is that a phenomenon that you would recognise?

A. In experiments in primates there have been particular viral strains which have induced an AIDS-like disease more rapidly than others. So there does appear to be a variation in the virulence of viruses in experimental conditions.

There are certainly viruses which are with less virulent. There is a very well documented series of individuals in Australia who are infected by blood transfusion, almost certainly from a single donor, who stayed well for many years and that virus was shown to have a mutation in one of its essential proteins and didn't replicate very well. So that was a much less virulent virus, although that's a rather unusual circumstance and it is not one that has been seen, although the same thing has been produced experimentally in the primate model. Because the virus mutates so much, the concept of a very, very virulent virus versus

a very, very non-virulent virus is not quite as relevant because the virus can change so rapidly, and so if being virulent was something that benefited the virus, it would do it in everybody.

So I don't think that there is good evidence in humans that very rapid progression is to do with particularly virulent viruses. If it is, I think it's a factor and not necessarily the major factor. I would suspect what was as relevant, if not more, was the immunological competence of the host. Certainly your point about somebody being older getting illness more rapidly: people who have had multiple exposures to other agents, such as non-A non-B hepatitis, may also have additional risk factors and there may have been other things we don't know about in these individuals' genetic make-up.

Q. Yes. We have seen one of the particularly challenging articles refers to, I think, HLA haplotype as being associated with a particular progression of disease. That's a particular genetic make-up, is it?

A. Yes. So in brief, the HLA proteins are proteins which we have on the surface of our cells and they display in them in a little groove, samples of the proteins we have inside our cells. So that our immune system can see whether there are virus proteins inside our cells

because there will be a little bit of virus protein stuck on the outside of our cells, and because we are all very, very genetically different, some of us are more able to resist infections because we have a group of proteins which are better able to present some of these virus peptides than other people do. But we are all variable. So some of us are good at some things and some of us are better at others. There is the odd person who gets chicken pox twice, for example, most of us only get it once. It's that sort of difference in our immune capable.

So there are probably not two individuals who would have exactly the same response to any infection, unless they are identical twins. So there will be groups of people -- and the HLA type is the most significant variable -- who are more likely to get infection moving to disease more rapidly and others who are less likely.

That probably accounts, in part at least, for these so-called long-term non-progressors and elite suppressors.

Q. Right. We know that with Hepatitis C there are now some people -- they are in a minority -- whose bodies naturally clear the virus. That isn't so with HIV but do you think that is just a phenomenon of recency, because it has so recently crossed over? If HIV had

been left unchecked, there might eventually be people whose immune systems could defeat the virus?

A. Once the virus gets in, I think it's in because it integrates its DNA into the genes of the cell which non-A non-B hepatitis doesn't. It remains free, so you can always eliminate an infected cell. What HIV gets into a cell and gets into the DNA, it may go to sleep and go latent. So there is no evidence that that cell is infected at all because there is no proteins being produced.

However, whenever that cell divides, just like every daughter cell gets a copy of every gene, both daughter cells will get a copy of HIV. It is the latent population of cells which makes HIV, at the moment, impossible to eradicate, because once it's in, it's in, and the latency means the immune system can't see infected cells and drugs can't attack the infected cells. So it's a biological difference between HIV and Hepatitis C.

Q. Right. For those people who can clear Hepatitis C, that is a successful antibody response, I take it?

A. It's a mixture of antibodies and also what we call the cytotoxic lymphocytes, which are the cells which kill the cells which have virus in. So you need antibody to mop up free virus which is floating arrangement to stop

it infecting new cells, but you have to kill the factories that are producing the virus which are the infected cells. So it is the two arms of the immune system.

Q. Right, and one of the additional difficulties with HIV would be this phenomenon that you described this morning, about its capacity almost infinity to mutate?

A. Indeed, and that means that we are always one step behind with our antibodies and our cytotoxic T cells. And of course, the other difference is that Hepatitis C infects liver cells, so that your lymphocytes can kill off every infected liver cell and your liver will generate new ones for you. But if your immune system is killing off the cells that have HIV in, those are also cells which make your immune system work. So your immune system is actually killing off itself to a certain extent, and that's the origin of the immunodeficiency.

Q. Right. Going back, Professor Lever, to what information should have been given to patients. Can we return, please, to Professor Lever's report and look at a section where this is considered. There is a paragraph, 8.51 to 8.54.

