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Wednesday, 29th August 2007

(10.30 am)

LORD ARCHER OF SANDWELL: Right, shall we begin.

DR JACK MELLING (called)

Dr Melling, good morning.

DR MELLING: Good morning.

LORD ARCHER OF SANDWELL: Thank you very much for coming. I don't have a statement from you. Don't worry about that, but you can make whatever presentation you think appropriate to us. You don't mind if I interrupt.

DR MELLING: Please, I think that is the most efficient way. I don't really have a script, I will not get lost.

Lord Archer of Sandwell, Dr Jones, Ms Willetts, thank you for the invitation. I accepted really for two reasons. One is that I think these types of illness that result from products that are meant to be of help really I think are important and of significant interest, and also it happened that I was a member of the Committee on Safety of Medicines (Biological Subcommittee) at the time.

LORD ARCHER OF SANDWELL: Yes.

DR MELLING: I wasn't intending, apart from referring to minutes that -- I wasn't going to refer to that directly, partly for reasons that I guess I am still bound by confidentiality, and partly because I am also

bound by a bit of memory loss going back that far, so I want really to try to speak a little more generally and if I may, try to identify questions and issues that you and your committee may find useful or helpful and -- in your discussions with other people.

LORD ARCHER OF SANDWELL: Thank you.

DR MELLING: I thought -- and again having consulted with Vijay -- I would just start, because I gather no one else was going to do this by giving a bit of background in terms of what is involved in product licensing.

LORD ARCHER OF SANDWELL: This has been something which we have wanted to hear about for will some time now so we very much welcome it.

DR MELLING: I think the best way I can probably do it, I will describe the procedure in a sense as it is or has it has now developed and try to take us back a little to maybe how things were in the early 1980s, and then I think we can maybe begin to see some of the thinking and decision making in context.

Essentially, in order for a product to be granted a licence and to be approved for sale it has to go through a number of stages. There is obviously the research and development and there is animal testing. Usually then a product would go into phase I studies in humans, which would involve really a handful people,

almost certainly less than 20 who would normally be simply healthy volunteers who would not be being treated, in a sense, by a product. This would be an initial look mainly at safety in humans to move on from the animal testing.

That would then be followed by phase II studies which would involve a larger number of people. Again, it depends on product. Up to 100 or so. And there you probably would be looking at some people who would have a possibility to benefit from treatment, but again the main aim of the phase II study is to fairly evaluate safety and at that time point also to begin to look for immunological markers that may indicate whether it is going to be efficacious or, if it is not a product that produces an immune response, some other biological marker that would show -- for example, if you were trying to develop to reduce blood pressure in that phase II you would be looking to see was there an effect among that group of people.

LORD ARCHER OF SANDWELL: That is something that would not normally be looked at in phase I?

DR MELLING: Right. The two sometimes get a little bit blurred but essentially that is the main distinction.

LORD ARCHER OF SANDWELL: Yes.

DR MELLING: Then after that products would then move into

-- and by way, certainly at those early phases -- I think this is true but maybe need to check -- for phase II I think there needed to be a regulatory approval in order to go into phase II. I have a feeling there was not a regulatory approval required to go into phase I.

LORD ARCHER OF SANDWELL: Is this what has been referred to as a "named patient use"?

DR MELLING: Yes, in part. A named patient use -- it is different. A named patient use is where a product exists that is not necessarily licensed or approved for a particular use, and a physician is allowed, on their own authority and understanding, to then use that product for treatment of a particular patient or patients plural, but the risk in that sense lies with the physician, if they get it wrong, whereas with a product that has a full licence approval, there is, as it were, much less risk attending.

LORD ARCHER OF SANDWELL: It is a pretty good story to say the committee looked at it and said they were satisfied.

DR MELLING: And then phase III studies can involve, actually depending on the particular, you know, illness, could involve several thousand people, and the main aim of the phase III study is to look at efficacy and so these studies are normally double blinded. Neither the

physician nor the patient knows whether they are receiving the drug or vaccine or they are receiving a placebo and there is then an evaluation at the end of the study when the blinds are taken off, and then the statisticians get to work and then really work out whether or not that particular treatment was effective.

In phase III because of the large number of people this also further raises human safety in that the people running the trial, part of protocol really is looking for adverse reactions of various sorts.

LORD ARCHER OF SANDWELL: But it wouldn't be used until it had passed the phase II satisfaction?

DR MELLING: Moving to each stage depends on successfully completing the previous stage.

LORD ARCHER OF SANDWELL: So you wouldn't expect it to have adverse effects -- or would you?

DR MELLING: Unfortunately, I think the answer is yes. Humans differ greatly and what is okay for me may not be okay for someone sitting next to me and until you get enough people being exposed or being treated with a particular drug, you really don't know what proportion of people may have an adverse reaction and in recent years, and particularly in the USA, even after phase III -- and if everything went well in phase III and a product is approved and licensed there is now what is

called a phase IX, which I think here is called post-marketing surveillance -- in the USA they call it phase IX -- and that is where the drug is in general use, there is constant monitoring. Because I think, over the years people have got used to the idea that it is only when something is being used on a very wide scale that you actually see the occasional or rare cases of some form of adverse reaction, and at that point licensing authorities really have to review this and say: if there are such adverse reactions are they of a nature of severity that they should consider revoking the licence?

I will come back to that issue in a moment.

MS WILLETTS: I suppose the classic example would be thalidomide which went through phase III and was widely used and found about the problems afterwards.

DR MELLING: In fact your comment was timely because I was going to say having discussed current practice, really, how did we arrive at this and I think this is relevant to this enquiry. As a result of the thalidomide tragedy the UK passed the Medicines Act in, I think, 1968 and the result of this was that the procedures I have just described really came into being, such that whereas before a manufacturer with relatively few constraints could put almost any product on the market, after the

Medicines Act then products had to go through the steps that I have just described.

LORD ARCHER OF SANDWELL: May I just ask -- I am unloading all the questions that have been buzzing around in my mind for some time. The 1968 Act, the person responsible for licensing is the secretary of state?

DR MELLING: That's correct.

LORD ARCHER OF SANDWELL: But clearly advised by the committee, and then presumably it goes through various desks in the department before it ends on the desk of the secretary of state.

To your knowledge has there ever been a case where the secretary of state has said: I am rejecting the advice I have been given?

DR MELLING: I am not aware of it. There may have but I am not aware of it.

LORD ARCHER OF SANDWELL: Thank you.

DR MELLING: The Medicines Act was passed in 1968, and at that time there were already a number of products already on the market and by and large, these products were granted what were called "licenses of right", so they were in essence grandfathered in. There then began -- I can't tell you how long after 1968 -- a process of review of those products which had licensing of right and essentially they were then treated as if they were

a completely new product and the manufacturer then had to provide to what was then the Committee on Safety of Medicines evidence of safety, efficacy and a component called quality. Quality is the ability to produce the product consistently, so if you produce it today and you produce a batch in the year's time, they have to be the same, which is not as easy as it may appear.

Now, what I don't know but again it may be worth this committee at least asking the question, I don't know whether any of blood products at the time they were being used in 1982, 1983, were still products with a licence of right, or whether they had been through the review process and in effect had become fully licensed products.

LORD ARCHER OF SANDWELL: Is there a record which we can look at which would answer that question?

DR MELLING: Not -- I personally don't -- I am sure within the department --

LORD ARCHER OF SANDWELL: The department would probably know, yes.

DR MELLING: I would have thought it would not be particularly sensitive information.

LORD ARCHER OF SANDWELL: Well, we will deal with that.

DR NORMAN JONES: Quite possibly Dr Foster might know.

LORD ARCHER OF SANDWELL: Yes.

DR MELLING: And then going through this whole licensing process, really ultimately what is involved is evaluation of risk and benefit and of course the reality is that no medical treatment or procedure is without risk and so before embarking one says: is it better to do this than just leave things alone? And I think again this is a key issue in the current circumstance and I will come back to it.

What I think is very important also to understand is that before a product is licensed the onus of proof is really on the manufacturer to show all the things that I have just described, and this is purely my opinion, but once a product has been licensed I think that balance shifts significantly. A watershed is crossed, and the department, the licensing authority, takes almost a piece of ownership of that product, and there is -- if, then, there is a question over its safety or its efficacy or some other factor, the fact that had has gone through this very vigorous licensing process I think means that the evidence to the contrary then has to be very strong. I would guess it is a bit like a criminal convictions. Once somebody has been convicted, it is very tough to that get that changed and I think there is an analogy there with products.

LORD ARCHER OF SANDWELL: It is the question: why have you

changed your mind?

DR MELLING: Yes.

Anyway, and I think that maybe with the help of other people you may be able to try to establish what this, in a sense, dynamic was in respect of products that were licensed where questions about them were raised, what was that like in the early 1980s. I think now -- and I am familiar these days more with the USA -- but I think now there is more willingness to accept that even a product that has been approved and has been used for some time still may have drawbacks and may need to be further looked at.

But I think probably 20 or so years that was less true.

LORD ARCHER OF SANDWELL: May we just eliminate, if we can eliminate it, one consideration: the committee is concerned with safety and efficacy, as I understand it; is it in way concerned with cost, or is that a matter for other people?

DR MELL: No, as far as I am aware these committees are concerned with safety efficacy and what I call quality, and these were the three things that the committee looked at. This is true of the FDA as well.

LORD ARCHER OF SANDWELL: So they will also look at a cost benefit ratio?

DR MELLING: That would be part, in a sense, of the efficacy and safety.

LORD ARCHER OF SANDWELL: Yes.

DR MELLING: So it would not be a cost benefit but a risk benefit?

LORD ARCHER OF SANDWELL: That I understand. The committee wouldn't be concerned in saying well, this is cheaper than the alternative, so we would give -- we start off with an advantage for this one.

DR MELLING: No. That role, I think, tends to fall to the officials within the system, and the two, in a sense, do meet, in respect of some of these advisory committees because if you look at the people who sat around the various tables you would see there are a mixture of external experts and advisers and internal people, and of course the internal people are answerable, you know, through the various levels in the Civil Service up to ministerial level.

LORD ARCHER OF SANDWELL: You wanted to --

DR NORMAN JONES: Just going back to your previous point, basically relating to the fact that disadvantageous side effects could arise late in the day, the evidence was there even in the very early 1960s from the butazolidine experience, was it not? Very early.

DR MELLING: Good point, yes.

LORD ARCHER OF SANDWELL: Evidence of the risk, but possibly not the magnitude of the risk.

DR MELLING: And I, again I think this rather difficult and occasionally subject to evaluation of risk versus benefit.

Let me just move on, and I am sure you will hear in much more detail about this, so I will not labour the point, but just to put it in context, I have looked at what I could find about the state of the AIDS epidemic in 1983, and from the figures I found, in May 1983 there were nine cases in the UK of diagnosed AIDS and three people had died.

In the USA, in June 1983 there were just over 1600 diagnosed AIDS cases and about 650 people had died.

So this epidemic was still really on the low part of what obviously became a very steeply rising --

LORD ARCHER OF SANDWELL: There may have been many people affected but at that stage it wasn't known.

DR MELLING: Correct. Now, as a result of particularly what was happening in the USA in late 1982 and through 1983 there were many meetings in the US involving centres for disease control, food and drug administration, National Institute of Health, in some cases the manufacturers of blood products, and if you read the reports some of these meetings were very heated, with the CDC, FDA

participants apparently warning of the sort of risk that we now know came to fruition and the manufacturers being in somewhat of a state of denial that what they saw as -- indeed it was -- a highly beneficial product could actually have potentially horrendous consequences.

Again unless you have already accessed this information, it may help to try to access some of that, to see what the thinking was and what the background was, and again, in the USA, it tends to be much easier to access this sort of documentation .

LORD ARCHER OF SANDWELL: I suppose it begs the famous questions: they would say that, wouldn't they?

DR MELLING: And again I think, also moving on from that, I would also raise another question, which was that in the international medical regulatory community these things are not going on in isolation, there is constant contact and communication. So again I think a relevant question really would be: what, in the early middle 1983 period, did the Department of Health know about this quite heated debate that was going on in the US and how and did this reflect on any action or inaction?

If I can then -- I think just lastly, if I could just touch on the minutes of the CSMB, and I was looking at the conclusions on page 2, and this is minute number 5.

LORD ARCHER OF SANDWELL: This is of the committee or the subcommittee?

DR MELLING: This is of the subcommittee.

LORD ARCHER OF SANDWELL: The subcommittee.

DR MELLING: I think clearly minute 5.1 was generally correct and indeed I think showed an appropriateness and most of that I guess would be pretty much true today.

In 5.2 --

MR MEHAN: Can I ask you to read that 5.1 for the benefit of the record.

DR MELLING: Yes:

"The cause of AIDS is unknown but an infectious aetiology seems likely. A previously unrecognised or new agent may be responsible but repeated exposure to or reactivisation of known agents (eg CMV, EBV) may be involved. Heightened susceptibility may be an important factor, for example immunological deficiencies induced by unusual sexual practice or exposure to blood products. Based on the clinical evidence, transmissibility of the supposed agent or agents appears to be low, requiring intimate contact or introduction into the tissues."

I think by and large that evaluation has stood the test of time.

In minute 5.2, which again I can read -- maybe

I will do that first:

"Patients who repeatedly receive blood clotting factor concentrates appear to be at risk, but the evidence so far available suggests that this risk is small. The risk appears to be greatest in the case of products derived from the blood of homosexuals and IV drug abusers, residents in areas of high incidence, (eg New York and California), and in those who repeatedly receive concentrates in high dosage. Balanced against the risk of AIDS (and other infections transmitted by blood products) are the benefits of their use; in the case of haemophilia they are life saving."

I think that an issue that I think now -- and I currently work for the US Government accountability office, and we are what is called the ultimate Monday morning quarterbacks. We are allowed to look back at what people did and be critical and in that spirit, looking at 5.2, a significant (inaudible word) really would be how many people at that point were showing signs of problems and that is not in the minute, and in a sense what was again the dynamic of that. Once again, and I could -- I think I could share this perhaps through Vijay -- there is written material which indicates that there was a lot of debate, certainly in the US, over this issue of degree of risk, and really

how this should be assessed.

LORD ARCHER OF SANDWELL: When we are discussing risk, there are two factors, aren't there? There is the degree of risk of it happening and the seriousness if it does happen.

DR MELLING: Correct.

LORD ARCHER OF SANDWELL: I take it at that stage everyone appreciated the seriousness of the condition if it happened.

DR MELLING: I believe that is so.

LORD ARCHER OF SANDWELL: Yes.

DR MELLING: And then 5.3:

"The possibility was considered of withdrawing clotting factor concentrates from the market and replacing them with cryoprecipitate. It was concluded this was not feasible in the UK on grounds of supply."

Now, I think that this really goes back to a point that you made earlier. The words say "on the balance of supply" and I think it would be a good question perhaps for your group to at least ask is: does "supply" mean quantity and the amount, or does it also involve what cost issue of making the change, since there could be -- well, there could be a limited supply of the material, simply there is only so much available, or of course it could be that supply is limited because there would be

a much bigger bill to pay.

LORD ARCHER OF SANDWELL: Would this be the subcommittee saying, "One of the things we should consider is the cost element" or would they be saying, "The likelihood of whoever it is agreeing to pay that price".

DR MELLING: I think, as I am reading this minute, the emphasis would appear to be on availability of material.

LORD ARCHER OF SANDWELL: Well, I follow that, yes.

DR MELLING: However, knowing Government systems as I now do, maybe there is in the background subtext.

LORD ARCHER OF SANDWELL: Well, yes.

DR MELLING: And I think in this context it would be important if you are able to make any evaluation.

LORD ARCHER OF SANDWELL: Yes.

DR MELLING: And then in 5.4:

"The possibility was considered of withdrawing US preparations from the UK. It was concluded it was not at present feasible on the grounds of supply. Moreover, the perceived level of risk does not at present justify serious consideration of such a solution. Efforts, however, are being made to secure UK independence of foreign suppliers' clotting pack concentrates. This should reduce markedly, although not eliminate, the risks to recipients of these products, and the subcommittee strongly supports this aim. The

subcommittee was also informed that the UK Haemophilia Centre Directors have adopted a policy for use of US Factor VIII in order to minimise risks as far as possible."

Now, I think that in respect -- I think this is an important minute in this context, because I think it raises two issues. The reference to the haemophilia centre directives -- and I am sure you will talk to other people later who can give you more insight -- suggests there was some policy that involved not giving potentially risky material to people who did not really need it. I don't know if that is the case, but I think it would be good to determine if that was the case.

Also in that context, I think it would be also useful to enquire whether there was any direction or recommendation from the department of health to the haemophilia centres, in respect of use and again you know or you will hear that although people may suffer from haemophilia not all people suffer to the same degree and some people can manage or could manage with really limited treatment of Factor VIII but other treatments that if they had a bump or a knock or whatever to really reduce the problem.

LORD ARCHER OF SANDWELL: I see we have seen some references in writing to a distinction between treating children

and treating adults, for example. That is what you mean?

DR MELLING: That would be a part of it, yes. And again, I am really posing a question this morning. How much effort was made to say: okay, we see some risk with this material, therefore it will only be given to people who have a life threatening condition. Now, "Life threatening" again is a somewhat subjective judgment, but could eliminate a significant proportion.

MS WILLETTS: We have heard quite a substantial amount of evidence from people who are angry because they were suffering only from a mild form of haemophilia and their perception is that they were given a high risk product which was not particularly necessary because their condition was not actually particularly serious. I don't mean that that in a dismissive way, but they had it in a milder form.

DR MELLING: I think this is an important issue and I would have thought there are records and/or memories within the haemophiliac centres and treatment community as to, firstly, what was the policy and interestingly, I think, how did that policy, if it did evolve over time, as the risk perception became clearer and clearer?

LORD ARCHER OF SANDWELL: Yes, yes.

MR MEHAN: We do have minutes of some of those meetings from

the haemophiliac centres in the early days?

LORD ARCHER OF SANDWELL: Yes, we have.

DR MELLING: I think that just overall, reading this first hand since I don't know when, I get a flavour that there was a degree of weigh or inertia towards keeping products available and again I think may refer to what I described earlier as having crossed the licensing hurdle, then the onus was on saying there really is a problem rather than proving there wasn't a problem.

LORD ARCHER OF SANDWELL: Most of us tend to ignore evidence that the last decision we took was wrong.

DR MELLING: Exactly. And I think it is also the -- this could effect decisions about restricting use because if one is saying: we must restrict use, by definition virtually you are saying what we are using has some problem, otherwise we wouldn't restrict it, and similarly, with thinking: okay, can we substitute what is apparently a safer product, such as cryoprecipitate and again, it is that sort of underlying thought.

And I think really my last comment in this area would be, I think it would also be instructive, although we are looking currently -- at least I am -- at the 1983 period, it would also be instructive I think to look at at what point did thinks really change, in respect of perception of the problem and a need to take action,

because clearly that did happen, and it would, I think, be possibly instructive then to look at what was the build up of that, of the evidence, that really brought about that tipping point, because often by looking, in a sense, at something that everybody eventually agrees and says: yes, we had to do this --

LORD ARCHER OF SANDWELL: When did the alarm bells begin seriously to ring?

DR MELLING: The question is: if then, why not sooner? I think that would be a highly germane question, particularly in light of some of the debate in the USA.

I believe, sir, I have used up my allotted time.

LORD ARCHER OF SANDWELL: If I may say so, used it up very valuably.

DR NORMAN JONES: Thank you very much for very clear -- a very difficult question, but at least you may have a shimmy at it.

Going back to that meeting on 13th July 1983 and with all the advantages of retrospective viewing, can you think of changes in procedure which would in effect have led to the CSM being quicker off the mark with regard to identifying the scale of the risk? For instance, can you remember the frequency with which the recommendations made at that meeting were reviewed?

DR MELLING: No, I can't, and in fact that was one of the

reasons for my making the comment that I think it would be important, if you were able to access records, to be able to see how things then developed really from that point on, because I think that was almost the early warning flag and then clearly there were others subsequently.

LORD ARCHER OF SANDWELL: Clearly, research was going on all the time, of course, which might have triggered -- yes.

Thank you very much, Dr Melling. We're most grateful.

I think Dr Foster is next.

DR PETER R FOSTER (called)

Good morning.

DR FOSTER: Good morning.

LORD ARCHER OF SANDWELL: We have your statement. It is very helpful. I think it would be better, if you agree, if you make your presentation on the basis of the statement, or whatever you want to add, rather than leading you with questions, but you won't object if we intervene from time to time.

DR FOSTER: Thank you for inviting me here today, and I hope I will be able to assist you with your investigations.

I would like to comment on a number of topics, to give you background information and to describe my personal experiences, and there are three topics I would

like to cover.

Firstly, the licensing of plasma products; secondly, self-sufficiency and supply of Factor VIII; and thirdly, the development of heat treatment.

I will start by introducing myself. I am a chemical engineer by profession and I specialised in biochemical engineering with a PhD on the technology for the separation of proteins from one another. I joined the Protein Fractionation Centre at the Scottish National Blood Transfusion Service in January 1973 as a research scientist. PFC is where the SNBTS manufactured plasma products such as Factor VIII and Factor IX concentrates for the treatment of haemophilia. As well as other products, such as albumin for the treatment of casualties and the arrangement of antibody products known as immunoglobulins.

At that time in 1973 PFC was situated beside the Regional Blood Transfusion Centre at the Royal Infirmary of Edinburgh but planning was underway for a new facility on the outskirts of Edinburgh and this was commissioned in 1975 and operated routinely from 1976.

Staffing arrangements for a new centre were drawn up in April 1974 and I was appointed head of Research and Development. That was that is essentially the same position I hold today. I have been involved with a hold

range of plasma products since that time but problems with Factor VIII have dominated my work since 1976. Factor VIII concentrate was an extremely difficult product to prepare and my research was aimed initially at increasing output to try to achieve national self-sufficiency.

The knowledge that was gained from this work provided a foundation for the development of technologies aimed at eliminating risks of infection. I will say more about these problems in a moment but firstly I will say something about licensing regulation.

Plasma products are Prescription-only-Medicines and for legal purposes they come under the UK Medicines Act of 1968. The Government body responsible for enforcing this Act is the Medicines and Healthcare Product Regulatory Agency, the MHRA, and this was formerly called the Medicines Control Agency, the MCA. There were two principal types of licence which were awarded by the MHRA, a Manufacturer's Licence, which demonstrates that a premises and their operation are suitable for the manufacture of pharmaceutical products, and a Product Licence, which is sometimes known as marketing authorisation, which demonstrates that a product has been judged to be suitable for the clinical use specified.

Within the MHRA advice on Product Licensing was given by the Committee on Safety of Medicines, the CSM, and as well as considering clinical information such as data on clinical effectiveness and on side effects and other complications, the CSM would also consider issues such as product quality and product composition, the method of preparation and this would include the labelling and packaging and with regard to packaging all pharmaceutical products must carry warnings of potential side effects or adverse reactions --

LORD ARCHER OF SANDWELL: Can I just ask you a question which we discussed with Dr Melling? Dr Melling's view, as I understood it, is that although it is not strictly the business of the committee whether the cost benefit relationship is right, it is something which they can't shut out from their mind, partly because it would be pointless making a recommendation which wasn't likely to be accepted by someone because of the cost?

DR FOSTER: That is not my understanding. My belief is that cost would not come into these considerations.

To carry on, I believe that the warnings that went with products and the wording that was used in those warnings had to be approved my MHRA before a licence could be awarded.

For example, SNBTS was first granted a Product

License for Factor VIII concentrate in 1978. The packaging contained five warnings concerning the risk of hepatitis. There were two warnings on the outer cartoon, two warnings on the product information leaflet and one warning on the label attached to each and every vial. The wording for these warnings was submitted with the application for the licence and was approved by the MCA when the Product Licence was granted.

Commercial Factor VIII concentrates were first licensed in the UK in 1973, but to the best of my knowledge all coagulation factor concentrates carried warnings concerning hepatitis and I presume that these warnings and the wordings used were approved by the MCA. I should point out that pharmaceutical manufacturers do not deal with patients directly and depend on the doctor who is treating the patient to ensure that individuals are informed of risks associated with their treatment.

LORD ARCHER OF SANDWELL: You are speaking now about the early 1970s, are you not?