You refer to the UKHCDO meeting in October 1983, at which, I think certainly a Dr Chisholm is described and

maybe one or two others, saying that patients were starting to refuse to take up commercial Factor VIII because of the AIDS scare.

We are, Professor Lever, as you know, in this block setting the scene for a more detailed examination of doctor/patient communication, which we are going to look at in the next block. But obviously these individual doctor/patient communications took place against a backdrop of what was being said more generally. So given that you have gone on to comment on patients in this part of your report, I just wanted to ask you: around about now, what would you have been saying to patients about this? And particularly, obviously, patients who were receiving treatment with blood product concentrates? Would you have waited to see if they asked you anything about it or would you have initiated a conversation?

A. I know what I would do today.

Q. Tell us what you would do today for a start.

A. Today it's a much more healthy, two-way partnership between doctors and patients, in that I hope that I listen very hard to what they want to ask and try and respond to the questions they have, and make sure that I have explained things well enough to them.

In fact, very commonly patients will bring a lot of

information into the discussion, which is great. I think that wasn't the norm in the 1980s. I think there was still very much a residuum of the paternalistic approach to medicine, which is still prevalent in people today in some individuals, who will say to you, "I don't really want to know, doctor, just do what you think is best". But I think that's much less common than it was then. People were much more accepting of the opinions of the medical profession in a rather unquestioning way, and in these circumstances, as well, these individuals and their families will have been very acutely aware of what a miraculous change the medical profession had apparently made in the lives of the individuals with the onset of the clotting factor concentrates.

So there probably was as much faith, if you like, or confidence, at least, in the opinions of the doctors in this as there would have been in any discipline. Had it been the same today, we could say that treatment of HIV has advanced so much that people should appreciate that life expectancy has gone up enormously but, as I say, fortunately, the doctor/patient relationship is much more of a two-way dialogue, which I think is highly desirable, but I think at the time I can't pretend I would necessarily have been an outlier in behaviour.

Q. So as at today doctors have changed and patients have changed too?
A. Yes.
Q. Right. In the early 1980s, are you saying that the sort of doctor who said, "Mr So-and-so, there is something I need to discuss with you," would have been an outlier, this would have been the exception?
A. No, I don't think they would necessarily have been the exception. It sounds like a rather closed community in that case, but I think there was still a serious body of opinion as exemplified in some of the literature here, as to whether or not the patient should know about the diagnosis. And that today is clearly unacceptable, whereas it was accepted then, whether it was right or wrong.
Q. Yes. Still on this theme, one document that I wanted to show you is a Council of Europe recommendation, [DHF0022149]. This dates from June 1983. And this is a recital with various propositions on the first page but if we look at the second page, we can see for a start that this is a recommendation drafted to the governments of member states but the second bullet there is:

"To inform attending physicians and selected recipients, such as haemophiliacs, of the potential

health hazards of haemotherapy and the possibilities of minimising these risks."

So certainly the Council of Europe seem to have been saying in June 1983 that people should be told, patients should be told. First question I need to ask you, however, is where the Council of Europe sat in the firmament. We have had slightly differing answers on that. If you can think back -- and I know it's a long time -- was this something that people, doctors treating patients were aware of what the Council of Europe were saying, or was it much more remote than that?

A. I don't have any personal recollection of anyone discussing anything that the Council of Europe had said at the time. That's not necessarily representative and I was relatively junior at the time myself. I wouldn't have gone to seek out the opinion of the Council of Europe as a routine. So I suspect that this was relatively remote --

Q. Right.

A. -- from my practice.

Q. You have mentioned in your report that WHO at the conference in November 1983 appear to have recommended that patients with haemophilia and their doctors should be informed of the potential hazards of Factor VIII and IX products, including the risks related to AIDS. Would

the same be true of WHO, that a doctor seeing patients in a haemophilia clinic wouldn't have the recent recommendations of WHO at the forefront of his or her mind?

A. I think marginally more than the Council of Europe but again, not something that they would be thinking about consulting in their day-to-day practice.

Q. Right. Does this sort of material tend to come down through government channels rather than directly to individual doctors? Is that the way it works?

A. Well, if I'm truthful, I don't remember any Council of Europe pronouncements on this or other illnesses which have come down and influenced my practice. I would accept I might be an exception but we have these days so many different sources of guidelines anyway, this would probably not differ from what's said in those. I don't believe anyway that these were very influential bodies in terms of current practice, despite the fact that actually what they are saying makes very good sense.