DR FOSTER: I am, yes.

LORD ARCHER OF SANDWELL: Can you help at all with what kind of warning? We have all seen warnings on packages. Some are so small because you can't read them, some are overlooked because there is something on the top of them. Were these fairly clear warnings intended to be

taken seriously?

DR FOSTER: Yes, they were, and I can provide you with copies if that would help you. I do have copies from the past with both types of warnings that were used, both with commercial and non-commercial products.

MS WILLETTS: May I just ask which types of hepatitis warnings we are referring to? Are you talking about hepatitis B or --

DR FOSTER: At this time it would have been hepatitis B because that was the form understood to be transmissible by blood products but in some cases the general term hepatitis is also used, not just hepatitis B. But you can look at the wording yourself and judge for yourself.

The regulation of products manufactured within the National Health Service was complicated by the existence of Crown Immunity, which allowed manufacturers of pharmaceuticals within the NHS to be exempt from provisions in the 1968 Medicines Act. There were three NHS facilities in which blood plasma products were manufactured, the Blood Products Laboratory, BPL, at Elstree, just north of London, which now operates as a bioproducts laboratory, the Plasma Fractionation Laboratory, PFL, at Oxford, which was administered by BPL and which carried out coagulation factor research for BML -- and PFL closed in 1992 -- and thirdly, the

Protein Fractionation Centre in Edinburgh. I was not directly involved with licensing although I tried to explain the situation in Scotland.

The first director of PFC, Mr John Watt, was a member of the committee of safety of medicines at that time and he strongly advocated that the new PFC facility should be subject to the Medicines Act. There was uncertainty over the application of Crown Immunity in Scotland, and he was therefore authorised to apply for a Manufacturer's Licence, and this was granted to PFC to 1976 for a period of five years.

Applications were also made for product licences for Factor VIII and Factor IX concentrates, both of which were granted in 1978, each for a period of five years.

In 1981 when the manufacturer's licence was due for renewal, further legal advice was taken by the common services agency, which is the body in Scotland that administers SNBTS. Fresh legal opinion now held that Crown immunity did apply in Scotland. No application was made for renewal of PFC's manufacturer's licence.

Mr Watt, who had been director of PFC since 1966, left SNBTS at the end of 1983. Before leaving he submitted applications for renewal of the Product License for Factor VIII and for a Product Licence for intravenous immunoglobulin, which was a new product he

had developed. In each case, new product licences were granted for five years. Thereafter, no further license applications were made by SNBTS until Crown Immunity was removed in 1991.

Despite the provisions of Crown Immunity, PFC continued to interact with the MCA, encouraging informal inspections and acting on the advice given.

LORD ARCHER OF SANDWELL: So if there had been reason to wonder whether the matter should be reviewed you think at least somebody would have taken some action?

DR FOSTER: Yes; we were in continuing dialogue with the agencies, even though that was not a formal arrangement.

There was one implication of Crown immunity which should be noted: normally when a product or its method of preparation are modified an application must be made to vary the product licence. If a substantial change is made a new product licence application may have to be submitted.

When SNBTS introduced heat treatment to remove risk of infection from coagulation factors it did so by consultation with the MCA. If we had been required to apply for licence variations or for new product licences then the administrative formalities alone would have delayed the introduction of heat treatment considerably.

In these circumstances we believe that more patients

in Scotland would almost certainly have been infected with HIV and therefore we feel that freedom to make these changes quickly under Crown Immunity did benefit people with haemophilia.

DR NORMAN JONES: Dr Foster, could I ask you, does the paragraph you have just read in your view amount to a criticism of the state of play today?

DR FOSTER: Today it would take considerably longer to make the type of changes we made in the 1980. We made changes in weeks or months which today would take years.

LORD ARCHER OF SANDWELL: Not to put too fine a point on it, is that because you think the procedure now is over bureaucratic?

DR FOSTER: That is a difficult question. There are many opinions and expert advice taken and I think people are extremely cautious on any change to a product that might be seen as possibly causing harm.

LORD ARCHER OF SANDWELL: So you think there are very good reasons?

DR FOSTER: There are good reasons, but it does take a very, very, very long time.

LORD ARCHER OF SANDWELL: Yes, thank you.

DR FOSTER: Contrary to what you have been told, PFC has never had any of its licenses suspended or withdrawn by MHRA.

LORD ARCHER OF SANDWELL: I have no recollection of ever being told that? Am I wrong?

DR FOSTER: You were given evidence by one person who claimed this to be the case.

LORD ARCHER OF SANDWELL: I confess I don't remember this.

DR FOSTER: Nor has PFC been closed by the Medicines Inspectorate. PFC currently holds a Manufacturer's Licence, a Good Manufacturing Practice certificate, as well as Good Laboratory Practice accreditation, and we underwent a satisfactory inspection as recently at two weeks ago. PFC currently holds 19 product licenses, 15 of which are for plasma products and in this respect is one of the most successful manufacturers of protein pharmaceuticals in the UK.

However, it is considered that PFC is no longer economically viable as a supplier to the Scottish Health Service and a policy decision has been taken by Scotland's former Health Minister that Scotland will obtain its blood plasma products elsewhere.

A novel clinical product is still being manufactured at PFC for the Ministry of Defence. This contractual obligation is expected to be fulfilled within the next six months, after which PFC will close.

I would now like to comment on the issue of self-sufficiency and the supply of Factor VIII

concentrate, and I will begin with the international situation in 1970s, and in 1975 the World Health Assembly recommended that all countries should aim to meet their medical requirements for blood and blood products from their own population using unpaid volunteer donors.

Ten years on 70% of the world's plasma products continue to be derived from commercial plasma collected in the United States. Today that figure is 65%, demonstrating that progress towards national self-sufficiency has been limited worldwide.

The main reason why the United States has remained so dominant in my opinion lies in the volume of plasma that can be taken from a donor in the United States, which is much more than in other countries.

LORD ARCHER OF SANDWELL: So the supply of plasma, if you eliminated the United States, probably wouldn't be sufficient even now to meet the requirements much the world; is that the position?

DR FOSTER: That is very much the position, yes.

In the United Kingdom, the commitment to national self-sufficiency was first announced by the Government in January 1975. A few months earlier, a number of senior haemophilia doctors and the Haemophilia Society had urged the government to fund the purchase of

commercial Factor VIII concentrates on the grounds that 90% of patients were receiving inadequate treatment.

It is important to note at this point in time in the UK, life expectancy was 42 years for a person with haemophilia A and 34 years for a person with haemophilia B.

Commercial Factor VIII concentrates were purchased under a central supply contract administered by the Department of Health, with only Haemophilia Directors or their nominees having the authority to purchase. This centralised arrangement ended in March 1979 and individual health authorities were advised to make their own arrangement for purchase thereafter with only Haemophilia Directors or their nominees to authorised to purchase commercial products. I would like to stress that the UK transfusion services did not purchase commercial products nor did they import commercial plasma at that time.

LORD ARCHER OF SANDWELL: So there was a director contract between the haemophilia directors and the suppliers of the product?

DR FOSTER: There was a contract with the department of health.

LORD ARCHER OF SANDWELL: A central contract.

DR FOSTER: And after that the contracts was drawn up by

local authorities, after 1979.

LORD ARCHER OF SANDWELL: I was talking about after 1979.

DR FOSTER: Sorry.

LORD ARCHER OF SANDWELL: So after that, haemophilia directors, did they have a central purchasing body, did they apply to the manufacturers and say --

DR FOSTER: I can't give you a detailed answer on that, how they went about it. I think they were purchased via normal hospital pharmacies, but I can't be certain about that.

LORD ARCHER OF SANDWELL: I see.

DR FOSTER: To achieve self-sufficiency in the UK, the UK transfusion services had to supply the amount of plasma needed and fractionation facilities with the capacity to process this volume of plasma had to be provided. Planning for this was department on two crucial figures: The amount of Factor VIII required for treatment of haemophilia and the quantity of Factor VIII that could be extracted from each litre of plasma, that is the yield of Factor VIII.

I think you are aware that the use of Factor VIII concentrate in the UK exceeded all projections, and the Reverend Tanner has told you on the impact this had on the treatment of haemophilia from his personal experience.

Although the annual requirement was initially estimated to be about 40 million units of Factor VIII, actual usage reached 80 million units by 1984. This did not level off, and reached 160 million units by 1994 and 280 million units by 2004. These figures indicate how little treatment was being provided to patients in the 1970s.

In my experience, assumptions on the yield of Factor VIII also turned out to be wrong. With the actual yield in large scale manufacturing being much lower than had been assumed in 1974 by the MRC working party. There were a number of technical reasons for this, mainly associated with the difficulty of manufacturing Factor VIII concentrate and the instability of Factor VIII during processing, but also to changes in the way Factor VIII was measured in concentrates, which was changed in 1976.

The assumptions used for planning in 1970s meant that requirements for supply of plasma and its processing were underestimated considerably.

I will now describe what happened in Scotland. Initially, the same planning assumptions were used as in England and it was expected that sufficient Factor VIII would be obtained as a byproduct of albumin production which was the plasma product in most demand at the time.

When it was realised this would not be the case considerable effort were made to increase the production of Factor VIII concentrate. The amount of plasma required could not be met by recruiting more donors. Instead, plasma had to separated from blood soon after donation, leaving hospitals to use red cells instead of whole blood for transfusion, a concept known as component therapy.

MR MEHAN: Can I ask what period of time we are talking about?

DR FOSTER: Late 1970s, early 1980s.

This was a major change to establish medical practice, and to encourage hospital doctors to make this change, SNBTS medical staff embarked on a process of education and persuasion. SNBTS eventually stopped issuing whole blood altogether, unless it was first approved by an SNBTS doctor.

Whilst this was taking place, I was working on Factor VIII yield and we managed to increase this by about 60%. I will try to explain how this was done. I said earlier that Factor VIII concentrate was a very difficult product to prepare. The amount of Factor VIII present physically in blood is very small and I am talking here about the blood of a normal person, not someone with haemophilia. Factor VIII is a protein. It

accounts for about .0006% of the protein in human plasma. Treatment of haemophilia with plasma had limited success because it was not possible to get enough Factor VIII without overloading the patient's circulation. To treat haemophilia properly Factor VIII had to be concentrated into a much smaller volume. Hence the term Factor VIII concentrate.

There were a number of things that had to be done technically to achieve this. Proteins that would not dissolve in such a small volume had to be removed. Proteins that would damage Factor VIII also had to be removed, as did proteins such as immunoglobulin and albumin, which were needed to treat other patients. After all of this had been done, any bacteria that might be present had to be removed and this was done by filtering the Factor VIII solution through membranes with tiny holes, holes so small that bacteria could not get through, something that had not been possible with cryoprecipitate or with other types of Factor VIII concentrate.

Factor VIII was then put into vials and because it was unstable it had to be freeze-dried. After this it could be stored at 4 degrees centigrade and used immediately when needed.

The first step in the manufacturing process involved

the preparation of cryoprecipitate, a substance you have heard about already. Cryoprecipitate is a thick, sticky residue of protein which forms when frozen plasma is melted and dissolves as the plasma warms up.

Most of the Factor VIII in plasma goes into residue but it is still only a tiny proportion of the protein present. Factor VIII could be concentrated by separating the cryoprecipitate from the rest of the plasma and then dissolving it in one tenth or less of the original volume of plasma.

Further processing was then carried out on this concentrated protein solution. None of this was easy, mainly because most of the proteins present which make up cryoprecipitate are sticky. They do not dissolve easily and they tend to block the filters used to remove bacteria.

Factor VIII itself is very fragile, and tended to disappear for no obvious reason. That is why the yield was such a problem. To deal with this, it was necessary to track what was happening to the Factor VIII: where was it going, how was it being damaged?

In the 1970s, knowledge of Factor VIII was very limited and the scientific tools available were rudimentary by today's standards. There was no way of detecting Factor VIII directly. It could only be

tracked by its activity; that is, its ability to clot plasma from a haemophiliac. These tests have to simulate the blood clotting process and were very complicated. They had to be performed in specialist laboratories and even then accuracy was poor, even in the most expert laboratories.

There was also a type of damage to Factor VIII, called activation, that would give exaggerated readings in the plotting test, indicating a lot of Factor VIII was present when there was very little there.