Q. Right. Looking now at what our government was saying. I think you have seen a handwritten exchange of comments before but just to bring it up to the screen, [DHF0015006]. You can see from the top of the page that this is a newspaper cutting, where somebody in the

Department of Health and Social Security has marked with a X a quote about a patient with haemophilia developing AIDS and the doctors, the blood specialists, at Bristol Royal Infirmary, who have written this individual's story in the Lancet, are commenting that his case was providing further evidence for a link between blood products and AIDS. Then the person who has written the "X", if we go down the page, has then gone on to pass this over to somebody with the questions:

"Have you seen? On X is it okay for me to continue to say that there is no conclusive proof that the disease has been transmitted by American blood products? PS, congratulations on your promotion."

This seems to be 23 November 1983, doing the best we can for dates. Then the response is:

"Thanks. Yes, it is okay."

Do you want to comment on this, Professor Lever? This appears to be internal DHSS thinking on the line to be taken.

A. The juxtaposition of the wording of those two statements is not good. It appears to reflect a relative lack of taking things very seriously, certainly the evidence that was coming out. So I don't think it's a very impressive document in terms of what the medical profession or the individuals in this exchange should be

remembered for.

Q. Can we go back to your report, please? You refer again -- and we can see the comment just at the bottom of the screen -- to a comment, this time by the Haemophilia Society, saying haemophiliacs have no reason to be worried about using commercial concentrates. Again you think that was perhaps over optimistic and presumably represents a strong desire to reassure. So again we have the motivation of wanting to reassure people. But there is a comment in the Douglas Starr book about blood that certainly in America around this time no one was actually telling people with haemophilia the truth: not the government, not the mother organisation. That sounds like a fair comment. Do you think it's a fair comment?

A. I think people can only make comments on the information they are given. When one is faced with an inquiry like this, which has diligently sought out every source of data that one can possibly get, you are rather spoiled, by having access to many documents which wouldn't have been that easily available at the time. So I think it's a very reasonable comment that the Haemophilia Society would not have had as much information on which to make a balanced recommendation.

The comment I made there was not designed to imply

that the Haemophilia Society was doing a disservice to its constituency but more to raise the issue as to where the Haemophilia Society was getting its information from, and I perhaps should have made that more clear in my report.

Q. Yes, I think we all have an understanding that the Haemophilia Society will have turned to haemophilia clinicians and asked them for input in this very difficult time.

A. Exactly.

Q. Just to move on through your report, I think we have covered a lot of what is discussed in the ensuing paragraphs about Dr Gallo and then ongoing suggestions that the virus was not the cause of AIDS. In fact another doctor who has given evidence has said that until 1996 reputable journals continued to publish articles suggesting a non-viral pathogenesis for AIDS, but was that very much a minority view.

A. There were a series of things which have gone up until relatively recently, where, on the basis of diminishing credibility of evidence down to zero, various groups have sustained a position that HIV has got nothing to do an AIDS. At around this time there were a group of individuals, led by a well-known scientist called Peter Duessberg, who was an extremely distinguished

molecular biologist, who discovered some genes involved in cancer but who took up the cause that HIV was not related to AIDS because of the difficulties that there had been in finding the virus or finding enough virus in the circulation to prove that it was causing disease.

There were lots of plausible arguments about it and this was also supported, as, I have to say, was the antigen overload hypothesis, by constituencies within the gay population who had hypotheses that HIV had been a virus created by various United States government agencies and introduced into the gay population in order to eliminate them. That level of conspiracy moved on to the point where, when anti-HIV drugs started to be used and they were new and rather toxic, the argument was made that in fact not only was HIV created to damage the gay population but the drugs were deliberately toxic to try and hasten the demise of the gay population.

So there was that series of opinions, and Duisberg used to attend serious scientific meetings and clinical meetings that I attended and make fairly outrageous comments as to the plausibility of what was being presented by well meaning and sincere scientists.

There then followed, as I'm sure some people recall, a campaign in the Sunday Times arguing that HIV didn't cause AIDS, and when an influential newspaper like that

starts peddling opinion like that, it is very easy to persuade people who may have doubts reflected in the uncertainties from what they are hearing from more authoritative sources, and I suspect a number of people believed that as well.