Because of these problems experiments had to be repeated many times and even then it can be difficult to interpret the results. It was also hard to get plasma for research, because priority was given to making Factor VIII for patients. At one point we had so little plasma available that PFC staff volunteered to donate their own plasma to allow our research to continue.

As well as doing experiments in the research laboratory I also examined the production process carefully, because the production situation is very different to small scale laboratory experiments and findings from the lab could not always be reproduced in production.

I began by looking at the first step in the production process, the preparation of cryoparticipate

at large scale. The yield at this depth was much lower than expected. It was not clear how Factor VIII was being lost. One theory was Factor VIII was being damaged during the time taken to melt the frozen plasma. Another theory was that Factor VIII was melting back into the melted plasma because the temperature had become too warm.

These possibilities were not mutually exclusive, so both had to be addressed. But there was a contradiction: how could the melting of frozen plasma be speeded up and the temperature reduced at the same time? I designed equipment to solve this problem. This involved continuously feeding particles of frozen plasma to a small heated container from which the plasma could flow away from the heated surface as soon as it melted. This worked well, and the yield was increased by 45%, and the cryoprecipitate was much easier to dissolve than before.

I also fine tuned the other processed steps and, most importantly, was able to identify why Factor VIII was unstable during processing. I was able to correct this by adding a small amount of calcium, which helped to protect Factor VIII from the anticoagulant that had to be added to prevent clotting. This addition of calcium to stabilise Factor VIII later became important in the

development of heat treatment, both at BPL and PFC, and is widely used today in the preparation of both recombinant Factor III and Factor VIII derived from plasma.

By the early 1980s, the supply of plasma to PFC had increased by about three-fold. In spite of this large increase, PFC still had sufficient capacity to process the extra plasma, as plans to process English plasma at PFC had not come to fruition, leaving us with spare capacity.

DR NORMAN JONES: Plans to process English plasma didn't work out; why was that?

DR FOSTER: I am not sure I can give you a definitive answer on that. The arrangements were drawn up really in the late 196s and the early 1970s and I think the plan was suggested that about a third of the capacity for England would be processed at PFC and once the PFC facility was opened, this was the subject of ongoing considerations during the 1970s.

Certainly SNBTS were very keen to do this, there was no lack of willingness on our behalf, and I think the decision was taken to rebuild BPL in the early 1980s, the decision was taken to build that to handle all of England's plasma and that there would be no requirement for Scotland to be used.

LORD ARCHER OF SANDWELL: The problem, as I recollect we were told, was that the actual manufacturing facilities initially were found to be deficient, and there was a suggestion that the process ought to be closed down, until it had been cleaned up, not to put too fine a point on it.

DR FOSTER: Sir, I think you are talking about BPL. That was a problem at BPL. They were inspected in 1979 and after the inspection report the decision was taken to rebuild the factory.

LORD ARCHER OF SANDWELL: And that was why they took the decision to rebuild.

DR FOSTER: Yes, that is correct.

The combination of extra plasma and increased yield enabled SNBTS to be able to supply sufficient Factor VIII concentrate for the treatment of all patients in Scotland in 1983, making Scotland one of the few countries to have achieved self-sufficiency using donations from unpaid volunteers, and as far as I am aware, was the first country to do so.

In 1998, the use of UK donor plasma for the preparation of plasma products was banned as a precaution against the theoretical risk from variant CJD. This effectively ended the UK policy objective of national self-sufficiency. The Department of Health has

since purchased a commercial plasma supply company in the United States to safeguard plasma supplies to BPL. The United Kingdom now depend on the US commercial system for its plasma products.

I would now like to talk about the development of heat treatment for coagulation factors, and there are two types of heating that I will describe.

In one method, called pasteurisation, heating is carried out on a solution of Factor VIII after it has been dissolved in a lot of sugar. In an another method, known as dry heat treatment, the heating is applied to Factor VIII after it is freeze dried and sealed in its final container.

Initially, the objective with both of these approaches was to discover heating conditions that would destroy viruses responsible for non-A non-B hepatitis. Later this also encompassed the virus responsible for AIDS. The problem with hepatitis was not new. The possibility that human blood plasma products could transmit hepatitis had been known since the 1930s. Hepatitis was a major challenge to transfusion science and a considerable amount of research was undertaken to try to eliminate this risk. Hepatitis infection in haemophiliacs in the UK was first described in 1963. In 1967, international experts advised that recipients of

Factor VIII concentrates should be monitored for evidence of hepatitis infection.

Two different types of hepatitis were recognised at that time, one with a shorter incubation period, another with a longer incubation period, and these became known as hepatitis A and hepatitis B respectively.

It was the second of these, hepatitis B, that was implicated by infections by transfusions. The virus responsible for hepatitis B was identified in 1967 and the virus responsible for hepatitis A was discovered in 1973.

Screening of blood donors for infection with hepatitis B was introduced by SNBTS in 1970. When I joined PFC in 1973, research was still being carried out to try to find a way to remove the hepatitis B virus from coagulation factors, because it was appreciated that the screening test for hepatitis B was not yet sensitive enough to detect all infected donations.

Later we learned that hepatitis B was not the only problem, as there were patients with hepatitis which could be not be accounted for by either the hepatitis A or the hepatitis B virus, and this type of hepatitis was called non-A non-B hepatitis.

Non-A non-B hepatitis in haemophiliacs was first reported by doctors to a meeting of the World Federation

of Haemophilia in 1975. The World Federation of Haemophilia is an international body which represents patients, and to which the UK Haemophilia Society was a founder member.

Research was begun around the world, including research at SNBTS, to try to discover the cause of non-A non-B hepatitis, which was presumed to be due to one or more viruses. We now know non-A non-B hepatitis was caused by the hepatitis C virus, which was discovered in 1989 which researchers in the United States.

We also know now that hepatitis C accounted for 90% of the hepatitis transmitted by blood and blood products, even in the 1960s.

Whilst the search for the virus was going on, the problem that we and other fractionators faced was how to design a technology to remove a virus which had not yet been discovered without damaging fragile coagulation factors.

It was in 1981 that I learned that a company in Germany was pasteurising Factor VIII to try to destroy hepatitis viruses. This was being done by using a thick sugar solution to stabilise the Factor VIII, with the sugar having to be removed after the heating had been completed. The main problem was that the yield from this process was extremely low, partially because of

damage to Factor VIII during heating, but also because of losses that were incurred when the sugar was removed. Because the yield was so low, relatively few patients could be treated and most of the Factor VIII produced by the company was not heated and much of the Factor VIII used in Germany was imported from the United States.

In our research to increase the yield I have also mentioned that I identified why Factor VIII was unstable during the processing and I thought it might be possible to use this knowledge to increase yield over pasteurisation.

It was also necessary to remove a protein called fibrinogen which is present in cryoparticipate with Factor VIII and is even more sensitive to heat and I had discovered a way of removing fibrinogen, so we began to work to try to make pasteurisation viable, using these discoveries. There was considerable scepticism at this time over the idea that Factor VIII might survive heat treatment, and I remember one doctor who was convinced it would all turn out to be a mistake and that pasteurised Factor VII would not work in patients.

We continued our research despite these views and made sufficient progress that we were able to prepare some pilot production batches of pasteurised Factor VIII in 1983, to determine its effectiveness in patients.

The product was given to three patients. Two tolerated the product well, but one experienced an allergic reaction which his doctor judged to be unacceptable. The recovery of Factor VIII in his circulation was normal, and it was concluded that some other protein in the product must have been damaged by the heat treatment and caused this reaction.

We decided that the purity of the product needed to be increased much more and we began research on this in collaboration with scientists in the United States who were devising a technology for the preparation of highly purified Factor VIII.

The second approach to heat coagulation factors, dry heat treatment, emerged in 1982. Researchers in the United States had found that freeze dried Factor VIII could withstand heating in the range 60 to 68 degrees centigrade for a number of hours.

Freeze drying is used widely to stabilise biological products such as vaccines, so viruses would be expected to be more stable to dry heating as well as Factor VIII and this turned out to be case, as patients receiving commercial products which had been treated in this way continued to be infected with non-A non-B hepatitis. There was concern that heating might damage Factor VIII in a way that would cause patients to develop antibodies

which would stop the Factor VIII from working and there would be harm as a result. This did actually occur later in Europe where two pasteurised Factor VIII products had to be withdrawn for this reason.

Because of this fear, there was a reluctance to use heated Factor VIII concentrates without some evidence that viruses were being destroyed. The adverse reaction to our pilot batch of pasteurised Factor VIII heightened this concern.

Attention now became directed towards AIDS as well as hepatitis. HIV, the virus responsible for AIDS, was discovered in 1984 and, contrary to the claim by the Haemophilia Society, heating experiments with HIV and Factor VIII were first performed in autumn 1984 by scientists at the Centre for Disease Control in the United States, in conjunction with the plasma fractionation company there. They discovered that HIV that had been added to Factor VIII could be destroyed by dry heat treatment at 68 degrees centigrade.

Their results were not published in a peer review journal until August 1985 but the findings were so important that CDC summarised the results in its Morbidity and Mortality Weekly Report, MMWR, that was published on 26th October 1984.

PFC subscribed to MMWR, but its distribution was

slow, and so we first heard of these findings on 2nd November 1984, when they were presented at a conference in The Netherlands which I and some of my colleagues were attending. A speaker from CDC reported that HIV infectivity that had been added to Factor VIII was reduced 10,000 fold after dry heating for one hour at 68 degrees centigrade. Our Factor VIII could withstand dry heating for two hours at 68 degrees centigrade.

By this time, we had managed to establish a 12-month stock of Factor VIII because of the increased supplies of plasma and the yield improvements that I have described. We decided to dry heat our stock of Factor VIII at 68 degrees for two hours to provide heat treated Factor VIII as quickly as possible and this enabled us to recall unheated Factor VIII and let the Factor VIII that had been prepared from blood donations collected as early as October 1983 could be subjected to dry heating, effectively backdating heat treatment by over 12 months.

As a result SNBTS was able to distribute sufficient heat treated Factor VIII for all patients on 10th December 1984, and I believe Scotland was the first country in the world to move over completely to heated Factor VIII, even discounting the 12-month backdating

that was gained by heating our stock of Factor VIII.

There were still concerns that Factor VIII would be damaged by heating and would cause patients to develop antibodies that would stop Factor VIII from working. One senior haemophilia doctor wrote to us to complain that we had introduced heat treatment too quickly. Other experts wrote to the Lancet to argue against heat treatment, believing it would do more harm than good.

SNBTS considered these views carefully but stuck to its position. We know now that if we had not done so many more patients in Scotland might well have been infected by HIV.

In my research, I have been studying the effect of various additives on Factor VIII to try to increase the yield even more, and I used samples that were already available to see if dry heating at 68 degrees could be extended beyond two hours. I discovered that if a small amount of sugar was added heating could be extended to 12 hours and we made this change immediately and sugar was added to all batches of Factor VIII that were newly prepared, enabling these to be dry heated at 68 degrees for 12 hours.

I should point out here that the claim by the Haemophilia Society that infectious batches of Factor VIII could have been detected in 1983 by a HIV

screening test is quite wrong. SNBTS did screen all of its batches of Factor VIII for evidence of contamination once an HIV test was commercially available, but the original screening test, which detected antibodies to HIV, was not sensitive enough to detect contamination in concentrates and this did not become possible until 1991, when a more sensitive analytical technique was developed that could achieve this.

Following the advice of October 1984 from CDC, most countries moved to heated concentrates during 1985 to prevent HIV transmissions. A vaccine was available to protect individuals at risk from hepatitis B, including staff at fractionation centres, but the problem of non-A non-B hepatitis had still to be solved. Research was progressing internationally on a number of fronts. Despite its low yield, the pasteurised product in Germany was the only approach so far in which patients had remained free of hepatitis, although international experts did not regard their results as definitive.

We were aware that our NHS colleagues at BPL had made a breakthrough in their research and had managed to prepare Factor VIII concentrate that could withstand dry heating at 80 degrees, for 72 hours.

This was a remarkable achievement, which, according to the Lindsay tribunal in Ireland, was viewed with some

astonishment by other fractionators at the time. It had been achieved with a new preparation of factor VIII, called 8Y. This was five to 10 times more pure than established products and this greater purity was thought to be why 8Y was exceptional in being able to withstand this very high temperature.