I would hate to imagine how many people took it seriously and then ended up infected because they didn't believe it. The whole thing continued right the way through until very recently in South Africa of all places, where the government actually supported the concept that HIV didn't cause AIDS on the back of some bad science but also political concerns that Africa, Africans, were being blamed specifically for the outbreak of AIDS.

So there have been a series of denialist groups of varying levels of respect over the years. So it still hasn't disappeared until today in fact, but no one who looks at the evidence would really believe, much after 1984, and certainly after 1985, when virus testing was available and it became correlated exactly with disease manifestation, that the virus had nothing to do with AIDS.

Q. Can we look in more detail at the position at the end of 1984. You mention a letter from Dr Craske in October 1984. Actually, I think around this time

Professor Lever, there were two letters from Dr Craske, one in relation to what had happened to patients in England and the other one relates to patients in Scotland. So we should look at the Scottish version, [PEN0150250]. Much of the text of this seems to be the same as the English letter.

It's dated 30 November 1984 and I think we can see that Dr Craske is writing to Dr Ludlam, who has told him over the phone that there appear to be some patients in Edinburgh who have been infected with HTLV-III by Scottish NHS Factor VIII.

Can we just move through this letter, please. I'm not sure if we are at the bottom of the page. He says he is going to set out the following facts. Can we then go on to the next page, please?

We have looked at these facts before, Professor Lever, but, as you look at them now, they are not all accurate, are they?

A. They are not.

Q. Could you give us your specific comments on the list of one to six, please?

A. Well, number 1 says:

"Only a proportion of the patients transfused with an infected batch of blood are likely to contract HTLV-III infection."

If, by an infected batch, it means a batch which has infectious virus in, then the proportion must be near or at 100 per cent. The proportion is not stated.

If, as in the case of the recipients of concentrate where, because of the poverty of virulence of many HIV viruses, there may be a lot of dead virus in some batches, then those wouldn't necessarily be infectious, but the first statement actually says nothing.

The second one is true, in that people may already have contracted infection from other infected batches, which, as we know is not any sort of good reason not to protect them from further infections.

Number 3:

"34 per cent of symptomless haemophiliacs are positive for HTLV-III antibody."

This is an interesting comment on the perception of infection and the protective nature of antibody because in many infections, if you have evidence of antibody, it means you have actually cleared the virus or cleared the infection. If we checked everyone in this room to see if they had evidence of antibody against chicken pox, most of them would, and they have had it and cleared it.

HIV is different in that the presence of antibody is simply a reflection of the fact that the person is infected or alternatively, has been passively transfused

with antibody from somebody who is infected, in which case that antibody may disappear and that may have been a reason why some people apparently cleared antibody and were mistakenly believed to have cleared the virus. So the statement:

"It is likely a significant proportion of patients will remain in good health."

Has no basis because there is not a long enough follow-up of these individuals to say that. A partial defence is that again, there was no precedent for a disease being 100 per cent fatal and taking so long to cause its ultimate effect.

The last one of section 3:

"It's likely that the proportion of patients who contract HTLV-III infection who develop AIDS will be in the order of 1/100 to 1/500."

As far as I'm aware has no factual basis. The item 4:

"The incubation period ..."

This covers a little bit what we have already referred to, in that incubation period depends very largely on the host and the virus and potentially the dose of virus, and a mean of four years is not really accurately supported at that stage.

Number 5, this is true, that sexual partners of

recipients of Factor VIII may be at risk. In fact it was data from the haemophilia population that gave quite a good risk estimate of what the risk of sexual contact was in transmitting HIV.

Number 6 is correct.

Q. Can we read on through the letter, please, "Methods of investigation", which I suppose is fair enough as a survey of the patients. On to the next page, please. Number of forms and a structured plan for review. Can we carry on and look at what was said in relation to telling patients. Do you see it says that:

"The follow-up may be carried out using an alternative of two different strategies."

So firstly:

"If the patient has been informed of the risk ... testing could be carried out on each specimen as it's obtained at each four-monthly review ... it would be wise to warn the ... patient that his spouse may be at risk ..."

Then on to the next page, please, for the other option:

"An alternative strategy would be not to tell the patient ... but to observe him."

He says there are ethical problems which he is discussing in an appendix. Then investigation of

spouses, and then:

"Should the patient be told? ... Ideally I think he should."

Do you have any comment on this section of the letter, Professor Lever, about what communication, if any, should be made with the patient?

A. So the interpretation of the previous page -- a generous interpretation -- is that Dr Craske a saying theoretically there are two alternatives, as opposed to saying, "You may do one or you may do the other", and both are permissible. I think that would be an ambiguity which you could take from the use of the word "may".

This looks, in 2011, unbelievably paternalistic and almost arrogant to not involve the patient in this. I think even at that stage it would be perceived to be unusual but I think, as I mention in my report, there was at the time in Birmingham, over the following years, a move from parents of children with haemophilia, that they would like their children tested but the result not to be communicated with the parent or the child.

That reflects a number of issues at the time. One is stigma, which is really not to be underestimated. There is a well-known case of an American child who was banned from their school because of being HIV positive

and that was supported by the state. The amount of stigma for a young person being known to their friends as having something which is a disease caught by members of the population who would excite scorn or disparaging comment would also not be good for that child's upbringing. So there is that.

There is also the issue at the time about things like insurance, and certainly this was discussed very extensively by the homosexual population, in that they felt that they should not necessarily have to find out their result because otherwise when they were applying for insurance they would have to admit what had become a specific question on the insurance forms as to whether or not they were HIV positive or at risk of this. The insurance companies have since, I gather, just assumed there is going to be HIV positive people in the population and stopped making that an absolute question, but at the time there was the feeling that they would be discriminated against very much in things like insurance, as well as the social stigma.

So there was some level of opinion from the patient population that being kept out of the information loop wasn't totally wrong.

However, I think that is a decision which should be taken with the doctor putting to the patient that a test

can be done and does the patient want to know or not. So the patient is involved in the decision, rather than making the assumption that the patient should not be told. I think that's a different attitude.

It also reflects to some extent the fact that for many years -- and still to some extent today -- many blood tests are done and were done without fully explaining in detail what they were and the implications of all of them to people for things very much less severe than this. Antenatal tests for syphilis, for example, have been done without explicit consent for many years.

So not telling the patient today would be unacceptable; then, in these circumstances, I think was very undesirable. But there was a body of opinion to whom it would not have been too unusual to be discussing whether or not a patient should be told about whether a test was being done and the implications of the test.

Q. We should look at the appendix as well. I hope we have the appendix on this copy. No? Right.

I think the appendix features on the other copy of the letter. I don't know why we don't have it on this one. If you will allow me a minute, I will find the appendix.

If we call up [SNF0014020]. I think the appendix

for some reason is decoupled from the letter but this seems to be the appendix.

The appendix is here. Perhaps if we go to the end. The appendix is page 5. I think that's the English version of the letter and it has the appendix in it. He says it details a protocol. Then there is a bit of a repetition of the two options but he does go on to say at the bottom:

"In my view, option 1 is the only one tenable on moral and ethical grounds."

Do you see that?

So he seems to be saying in the appendix that the only option tenable and moral on ethical grounds is to tell the patient and his family.

A. Presumably that means giving the patient the choice of what they want to know.

Q. Yes. Can we look then at the minutes of the UKHCDO meeting in December 1984? [SNF0013850]. This is the reference centre directors who met on 10 December 1984.

There is discussion here too about these dilemmas. Can we move through the minutes and on to the next page.

This is the background to why the meeting is taking place, the availability of tests, and then Dr Craske is recorded as saying -- well, I think it's Dr Craske:

"It was considered that to know the antibody status

of every haemophiliac would be advantageous in determining the regime for treatment."

Then on to the next page, please. Discussion of testing and the introduction of testing of donations. Some input from Dr Tedder. Then on to the following page.

Just in passing, Professor Lever, that comment at the top:

"Dr Ludlam confirmed that in Scotland some patients who were previously antibody positive are now negative. Does this suggest passive transfer of antibody?"

Can you explain that to us, please? What's the thinking?

A. So in the protein concentrates which are being delivered or in blood transfusions, there will be passenger proteins, including antibodies, from the person who donated and they may include antibodies. We know this, of course, because when we treat people with antibody concentrates, we can detect antibodies against all sorts of agents, which the donors had themselves experienced. And so looking at an individual's antibody levels to particular pathogens when they have received an infusion of immunoglobulin doesn't give any useful information, and those antibodies will turn over at the normal rate of protein turnover in the blood.