However, unlike pasteurisation, there was no evidence available at that point that hepatitis could be destroyed by dry heat treatment, even at 80 degrees centigrade.

We continued our research to increase purity, as this was consistent not only with improved pasteurisation, but also with the view that greater purity was the key to be being able to dry heat Factor VIII at 80 degrees centigrade or at even higher temperatures, if that was needed to destroy hepatitis viruses.

A number of things happened later in 1985 which caused us to change this strategy. First, as a result of experiments done at PFC by my colleague Dr McIntosh, we discovered it was the method that had been used to freeze dry 8Y, rather than its purity, which had enabled hitting 80 degrees centigrade to be tolerated. This had not been realised by scientists at BPL and the method they had used to freeze dry 8Y had not been included in

their patent application. This explained why other manufacturers had failed to reproduce the process. We went on to discover it was actually the structure of the ice crystals that had formed during the freezing stage that was critical. The ice had formed a particular crystal structure in 8Y because of a chance combination of circumstances, so we designed a special freezing procedure to deliberately cause this precise crystal structure to form uniformly in every vial of Factor VIII.

8Y was introduced routinely by BPL in September 1985 and although it was not known hepatitis viruses were destroyed, it went on to show that routine large-scale manufacture was possible, and the product was well tolerated in patients.

Also in late 1985 we began to hear from the United States that dry heating might be less effective against HIV than had been believed previously. We wanted to be sure that patients would be safe from HIV. Now that we had identified why Factor VIII could withstand dry heating at 80 degrees, we decided to shelve our research on high purity to focus instead on developing a product similar to 8Y. This could not be done by modifying our existing Factor VIII concentrate and required a new product to be developed and a new manufacturing process

to be installed.

In pharmaceutical manufacturing it normally takes many years for a new product to go from research through to routine production; we began full scale production of our new Factor VIII, which we named Z8, in August 1986, just eight months after deciding to go down this route.

LORD ARCHER OF SANDWELL: Can I just ask you, if you can provide an answer, how was it possible to expedite the licensing process?

DR FOSTER: As I explained earlier, we were operating under Crown immunity and were not required to obtain licences. So we had a dialogue with the Agency but we didn't have to go through the formalities.

LORD ARCHER OF SANDWELL: No, of course.

DR FOSTER: About two months later, in October 1986, a preliminary report from BPL was presented to the UK Haemophilia Centre Directors, which suggested that 80 degrees dry heat treatment might be effective against non-A non-B hepatitis. These preliminary results were not confirmed until 1988.

Our new product, Z8, was available for clinical try in December 1986, and was released routinely from April 1987.

Throughout this period we worked in collaboration with scientists at BPL, assisting them in problems with

manufacture of 8Y, and undertaking laboratory studies with viruses on their behalf.

Although BPL was first in the world to achieve this advance in technology, most Factor VIII concentrate used in England and Wales prior to 1988 was imported and was not heated at 80 degrees centigrade. PFC was second in the world to master this technology, and was able to supply sufficient Z8 to treat all patients in Scotland.

I estimate this enabled Scotland to be about three years ahead of any other country in having sufficient Factor VIII concentrate for all patients that was safe from hepatitis C.

I would like now like to say something about fine concentrates that are used for treatment of haemophilia B. The UK was self-sufficient with respect to Factor IX, because there were fewer people with haemophilia B and because Factor IX concentrate was less difficult to manufacture than Factor VIII.

However, like all coagulation factors, Factor IX is sensitive to processing, and can be damaged easily.

Factor IX can be very dangerous when it is damaged. It can become what we call "thrombogenic", basically far too active, causing the blood to clot too much.

This problem arose in the 1970s when some patients in the United States died from this type of implication.

Research was undertaken to devise tests that could be used to screen batches of Factor IX to avoid this problem. SNBTS was at the forefront of this research.

This coincided sided with research taking place at PFC that was aimed at removing hepatitis viruses from Factor IX.

An experimental preparation of Factor IX concentrate from PFC that had been processed to remove viruses was found to be highly thrombogenic in animals.

The method also failed to remove hepatitis B completely.

By contrast, in an international study of different products our standard Factor IX concentrate was found to be least thrombogenic.

This risk was taken very seriously, so when we came to examine the effects of heat treatment on Factor IX it was one of the issues that had to be considered.

When we subjected our Factor IX to heat treatment it failed one of the lab tests that was used to screen batches for thrombogenecity.

Although we discovered a way of modifying the product so it passed the test it was decided that safety from thrombogenicity needed to be confirmed in animals. These safety studies were very complicated and very difficult to perform and were undertaken jointly with

BPL, with whom we were collaborating closely.

The animal safety study was completed successfully in July 1985, at which point Factor IX concentrate, dry heated at 80 degrees for 72 hours, was issued for clinical evaluation.

Earlier in 1985 a commercial heat treated Factor IX concentrate from the United States had become available, and had been purchased by haemophilia directors in Scotland.

Consequently, SNBTS stopped supplying its unheated Factor IX in May 1985.

We began to issue 80 degree heat treated Factor IX routinely from August 1985 and all of our unheated Factor IX concentrate was recalled as soon as our heated product had been distributed. I think the timescales in England were similar.

Dry heating at 80 degrees for 27 hours was later shown to destroy Hepatitis C virus as well as HIV, putting the UK some years ahead of the rest of the world in being able to provide haemophilia B patients with a Factor IX concentrate that was safe from infection of Hepatitis C as well as HIV.

LORD ARCHER OF SANDWELL: Thank you very much Dr Foster, that is extremely helpful.

DR NORMAN JONES: Thank you very much for a very clear

account of a pretty complex field.

LORD ARCHER OF SANDWELL: Indeed.

DR NORMAN JONES: Scotland obviously has a pretty good track record in this, largely, doubtless due to the work of yourself and your colleagues.

It has been pointed out to us that the Scotland was the first country in the world to become self sufficient in home grown Factor VIII concentrates and also the first to have hepatitis C safe heat treatment Factor VIII in sufficient quantities for everyone.

Now, in view of those two developments one might expect that the incidence of HIV and Hepatitis C infection in haemophiliacs subsequently would have been lower in Scotland than it was in England; do we know if that is true?

DR FOSTER: Taking HIV first. These are issues that we actually considered in discussions with the health committee of the Scottish Parliament in 2001 and some information is contained in the material we provided to that committee which is available on their website and at that time when we looked at the figures there were a total of 87 patients, haemophiliac patients in Scotland, resident in Scotland, who had been infected with HIV.

We have been informed of 20 patients that we know

have received our product and we accepted that was the cause of their infection.

How the remaining 67 were infected, we don't know. We don't know where they were resident when they were infected and which products they were treated with and that information isn't held by SNBTS.

Of the 20 we believe were infected by SNBTS products, the vast majority we believe were treated in a single batch. I think that has been well reported in the literature.

Hepatitis C -- before the mid-1980s, virtually all haemophiliacs were infected with Hepatitis C. I think that is now realised to be case, regardless of the treatment they had, whether it was cryoprecipitate, whether it was local concentrate, whether it was commercial concentrate. In the period between 1985 and 1987, when BPL had 8Y and we were still developing our equivalent of that, that period has been looked at in great detail by the Scottish executive because of questions have been raised in Scotland and we have released this information in papers under Freedom of Information, in 2005, and they have identified six patients that were infected in Scotland during that time, haemophilia patients, two of whom received cryoprecipitate, three of whom received concentrate

provided by us and BTS and one of whom received cryoprecipitate and concentrate.

So clearly Hepatitis C is still being transmitted during that period, not only by concentrate but also by cryoparticipate.

Thereafter, I think I am not aware of any further transmissions once our product was brought into routine use.

I don't know the situation in England. I don't know how many patients were infected with Hepatitis C in England in the period late 1980s when commercial products that were not heated to 80 degrees were still being used.

LORD ARCHER OF SANDWELL: You say there are you are not aware of any cases in Scotland. Would you expect to be aware of them if there had been any?

DR FOSTER: Yes. I think patients have been monitored very carefully and we would have known about that, yes.

DR NORMAN JONES: I think what you're saying is that strictly speaking, to answer my question, the facts aren't --

DR FOSTER: We don't hold these data. They are held by the directors.

DR NORMAN JONES: And of course it's complicated. It assumes identity of practice between the two countries

in terms of the use and indications, for instance, so I accept it is a complex issue.

Thank you.

MS WILLETTS: May I just ask one question, Dr Foster?

You mentioned a couple of places in your report about the claims made by the Haemophilia Society. One of these is a claim made that the infectious batches of Factor VIII could have been detected in 1983 by an HIV screening test, which you very clearly state is wrong.

Do you have, if you like, further evidence or references for that?

DR FOSTER: I can provide you with that information, yes.

MS WILLETTS: Thank you. And also you were talking about -- your point being that the society was mistaken in its claims and that the scientific evidence supports.

DR FOSTER: That is what I would say, yes.

MS WILLETTS: Thank you, that is very helpful.

LORD ARCHER OF SANDWELL: Thank you very much. Perhaps we can be touch in relation to that information.

DR FOSTER: Of course, yes.

LORD ARCHER OF SANDWELL: Thank you.

Well, we seemed to have finished what was proposed for the morning rather earlier than expected.

(12.07 pm)

(The luncheon adjournment)

(1.30 pm)

LORD ARCHER OF SANDWELL: Shall we reconvene.

Would you like to come up here? Thank you very much for coming. If it is all right with you, perhaps you will make your presentation and we will intervene if the occasion arises.

DR MARK WINTER (called)

DR WINTER: Thank you for asking me to come to talk to you. I am Mark Winter, I am a haemophilia doctor. I am director of the Haemophilia Centre in Canterbury which is a comprehensive care centre, so I am a member of the

UK CDO executive. I serve on a number of their working parties.

For a number of years I have been the Department of Health Appointed Medical Trustee to the Macfarlane Trust, so I have been involved with trying to support people with HIV nationally, and I was the founding medical chairman of an organisation called the National Haemophilia Alliance, an organisation established a few years ago, really in response to what had happened to people with haemophilia over the last 20 to 25 years.

The alliance is an organisation between the professionals who care for those with haemophilia and those with haemophilia and as I will say at the end we set standards for future care and we interact with those people who are now responsible for commissioning care.

LORD ARCHER OF SANDWELL: When you say you are the medical chairman, does that mean there are normally two, one medical chairman and one lay chairman?

DR WINTER: And a patient chairman.

So I am from those organisations, but I am really representing myself today, if I may, and obviously the views I am about to express are really my own, and also I am one of a very small numbers of doctors now who were around at this critical period of 1983, 1984, who are still working. It may well be that I am the only doctor

from the UK CDO, who attends -- I don't know, but there are very few of us left.

Obviously what I cannot do is make detailed comments to you about the 1970s and the political initiatives. I was not in post as a haemophilia consultant at that time.

I also really cannot make any detailed comments about matters regulatory, but I see from your agenda you have people from the Committee of Safety in Medicines who can give evidence in that regard.

What I can do, it seems to me, is to try to describe to you what it has been like as a doctor through all these very difficult times, in determining how we should look after people, and I have thought it most helpful in preparing my remarks that I should concentrate really on three different things: I wanted to talk about the events of spring 1984 and shortly before then, when the evolving epidemic from the US, in very small number of patients with haemophilia, was becoming apparent. I wanted to discuss a dilemma we faced in trying to address the issues about what sort of treatment should we then recommend for people with haemophilia.

I wanted to talk about the events of autumn 1984, when what we now know as the HIV test had just become available. Then finally I wanted to make some general

comments as a clinician about HIV and about hepatitis and about how the two viruses differ in many, many ways.

That is the way my evidence to you is set out.

MR MEHAN: Can I ask you to bring those microphones a little closer towards you.

DR WINTER: As we are aware haemophilia is a life long and severe hereditary bleeding condition. It is characterised by spontaneous bleeding into joints and muscles and it is relevant to ask the question: what happens if you don't give anybody any treatment? Here we are today discussing what happens when treatment went wrong; what happens if you have no treatment?

The Birch report of the 1930s showed that had if you have a severe haemophilia there was no treatment then. You were unlikely to live beyond the age of 20. Only 20% of people lived beyond 20.