So in those cases, it must be the case that antibody positives turning antibody negative, who remain well, had antibody from another source. That's also the issue at the time of birth, when, in the last few weeks of pregnancy, a large amount of antibody passes across the placenta into the foetus and the baby is born with a lot of antibodies circulating from his or her mother, which is a very important protective mechanism before the baby's own immune system works. But testing a baby at birth or soon after birth to see whether or not they have been infected with something can be misleading because you may be measuring maternal antibody as opposed to newly-made antibody by the baby.

Q. Right. Can we read on, please, into that section, "Advice to patients and donors£". We see that there was a long discussion on whether persons found to be positive were to be informed. It does seem to be implicit in that, Professor Lever, that the people concerned are not being told before they are being tested.

A. I think that comes up in several of the witness statements as well.

Q. Yes.

A. That's an historical issue, which actually has been redefined effectively by HIV itself because we still, of

course, get consent for HIV testing as a routine and it was the arrival of HIV which actually started people thinking and discussing seriously about getting informed consent for a test which had implications for a person's future. So this is, if you like, the pre-AIDS mindset -- the pre-HIV mindset, where it may not be necessary to actually tell people what they are being treated for; today seeming quite unacceptable.

Q. Then on to page 5. I think we can draw the same inference from the comment of the chairman:

"The chairman summarised by saying that testing should be instituted as soon as possible and that information on the test results should not be given automatically but if asked for."

Can we put that document to one side, please, and go back to Professor Lever's report. You have already covered that paragraph about antibodies --

THE CHAIRMAN: Ms Dunlop, the stenographer needs a short break.

MS DUNLOP: Yes, sure.

(3.14 pm)

(Short break)

(3.30 pm)

MS DUNLOP: Can we move on to the next page of Professor Lever's report, please?

We have covered, I think, the topic of antibodies. You go on to say, Professor Lever, that:

"The time between the acceptance that the virus, HTLV-III/HIV, was the causative agent of AIDS and the institution of donor testing and heat treatment of concentrates seems prolonged."

Donor testing is a separate topic for us and we will be looking at that in the autumn, but if you bear in mind that donor testing was instituted in September 1985, you think that that's a long time after the acceptance that the virus was the causative agent?

Are you counting from the spring of 1983 or the spring of 1984, really?

A. It's a qualitative comment, made with a degree of ignorance of the technical issues there. So I would prefer not to make too much of that.

Q. Right.

I'm sorry, testing actually was introduced on 14 October 1985. So it wasn't September.

Coming next on the screen, you have set out some information about drugs. So the very first drug that could be used was AZT; what, with limited efficacy?

A. The clinical trials effectively showed it didn't improve the long-term outlook at all, despite the very early

stages showing that it did inhibit the virus. Single agent therapy against this virus has proven to be of no use, as is the case against a number of other pathogens, but it was there and therefore it was used.

Q. Is that also true of the two drugs that we see in 1991 and 1992? Is that DDI and DDC?

A. Yes, and at that stage, partly because there weren't many drugs to choose from and partly because the paradigm still wasn't clear to the medical profession, they tended to be used as monotherapy, single drug, one at a time.

If you look at the history of people treating infections, partly because drugs become available one by one but partly because of a lack of perception of the fact that infectious agents can mutate to get round therapeutic agents, there does tend to be a history of using one at a time and then gradually coming round to using multiple agents.

That was the case for tuberculosis, where initially streptomycin was used by itself. But, although it was efficacious, resistence appeared. Isoniazid was used by itself. And going right the way through to Hepatitis B, where initially again a single agent was used, and now it's much more accepted to use more than one because it provides additional hurdles for the virus or the

pathogen to jump through. If the virus can mutate, a single mutation can invoke resistance to a single drug. If you give it three drugs that it has to evade, then that one virus would have to make three simultaneous mutations to evade three different drugs, and that statistically is much less likely.

Q. When we look at this table for the years where more than one drug is shown, are these all combinations or are some of them alternative forms of monotherapy?

A. They are all individual drugs, except for the one in 2000, that's lopinavir boosted by ritonavir, which is a combination drug, where the ritonavir enhances the pharmacodynamics of lopinavir so it persists for longer in the circulation and is more effective; but the others are all individual drugs.

Q. Right. When do we see drugs that are correctly described as antiretrovirals?

A. Well, they are all antiretrovirals.

Q. Right.

A. But the period of HAART, highly active antiretroviral therapy comes in the mid 1990s where one could confidently put together a cocktail, if you like, of three different agents to administer at the same time, so that the ability of the virus to develop resistance was severely restrained.

Q. Professor Lever, just to look back to the very start of your evidence where you were talking about the different conditions that affect somebody who has AIDS, we spoke a bit about malignancies and some malignancies are explicable by another underlying virus, and Kaposi's sarcoma was an example of that, but does having AIDS predispose you to certain malignancies generally, even malignancies that are not anything to do with a particular virus?

A. There is a general background increase in the incidence of almost all malignancies in patients with HIV because your immune system not only fights infections but it has a role in eliminating malignant cells. So that if you have an advanced immunodeficiency and you lack the sort of lymphocytes which can recognise that a cell has become cancerous, then that cell has a greater chance of developing into a full-blown malignant tumour. But that level of increase is much lower than the increased risk of getting virus-induced cancers, like Kaposi's sarcoma or cancer of the cervix, or these days there is a rising epidemic of anal cancers. There is also an increase in mouth cancers, tongue and mouth, all of those latter ones from papillomaviruses, which are relatives of the viruses that cause the common wart.

Q. Did you say anal cancer?

A. I did.
Q. That's caused by a papilloma virus?
A. I did.
Q. Right. What about colorectal cancer?
A. Not as far as we know.
Q. Not as far as you know caused by a virus?
A. Correct.
Q. But is it found in increased incidence among people with AIDS?
A. I couldn't give you figures but I think it probably falls into the categories of all tumours being slightly more common.
Q. Just to conclude looking at your report because I think we have actually covered pretty much all of it, you go on to comment on chapter 4, which includes extracts from witness statements. I think much of what you say here you have really addressed orally today as well.

We have understood from several witnesses that AIDS itself effected a huge shift in the attitude of the medical profession to information and dialogue with patients. You say patient empowerment has moved on hugely.

I think the very last thing I wanted to ask you about actually is the news last week that there have been recent developments in the search for a vaccine,

have there?

A. Yes.

Q. But only so far effective in monkeys?

A. It has only been tried in monkeys so far.

Q. Yes. I think envisaging what the next step might be is something that's rather difficult for us anyway.

A. Yes. The problem with trying to develop a vaccine for HIV is that successful vaccines for other infections have always been premised on the fact that a proportion of the population who encounter that particular infection successfully clear it. So a proportion of people who encounter Hepatitis B successfully clear it. Most people clear measles. So you can imagine a vaccine would be able to be made which would trigger the same sort of immune response which was protective.

The issue with HIV, as I referred to earlier, is that nobody who has been infected has ever developed an immune response which has cleared the virus from them completely. That's unique. And nobody has ever developed an immune response which completely protects them against a second infection. Both of those things relate, in part at least, to the fact that it is a very, very variable virus. It is not only that because Hepatitis C is probably even more variable, but some people clear that.

It's also the fact that HIV integrates, as we talked about earlier on, so it is difficult to find and eradicate. So the outlook for a protective vaccine against HIV is, in my opinion, not good because you can't do to the immune system what 40 million infections in real people has failed to do. The immune system has been tested out against HIV rather thoroughly over the last 30 years and found to be wanting.

That picture changed slightly, but not radically, with the recent publication of a vaccine based on another virus, in fact cytomegalovirus, which is alluded to in this report. Cytomegalovirus is a herpes virus which infects a large proportion of the human race. The incidence goes up by about 10 per cent per decade in the West, so about 10 per cent of 10-year olds, 20 per cent of 20-year olds, et cetera. So many people, by the time they are in their 50s and 60s, are infected with cytomegalovirus. Most commonly it causes no detectable illness at all. In some people it causes a glandular fever-like illness, but in most nothing.

That's also related to what I said earlier, that this is a virus that has been with us for thousands of years and we are both rather well accustomed to each other. It doesn't kill us and we don't eradicate it.

What it does do, rather exceptionally, is

continually trigger the immune system. It continually shows off some of its own proteins to the immune system. So you have got ongoing, throughout your life, once you've been infected, a detectable immune response, an active immune response to cytomegalovirus.

So the clever trick which was done by the specific researchers in question was to put some of the proteins of HIV inside cytomegalovirus and then infect the monkeys with the cytomegalovirus, which was making HIV proteins -- or SIV proteins in this case -- and that meant that the monkeys were continually showing their immune system SIV proteins and there was a very active immune response all the time.