A report from Finland in early 1960s said the average life expectancy for people with severe haemophilia was about 25 years. So severe haemophilia is naturally a fatal condition. Without treatment you will die and you will die of spontaneous bleeding, usually into the brain but perhaps into the gastrointestinal tract. The former was what happened to the relatives of Queen Victoria 120 so years ago. No treatment, and they bled into their brain and died at

a young age.

We have evidence that haemophilia has probably been around for a very long time as a disease. There are very ancient descriptions but as you will gather there was no treatment of any sort, remarkably, until early 1960s. If you give someone blood or plasma you are not doing them any good. You are giving them lots of things they don't need, like red cells, plasma and white cells. Factor VIII and Factor IX only circulate in absolutely tiny amounts in the blood, so it is useless to give blood or plasma which is what my more elderly patients would have received.

We need a way to concentrate Factor VIII and Factor IX out of blood and that was really only available in the first time in the 1960s when cryoprecipitate became available, but mainly in the early 1970s when the concentrates came in.

The concentrates came in the very early 1970s, and they were a revolution. I mean, before 1970s, children with haemophilia could not go to a normal school. There was a special boarding school for children with haemophilia in Hampshire, the Lord Mayor Trelore of 1890. Some of my patients went there. Life was not at all normal. There was no home treatment, everything resolved around hospital, so suddenly when

the concentrates came in, they were small volume, suitable for storage in a domestic refrigerator, didn't cause side effects, we knew how much Factor VIII was in each bottle, none of these things related to cryoprecipitate. It was a revolution; for the first time patients could get some control back over their lives. They went to normal schools, we started home therapy programmes, they didn't have to go to hospital very often. Episodes of acute bleeding could be very easily treated. Dental surgery, which used to be a big drama, could easily be managed. It was a revolution and in retrospect these years from 1974 onwards, for a few years we talk about the golden interval, time when after years of darkness, at last treatment appeared to have really made a huge jump forward and given these people with haemophilia some sort of meaningful quality of life.

It was really very soon after introduction of these concentrates that there were reports of biochemical abnormalities of liver function, and these patients were perfectly well, but on screening their blood and doing their liver function test they had abnormalities of their liver function test that were most consistent with a type of hepatitis and at that time only two types of hepatitis were known, hepatitis A and hepatitis B, and

only a very small number of these patients were positive for either hepatitis A or B, so doctors like me, before my time, said: we speculate and theorise this must be a third type of hepatitis, which we will call non-A non-B hepatitis, subsequently identified in 1989 as hepatitis C.

So as I say, from a pretty early time it was suspected that these concentrates must be transmitting some type of third hepatitis virus, but as the patients were well little was thought of this for a number of years. It was not thought to be of very great significance.

There was an awareness, right from the start, because I had been training haematology in the mid-1970s. Doctors and patients did talk about the sources of plasma. There was a belief that US concentrates was -- there was a belief that US concentrates, coming as it did from commercial blood donors, was more likely to transmit viruses, than the UK derived plasma which as you know came voluntary donors. The UK was not and never was self-sufficient.

There was open discussion about this and that discussion did extend to the patient group and I had several patients in my own centre and when I went on residential weekends with the Haemophilia Society you

would be told by a patient, "I refuse to have US plasma, I only want UK plasma", so there was an evolving view that it would be prudent to become self-sufficient in blood products and it was for those reasons, as you have heard from Lord David Owen in your previous testimonies, that approaches were made to the Department of Health that we should as a country become self-sufficient in blood products.

In the summer of 1982 the first patients with haemophilia in the US were described as having AIDS. Prior to that, a viral cause of AIDS was not by any means the most popular theory. When AIDS first broke in 1981 amongst gay patients in San Francisco the most common theory was it was something to do with the immune system being suppressed by perhaps the gay lifestyle but when HIV or AIDS broke in 1982 in haemophilia patients, then obviously enough it must be a transmissible agent.

So by January 1983 the New England Journal of Medicine, probably the most prestigious medical journal, ran an editorial in which they said: there is evidence, evolving evidence, that a small number of patients with haemophilia in the US are acquiring this new disease and they therefore must be acquiring it from concentrate and we would recommend that consideration be given to reversing back to the previous treatment, which was to

give cryoprecipitate. The critical difference between the two was obviously the Factor VIII and Factor IX concentrates, because Factor VIII and Factor IX circulate in the blood in such tiny amounts, are made from many thousands of blood donors, whereas cryoprecipitate is made from a single donor.

So the recommendation was why not go back to treating with cryoprecipitate. Haemophilia doctors were really very reluctant to do that. They were reluctant to do it for a number of reasons. Firstly, because it would have been a retreat from the golden interval. There was a revolution that was obvious to people with haemophilia. The commonest cause of death remained cerebral bleeding and doctors were very worried about cerebral bleeding. Cryoprecipitate is not as effective as Factor VIII and it has practical problems. It cannot be stored in a home fridge, so they would have had to retreat from the home therapy problem.

It causes side effects, it is quite large volume, which makes it difficult for children, and we didn't know how much Factor VIII was in each bag of cryoprecipitate so you couldn't work out a scientific dose for each patient. So even if we wanted to go back to cryoprecipitate, there were a number of practical problems and as we may have heard and perhaps we will

hear later there were in any case supply issues. The Committee of Safety of Medicine said: there's not going to be enough cryoprecipitate even if you want to go back to cryoprecipitate.

So I think that the philosophy of the day was there were very, very small numbers of AIDS patients generally in the UK. There were these reports of very small number of American patients -- this is still 1983 -- what was the implication of this? We were very reluctant to go back on what was obviously a major therapeutic advance. The patients were very reluctant to go back. In May 1983 the Haemophilia Society asked the Department of Health not to restrict the importation of US Factor VIII and Factor IX, so it was not only the doctors who did not want to abandon concentrate; it was the patients as well.

In May 1983, the same month that the society had approached the Department of Health, the executive committee of the UK CDO -- it is minuted and this is all in the public domain -- and I quote:

"There is insufficient information to warrant changing the type of concentrate used in any particular patient and it was agreed that there was as yet insufficient evidence to warrant restriction of the use of imported concentrate in view of the immense benefits

of therapy."

By July 1983, there had been some more cases of AIDS amongst haemophilia patients in the US, and the UK CDO executive recommended in that month, July 1983, that cryoprecipitate should be used in selected groups of patients, and those were: children under the age of four years, and patients who had never received Factor VIII and patients with mild haemophilia.

By then --

LORD ARCHER OF SANDWELL: May I just interrupt for a moment. I can understand why people with mild haemophilia were probably thought to have a different ratio of risk to effectiveness, but why patients who had not previously been treated? Why children?

DR WINTER: Because we knew, or suspected by then, that every -- as I will come on later in my testimony -- that every by then who had Factor VIII or Factor IX, Factor VIII particularly, in 1970s was extremely likely to have been infected with this third hepatitis virus, at the very least and therefore we were very anxious about anybody who was not yet infected.

That was the reasoning, I assume.

They also recommended by then this drug Desmopressin or DDAVP as we now call it, had been -- the use of DDAVP, which is an analogue of a natural brain hormone,

Desmopressin, in Milan in 1977. He had demonstrated that if you had mild haemophilia, or you were a haemophilia carrier or you had mild von Willie bands disease, that this was a really useful treatment. It elevated the levels of Factor VIII into normal range for three to five days, so this is a drug we use a great deal now. It is given by injection under the skin or by intravenous injection, and it is a very effective treatment where you want to transiently raise Factor VIII levels for a few days, say because a patient is having a tooth out. That information was available in the late 1970s, so in that advice given July 1983, the executive committee did stress to other doctors like me that for mildly affected patients, you should be considering the use of DDAVP.

For all this time, for the next 18 months, there was lack of knowledge, there was uncertainty as to the significance of all these evolving events. For instance, in November 1983 the then Health Secretary, Kenneth Clark, announced to Parliament:

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

The following month, December 1983, we have an Annual General Meeting of haemophilia doctors. It is minuted, and in the public domain, that there was

a question from the floor to Professor Bloom (from Cardiff), who was a very leading haemophilia doctor who has since died -- the question was:

"Would it be prudent to switch to cryoprecipitate?"

And Professor Bloom is minuted as replying, and I quote:

"There is no need for patients to stop using the commercial concentrates because at present there is no proof that the commercial concentrates are the cause of AIDS."

After discussion it was agreed that patients should not be encouraged to go over to cryoprecipitate for home therapy but should continue to receive the NHS or commercial concentrates in the usual way.

So these were all the events happening around this time in 1983 and I would wish to make a few reflections on those opinions.

I have already said to you that doctors and patients were very reluctant to retreat from the obvious advantages and we remained very concerned about cerebral bleeding.

A further very important dynamic was that there was no standard body for providing us with advice in matters virological. These days, for instance, we have variant CJD, which is very much a live issue for patients with

haemophilia. We have a national advisory panel for variant CJD, that even in an uncertain time, when we have uncertainty about CJD, issues doctors like me with very clear advice and guidance about what we should and should not do.

So such advice was available to us at that time. The Department of Health did set up an expert advisory group on AIDS, but that group did not meet until 1985. So at these very critical times, when we did not know how to interpret the evolving evidence we did really know not what to do. There was nobody virological saying, as a national group, "This is what we advise you to do". That advice did not exist. What I do recall --

LORD ARCHER OF SANDWELL: If I may interrupt, were people lobbying the department at this time saying it is about a time you set up a committee to give this sort of guidance.

DR WINTER: I don't recall that. What I do recall is that UK CDO had set up what you might call ad hoc arrangement with a virologist in Manchester, Dr John Crass. And Dr John Craske worked tirelessly for a number of years on our behalf, and he was the only one, as I recall, who gave us virological advice, and he would appear at all our meetings and as we will see in a minute, he wrote us letters and said, "This is what I think we should do".

He was the advice and as I say, he worked absolutely tirelessly on our behalf.

And I guess you may say -- virology now is a thriving science. In those days very little existed. Very little was known about viruses, and virology was a branch of micro biology and hardly any hospital had virologists. Virology really grew and expanded because of AIDS. The explosion of knowledge that came from the AIDS virus really generated steam, if you like, which led to the creation of another branch of the pathology, of virology, so there was no national virological advice. The science of virology was not well advanced and there was only Dr Craske who could give us virological advice, absolutely invaluable though it was.

There was, as recall too, in the lack of very clear advice from the UK CDO executive, doctors like me, we just did not agree. Some people thought that the American evidence was terribly important. Other people would say it is only a very small number of cases. "How do we know there weren't other factors that might have caused the AIDS?" "We just need more evidence before we can change our practice".

However, by early 1984 the number of patients with haemophilia in the US was such that a group of us felt that we had reached a stage of very compelling evidence,

and we were at that stage extremely concerned that the US concentrate in particular might be transmitting the new virus.

Parallel around these times for a year or so, there was experimental evidence that if you heat treated Factor VIII you killed the virus, and so several commercial companies -- these would be American companies -- had been working with heat treated Factor VIII to see whether viruses might be removed by that heat treating process.

There was no evidence, clinically, that their treatment worked at that time because it had never been given to patients.

But if you spiked these concentrates with HIV and then heated them, and then re-tested the concentrate, you found that the HIV had been destroyed, so there was experimental evidence to believe that heat treating might get rid of viruses such as hepatitis and HIV, and in February of that year four doctors, my colleagues at Saint Thomas' Hospital and the Royal Free in London and Sheffield, we were sufficiently moved by this information and by our concern at what was happening -- we approached a company called Alpha Therapeutics, who in February of that year had a licence in the US to use the heat treated product. There was no licence in this

country. But we were sufficiently concerned about what was happening that we had reached the point of saying: we want to do all we can in a situation where somebody needs Factor VIII to not use either the currently available commercial American Factor VIII or the currently available voluntary UK Factor VIII, and we therefore discussed with them whether we might be able to use, as we were allowed to do, under the regulations of the time, could we use Factor VIII on a named patient basis, and in May of that year we got some of that heat treated Factor VIII as we will see in a minute, and we used it.

I stress to you, this is one of those decisions or recommendations that, as a doctor, one finds spectacularly difficult. Firstly it was a reversal of the culture of the day. The culture of the day was, as I have said to you, if you like, US concentrate was not as good as UK concentrate, you shouldn't have US concentrate if at all possible, and here was a small group of us saying you should have heat-treated American rather than unheat-treated British, even though the former comes from commercial blood. It was a reversal of the accepted philosophy and it was very controversial, and there were other doctors who perfectly reasonably said to us: well, we really don't

agree, and in support of their stance, there were no cases of AIDS, at that time, in cases that had been treated exclusively with UK Factor VIII and there was no clinical evidence, they would say to us, that heat-treatment worked-- that was because the trials hadn't been done. And thirdly, there were concerns, which was reasonable enough to express, there was a fear that if you heated the Factor VIII you might change its nature, and if you changed its nature, there was a worry that when you gave it to patients they might develop an antibody or inhibitor against Factor VIII, which occurs anyway in 10% to 20% of patients, and this is a very serious complication which prevents further treatment with Factor VIII. So these doctors said we are very worried about using heat treatment, "we don't know whether or not it knocks out viruses" -- it did, as it happened, knocked out HIV -- but, they said, what happens if it denatures Factor VIII, and these patients get antibodies? Then we really are in a terrible situation.

So this was one of those situations where doctors, at that time, we just disagreed, to my recollection, and some of us went ahead, and on a named patient basis, in 1984, approached patients who needed Factor VIII, so these were patients who were having surgery or had acute

trauma. We had no way round giving them Factor VIII and doctors like me said to them we have a choice, you can have the currently available licensed Factor VIII, whether it is UK or US. There is good evidence that it will give you non-A non-B hepatitis. It might give you this new virus, HIV. Or we could try, as we have to use Factor VIII, a different type of Factor VIII which I can get you on an experimental basis. You would be a named patient, you would give your consent and sign a form, and this new Factor VIII is heat-treated. There are reasons for believing this might knock out viruses -- which of these two would you like to have? It was a very difficult situation.

As it happened, this premise was correct. As it happened, heat treatment did eradicate or eliminate HIV. Heat treatment did not always eradicate and eliminate other viruses such as hepatitis.

These concentrates were in any case in pretty short supply at that time so even if all the other doctors had said: yes, we completely agree with you, there wouldn't have been enough concentrate to go round, and to my recollection it would have been July 1985 when the complete switch to heat-treated Factor VIII took place in this country.

So those are the comments I would wish to make about

the spring of 1984.

I now want to talk about a little bit later than this, a different phase of the crisis to talk about what happened when we got what we now know as the HIV test.

I stress to you again, throughout all this time you could talk to other doctors or other scientists and everybody would say to each other: we don't know what this data means. You would get a number of views, whether you went to see a professor of microbiology or spoke to someone in the US, everyone would say to you: it is very worrying, but we don't know what it means.

Just to capture a reflection of that, in November 1984, Dr Craske, in one of his very helpful communications with us -- he wrote to all the haemophilia doctors, this is in the public domain -- he was trying to set out what he thought we ought to do, and in November 1984 he makes the following statements to us:

"Only a proportion of patients transfused with an infected batch are likely to contract HIV."

He says:

"It is likely that the proportion of patients who contract HIV and subsequently AIDS will be of the order of one in 100 to one in 500, that the prognosis

long-term for patients with HIV is unknown, that there is evidence that HIV can be transmitted by sexual conduct, that it is not possible to distinguish these patients who are likely to transmit HIV by means of laboratory tests."

So here he is making these statements. Some of them, as we can see, are completely true. Others are proved not to be true. I stress this is in no way a criticism of Dr Craske. I produce this evidence as a reflection that even the best virologist of the time could not tell us, as haemophilia doctors, if we asked them, "What does this all mean?" they would say some things that in retrospect were true and some things which were very wide of the mark, indeed, as proved to be the case.

The HIV virus was isolated in August 1984 and in August of 1984 a test was being developed, and in the UK it had been developed in one laboratory, that of Dr Richard Tedder at University College Hospital in London. UK CDO made an arrangement with Dr Tedder and around that time we could send off by agreement samples from our patients who we suspected, because they had been exposed to Factor VIII previously, might have this new virus. That was August 1984.

Haemophilia doctors had always screened patients for

viruses. It follows from my remarks that concentrates were very early on seen to transmit hepatitis A and B. Part of comprehensive care programme that patients had every three months was that they would see a doctor like me, have a clinical review, they would perhaps see an orthopaedic surgeon or a rheumatologist and they would have blood tests done, and those blood tests would include: what was their Factor VIII level, had their developed one of these inhibitors against Factor VIII and did they have hepatitis A and did they have hepatitis B and were they immune to these viruses? And if you like, this is what evolved from Factor VIII concentrates. It was part of the package of care. So there was a feeling that it was right and proper to do this viral screening and that did lead to some, in my view, diversity of practice when this HIV test came in.

Some centres like mine said to patients: we do now have this new test and we are recommending that you have it done. But other centres, I am aware, did not tell the patients that the tests were being done. They saw it as their responsibility, if you like, as an extension to the blood tests they were already doing, because they were already screening for hepatitis A and hepatitis B.

I should say this was a very widespread practice in other case and I will quote to you -- you have had

previously quoted to "The End of Innocence" by Simon Garfield. In that book, he quotes doctors at the Hospital, one of the major AIDS treatment centres -- not haemophiliac patients, AIDS patients -- he quotes on page 55, a doctor saying:

"We performed a large number of HTLV-3 tests without written consent. Blood was taken from patients with AIDS, patients with lymphadenopathy... and controls."

So this was a pretty widespread practice, very different to now. The idea that you needed to explain at all times to a patient what blood tests you were and were not doing was not held to be the case.

Parallel with that -- I mean, I was also a leukemia doctor -- what we were taught, working with leukemia patients and cancer patients, the practice of the day was that when you made a diagnosis of cancer you first went to the relatives, you told the relatives what was wrong with the patient and you then said: do you think we should tell the patient, your husband, your wife, would they want to know? This was the culture of the time. So I would wish to stress the way things were then. The patient, unlike now, was not right at the centre of the treatment process, the decision making process. There was a view by some haemophilia doctors that it was their responsibility to do this test and it

wasn't necessarily important to tell patients at that time that the test was being done.

Other centres did inform the patients that the test was being done.

I also --

LORD ARCHER OF SANDWELL: Partly not wishing to alarm the patient, presumably, and partly a general deference that patients thought doctors knew better than they did.

DR WINTER: A combination of both things and also a sense of responsibility. It was their responsibility, a new test being available, to do it.

I would also wish to stress that there was no concept of what we have now, of pre-test counselling. That was something that resulted from AIDS. The idea that by having a test you might jeopardise future mortgages or insurance policies, just by the act of having the test, was a concept that came out because of AIDS testing. It followed AIDS testing. It could not have preceded it, so there was no knowledge or understanding that we should say to patients you may or may not have this test, as we now would, and you should be warned if you do have this test you might have problems in the future getting life insurance or mortgages, even if you test negative.

That was not part of the practice of medicine in

1984.

On 26th October 1984 I received the results of Dr Tedder's result for my centre. I sent off 31 samples, 31 envelopes arrived and of those 30 were positive. I had one regularly treated patient who did not have HIV. The obvious next step for people like me was to say: okay, here I am, I have all these positive samples, I need to talk to the patients, what does this result mean? "Antibodies to HTLV3". If I have antibodies to mumps and measles and chicken particulars of claim, I am immune to it. If I have antibodies to hepatitis I am probably not immune, so into which of these two camps did this result fall into?

There was also concern at the time because this test was new about false positives. We were worried that some people who tested positive were not really positive and there was this doubt about the validity of the assay that led to some delay in the introduction of the test for blood transfusion screening.

There were doubts about the validity of the test.

And I quote again my colleagues at the hospital. Professor of Infectious Diseases, again in "The End of Innocence", Simon Garfield's book, I quote:

"He was telling his patients exactly the same month as I was trying to work out what to tell mine. He was

saying:

"We don't know what this test means. It may well mean that you have been infected with the virus and have recovered. You have antibodies and you may be immune."

So we didn't know. It was clear that some AIDS patients had the positive test, but was it the same the other way round. It was very difficult, therefore, to work out what we should say, and on the basis that we received the results on 26th October 1984, we then had to work out amongst ourselves, with Dr Craske, what we should say.

To my recollection it wouldn't have been reasonable to expect any patient to be told their result until probably December 1984, at the earliest.

I did tell all my patients the results. I sat them down one by one, I said they were positive for the new test, I said we didn't really know what it meant, I said we followed them carefully, I said they would be following their immune function and I said there was some evidence that we had that the virus could be passed on through sexual activity and we gave them advice about that and together with two or three other centres we then carried out studies which we published to see whether any of the wives & partners of our patients had the virus; quite a few did.

Again, I would say to you Dr Craske tried to give us helpful advice about what we should do in response to this test. In November 1984, when these test results were coming out, he writes to us to say, and I quote:

"Ideally, I think the patient should be told, but this will depend on many factors, including the amount of anxiety concerning AIDS there is already present at the centre, and the degree to which patient is capable of understanding the situation. An alternative might be to inform the patient's spouse or another close relative, as is done when patients develop malignant disease. This will be at the discretion of local haemophilia centre director."

This really affirms, I would suggest, the evidence I have previously given to you; the culture of the time, maybe we will not tell the patient this bad news. Maybe we will, maybe we will not. We will tell the relatives.

Before the end of the month the UK CDO executive wrote to us on 10th December, and said to us, I quote:

"Patients who ask their HTLV3 antibody results should be informed of them. Otherwise, it is up to individual directors to decide whether or not they wish to tell their patients."

So can I make some remarks to reflect on that. Why was it that that practice and practices occurred?

I have already made some comments about the lack of standard virological advice. I have made some comments about the culture of the time. I have made comments about the sense of bewilderment in the scientific community.

Another point I would make -- some of my colleagues may not agree with this, but I wish to point out the way in which doctors like me were trained differed. When I entered haematology training in the mid-1970s I had done general medicine beforehand and I had passed the membership of the Royal College of Physicians, and I had worked with general medical patients.

Haemophilia was really a branch of pathology prior to that and the senior haemophilia doctors had worked in laboratories. They were very gifted academics; they were scientists. They were not experienced in, for instance, dealing with very sick people. Although they knew their patients very well, and lifelong, they were not experienced at breaking bad news, and they were certainly not experienced in talking to patients about sexual transmission. So I would express a view that for some doctors it became quite a difficult thing to talk to patients to talk to patients they had known all their lives, diagnosed when they were children, to see them suddenly confronted by this terrible news and start to

get ill. I think some of my colleagues, not being trained in general medicine, found it difficult to cope.

You will understand that really, from that time onwards, from 1984 we had evidence that about 90% of the regularly treated patients in England had the virus. There was no treatment, you could use antibiotics, and people started to get sick, and it was really what one can only describe as the darkest of times. These were people with a severe life long and very painful bleeding disorder, with terrible joints as a result of having no treatment until they were teenagers or beyond and to whom we now had to say: you have hepatitis and HIV, and they started to get sick and they started to die of AIDS.

If that was not bad enough, there was, of course, the intense stigma surrounding the disease. Many of our patients found it extremely difficult to tell their friends, some didn't even tell their families, and that brought relationships very close. You acted as a doctor, a friend, a confidante, a companion, because they needed more out of you than being a doctor. They needed to talk to you, often. They couldn't talk to anybody else, and these patients were also subject to acts of discrimination, as you will have understood.

There were particularly difficult problems

concerning the management of children. We had 18 children in our centre. People did not know whether to tell the children. I thought it was right to tell the children. The patients asked me to tell the children so I did tell the children individually. I told them when they were well and usually in the summer holidays and usually pretty briefly and then we followed it up with further information. There were very serious issues concerning schooling. Some of the schools said to us: your child with haemophilia cannot stay in this school. We cannot have a child with HIV in this school, we will have to take the child out of the school. We have a lot of work to do with the education authorities in persuading teachers that these children were not at risk, in the setting of the classroom, of transmitting the virus. In one school they appointed a nurse to sit behind the child with haemophilia at the back of class, with a pair of gloves and some disinfectant, so if the child had a nose bleed she would jump in and address the issue.

These were very difficult times and these poor children were often handled in a very inappropriate way by the schools.

There were finally particularly difficult issues concerning the mothers of our children with haemophilia.