Normally, with a killed vaccine you inject something, it is there for a little while and then it disappears, so the immune stimulation goes away. But this approach gives prolonged immune stimulation and I forget the exact numbers, but about half the monkeys who were then infected with the SIV didn't clear the virus but they suppressed it to undetectable for a very long period of time, which was unexpected and unusual. Normally the virus would have replicated very robustly.

So it suggests that if you present parts of HIV to the immune system continuously, you may be able to keep a level of immune response going which would suppress

a real HIV that came into you. It doesn't say that you would prevent yourself getting infected. That is still a problem.

We don't know for certain, but this may be, at least in part, the basis of the observation some years ago, which was very puzzling at the time, that there were a group of prostitutes in West Africa who were clearly, through their work, being regularly exposed to HIV but were not becoming infected. It was thought at the time that they must have some rather special immune possibility, HLA proteins, which were very good, or something like that. But, although the follow-up on them hasn't been perfect, a number of them gave up being prostitutes and then returned to being prostitutes and became infected. So it showed that they didn't have any sort of memory which protected them against a subsequent infection.

One hypothesis is that, because they were being very regularly exposed to virus because of their profession, that was analogous to this cytomegalovirus presenting the proteins. Bearing in mind what I said before, that the vast majority of HIVs are not infectious, it means that these people were being exposed to a very large number of, if you like, dead viruses, and that was just triggering enough immunity to protect the real ones from

coming through. The difficulty, obviously, is one could never design an experiment to prove that in humans, but it's a plausible hypothesis.

Q. Yes. So for these reasons you are not really optimistic that vaccination is going to prove to be a reasonable part of the human defence against HIV?

A. I think it's not going to be a conventional vaccine. The conventional vaccines that have been tried have not worked and I think we are dealing with a virus which is rather different from the ones we have encountered before. I don't think it's impossible that one will develop a vaccine but it may be something that has to be given rather regularly, rather than just a one-off MMR equivalent, something like that, and I think it will have to do different things to the immune system than current vaccines do.

In the immediately foreseeable future -- I have to say this is not necessarily a majority view; many people are working very hard on developing a conventional vaccine and believe that they can do this. I'm slightly more sceptical, based on the fact that the virus so far has managed to beat the immune system rather comprehensively.

Q. Certainly from the reading we have done, really from the mid 1980s onwards people start talking about a vaccine,

and perhaps the passage of time since then tells its own story.

A. I think the equivalent of the secretary for health in the UK was noted, after Gallo's announcement that they had identified HIV, as saying there would be a vaccine within a year or two years. That was 1985.

THE CHAIRMAN: Ms Dunlop, Professor James is going to ask a question but I would rather he ask than I try.

MS DUNLOP: Well, I've asked all my questions, sir, so what I was going to suggest was that -- I'm sure that others will have questions -- would it be appropriate just to stop for today? I don't mean before Professor James' question, obviously.

THE CHAIRMAN: It is. I have another commitment tonight, which will mean that I was going to have to rise promptly anyway, but Professor James' question might just round it off.

PROFESSOR JAMES: Yes. It just occurred to me that, by analogy with your hypothesis about the prostitutes in Africa being exposed so frequently, through their profession, they actually mounted a continuous, albeit temporary, immune response to possible infection, do you think conceivably that could have occurred in some patients with haemophilia who were treated consistently and repeatedly with commercial, in particular,

concentrate because of maintenance therapy and so on? By analogy? Or is that a fanciful idea?

A. Are you suggesting that they may be the ones who didn't get infected?

PROFESSOR JAMES: I'm just suggesting it's conceivable.

A. I don't think longer that is the case, for two reasons. One is that delivering an immunological stimulus via the blood is extraordinarily effective at getting an immune response and also infecting, and I think that would have been so effective at infecting they just didn't get infected. I'm sorry about the alliterations.

The second thing is that I think a major aspect of the repeated exposure and the protection -- and this gets a little bit technical but I'm sure you will understand this -- is that much of the stimulation was to what's called the innate immune system, which is the non-specific inflammatory system, which has no memory but protects us very briefly against things like cuts and burns and things like that. So I think there was a lot of general inflammation, which prevented infection.

PROFESSOR JAMES: Thank you.

THE CHAIRMAN: Very well. Tomorrow morning.

(3.50 pm)

(The Inquiry adjourned until 9.30 am the following day)