One of the particular features, if you work in a haemophilia centre, is that there is a very close bond between the mother and the affected child. Part of this reason is doubtless because the mother is looking at this child and saying: I gave you this gene. You have my gene, and for some of these mothers, there was an awareness that it must have been them that actually injected the contaminated batch, because these children were on home therapy programmes. So we spoke of the double guilt of the mothers. We worked with them to counsel them and support them. This sense of: my child has haemophilia because of me and now I have infected him, how can I live with this? We worked with them to try and help them get through these emotions.

In the final part of my submission I just briefly wanted to make some comments which I do think are particularly relevant to the inquiry about HIV and hepatitis C.

In my view there are important differences between the way these two viruses were acquired by people with haemophilia. I have already given evidence that from the early 1970s there was evidence that the concentrates of the time were transmitted hepatitis B, non-A non-B was first reported in 1975, studies from the UK in 1975 and 1977 showed that two thirds of regularly treated

patience had abnormal liver function tests.

We now know from subsequent studies that the incidence of hepatitis C in US plasma at that time was around 1% to 3%. Here is a critical point. Factor VIII is made in batches of around 20,000 patients, so if you receive Factor VIII from concentrate, made from a blood donation pool where up to 1 in 30 have a virus, you must be getting several hundred different hepatitis C virus infections every time you have a treatment and some of these patients were getting three treatments a week.

However, so we can conclude, it was inevitable in the 1970s that if you had US Factor VIII you got hepatitis C, and there is evidence to show that from studies, from patients who had never been treated with Factor VIII, given it for the first time, they got hepatitis C.

However, a further critical observation is to look at the incidence of hepatitis C in UK plasma and there are studies that will tell that in early 1980s, that incidence, while less than America, was still in the order of 0.5 to 1.5%. So one can reach what I hold to be a very important conclusion. Even if the initiatives towards self-sufficiency in, shall we say, 1977 had proved to be successful, and a switch to UK-only plasma had been achieved, given that that switch would have

been to a plasma source with 1% to 3% hepatitis C to 0.5 to 1%, shall we say, and given the vulnerability of the concentrates, because of the huge number of patients in each batch, you can conclude that a switch to UK Factor VIII in the 1970s would not have saved the hepatitis epidemic. If you got Factor VIII in the 1970s from -- whether it was commercial blood, voluntary blood or US blood or UK blood -- you got hepatitis C. The only people, therefore, who could have been spared hepatitis C in the 1970s were those patients with mild haemophilia, or who were carriers of haemophilia who could have been treated instead with DDAVP, as Professor Manucci had published by 1977.

With HIV, the system is very different. A very important study was carried out by my colleague Dr Peter Kernoff at the Royal Free Hospital, who died quite recently. Dr Kernoff, in his practice at the Royal Free, always stored blood from patients and when the HIV test became available in October 1984 and he had the results, he found that about 100 of his patients had HIV, and he was able to go to the stored blood and retrospectively store that blood and establish when that HIV infection had occurred in his patients, and remarkably he showed that nearly all those patients had been positive for the new virus for several years. That

is an absolutely critical observation. All the evidence I have given you about: should we use cryoprecipitate in 1983, should we use heat treatment in 1984 -- actually, nearly all the patients had already cirroconverted. So all that body of evidence I gave you, if you like, was probably not relevant to saving people from viruses, because we know from Dr Kernoff's data that by then nearly everybody had HIV.

But the really critical part of his data was that before 1980 in his store of blood it wasn't there. We now look at the situation in Scotland. Unlike England, Scotland was essentially self-sufficient in Factor VIII and when the test became available, there was hardly any Factor VIII in Scotland, hardly any HIV in Scotland. In England, 90% of the regularly treated patients had HIV. In Scotland, at first testing there was a very, very small number, to my recollection.

There was then one donor in Edinburgh, who infected, to my recollection, 17 out of 28 patients who received one batch, subsequently named the Edinburgh Cohort.

But the critical observation is there was very little background HIV in Scottish blood so one can conclude, or one can speculate, rather, that unlike hepatitis, where UK plasma had significant hepatitis, that if a switch as a result of Dr Owen's initiative had

been made in 1977 from US plasma to UK plasma we would have been moving from a plasma source which, in retrospect, was high for HIV to lower, at least, for HIV, and one can speculate -- you note my choice of word -- that if Dr Owen's initiative had borne fruit that at least some of cases of HIV could perhaps have been prevented.

I stress my remarks are speculative. I bring to your attention the observation that in Australia they were self-sufficient, they only had Australian plasma, they did still have quite significant HIV. But you understand the point I am trying to make. The two epidemics were different. The hepatitis C could, by and large, have not been prevented in 1970s. There is data I have presented to you that might lead one to conclude that perhaps at least some of the HIV cases could have been prevented.

If you are a doctor like me looking after these conditions -- and I have been a HIV physician, I still look after gay patients as well as haemophilia patients -- these two conditions are very different. People with HIV usually have symptoms at a pretty early stage of their illness. They lose weight, they get night sweats, they get enlarged lymph glands, they get thrush, they feel generally pretty unwell. As this

inquiry has already heard, many patients, but not all, with hepatitis can be asymptomatic for a number of years before becoming unwell. A small minority of patients can get very significant symptoms with hepatitis: tiredness, abdominal pain and nausea. But some patients can feel actually very well. In my centre, we have been eradicating hepatitis C from a number of hepatitis patients and when you say to them, "How do you feel after all this treatment?" you are often told by the patient, cheerfully, "Absolutely no different, because I didn't feel ill to start off with".

There are other patients who have had symptoms who do feel much better after treatment.

With our Macfarlane Trust data, we can say that at 1,246 registrants who had HIV only 366 currently remain alive. So very nearly 80% of people with HIV die.

As you will be aware, the UK CDO has what is perceived to be a very robust reporting system. Every patient is reported and sent under the Data Protection Act to a national register held by a computer in Manchester and one of the parts of data we submit every year is we report data on deaths, and that UK CDO data will show that for the last 20 years the total number of deaths to liver disease is actually around 100. So if we know that around 4000 patients

with haemophilia got hepatitis C that represents a mortality in the hepatitis population of around 2 to 3%, shall we say, compared with a mortality of around 80% of HIV. So of the two viruses you are many times more likely to die if you have HIV infection, than if you had hepatitis C infection.

Many of our patients had had both HIV and hepatitis C. The major clinical problem at the moment with these patients is not HIV but the liver disease. Management of HIV is now greatly advanced. There are very major issues about management of hepatitis, in co infected patients. Nearly all the deaths in the Macfarlane Trust for the past few years have been due to liver disease and we very badly need better medication, better treatment for hepatitis for those who have both hepatitis and HIV.

We also do have concerns to eradicate hepatitis C in those patients who only have hepatitis C. There is data now that after 30 years of infection -- and these patients are coming up to 30 years -- that in some patients the rate of inflammation in the liver can accelerate, and the rate of development of hepatoma, a rare liver cancer, can accelerate after 30 years. So we are very active now and very concerned to wherever we can to eradicate hepatitis from our hepatitis C parents.

If I may make very briefly one or two comments to conclude. I have been a trustee of the Macfarlane Trust for a number of years. I have worked with HIV since 1983. I have known many of the patients with HIV personally and have worked with them closely. I know their problems well, and after all this time, even though their physical health may have improved, even though their treatment may have improved, even though the drugs are better, the most obvious thing you want to say about these people is that they are worn out. It is the only phrase you can use. Their spirits are worn out, their relationships are worn out, their resources are worn out, their finances are worn out, so although their physical health may be better, at the Macfarlane Trust we very much hope the Government will respond to this enquiry by recognising the continuing needs of people with haemophilia and HIV and hepatitis, and will continue and indeed increase the amount of support that is given to them.

These people have had the most unimaginable suffering over the past 20 to 25 years, and they have major problems in their lives. I also have a view that the support that widows have received is not what they had a right to expect.

I do accept, as a haemophilia doctor, that there has

been heterogeneity of care. That is always the case in any illness, actually. If you go to a haemophilia residential weekend and sit with a group of patients from all over the country you will find they get, even now, remarkably different treatment. And so it happens. But I do accept as a haemophilia doctor that some patients got much better treatment than others and I do accept that some patients didn't get information about the blood test when they should have done. I accept that some patients didn't get told the result in the way that was proper, and I do accept that some patients didn't get the level of treatment and support they had a right to expect. I have set out in my submission today why I think that was.

I think my medical colleagues at the time, some of whom have since died, did act with the best of intentions. We don't take the Hippocratic oath any more, but we do abide by "firstly, do no harm". It was a terrible shock, these older doctors that I worked with had diagnosed these people at birth, knew the people very well, had seen them grow up, and to have to then say to them, when they were teenagers, "You have HIV" and then see them die of AIDS was a terrible thing and I do support my medical colleagues, even though I do admit that, as doubtless others have said to you, there

was heterogeneity of care.

Finally, I just would like to make a very brief remark about the future. If presumably the purpose of an inquiry is to learn from past mistakes and to make sure they never happen again, one of the ways we could improve things in the future is to look at the work that we have been doing on the National Haemophilia Alliance, this group that we founded a few years ago. One of things we have said is that there should never again be heterogeneity of care and we have produced, and I will give you the document, this a national service specification for haemophilia services. This sets out to doctors, "This is the standard of care you should deliver", and this document is directed at commissioners This document is approved by the Department of Health. It says to commissioners, "This is the level of care you should commission". So we hold this to be a very important document, because it stops doctors in different parts of the country in doing things differently. It say it is to doctors like me, "We really expect you to follow this, and if you don't agree with it, you had better discuss it".

However, there are recommendations I would like to see. There are something like over 100 haemophilia centres in the country; with a disease that now

thankfully has very good management we do not now need that many. There are some centres with very small numbers of patients. Whilst the larger centres do have very robust formal triennial audit, and I am pleased to say that that audit now not only includes doctors but we have nurse auditors and patient auditors -- quite recently my service was audited by a doctor, a nurse and a patient from different parts of the country, and that is a very good and robust system. That system does not apply to smaller haemophilia centres, so questions do need to be asked now that effective management of haemophilia is here, with recombinant Factor VIII, why do we still need more than 100 haemophilia centres.

Secondly, can we please have a proper network, a mapped network of care, across the country? Can we have a commissioning road map, so that wherever you are in the country you know where your nearest major centre is, and the commissioner of care is not only mandating care against the national service specification, he is insisting that patients are followed according to that care and a managed network, and can we please have a proper audit process for all haemophilia centres and not just the major centres. That would be a significant further step forward in improving the standards of care for people with haemophilia, and with that, I conclude

my evidence to you.

LORD ARCHER OF SANDWELL: Well, thank you very much Dr Winter. You have certainly given us a number of insights which we had not received before.

Could I just ask for your help -- I don't know whether this is a fair question -- you said that people ought to be properly compensated and obviously this is from your own experience, but I am not sure whether compensation is the right word, is it? There is a need which ought to be ministered to.

DR WINTER: Yes, I do not think I used the word "compensated".

LORD ARCHER OF SANDWELL: No, I think I did.

DR WINTER: The word I would wish to use is "support". These were patients who were told, "You are not going to live for very long." One of my patients said to me, famously, "You have broken all the rules. You have said to me I am going to live and you have made me better. You told me I was going to die and I have spent all my money. It didn't worry me if the Hoover didn't work and now I do need to worry if the Hoover doesn't work," et cetera. So these were patients who didn't expect to leave, and they have real needs 23 years into the epidemic, for reasons that you have heard from the Macfarlane Trust in their submissions and doubtless you

will hear tomorrow, when the Haemophilia Society return.

LORD ARCHER OF SANDWELL: I was just wondering whether you had any views on categories of grants. Obviously something depends on whether someone who cannot work has any dependants, whether someone is left without a means of generating an income and so on. Have you any thoughts about the different categories that ought to be addressed here, or are you content with the ones that there are at the moment?

DR WINTER: One of the philosophies we try to follow in the Macfarlane Trust is to enable people to make their own decisions, firstly, to get away from the culture of dependence on the Trust. In one of our major reviews the people with HIV told us, "I don't want to the recipient of all this money the whole time, I really want to be independent". So one of the cultures we have tried to foster is to enable people to be self-sufficient and we particularly look to fund initiatives where people were sent on training courses and educational courses with a view to going back to work, so rather than just giving them increased financial support we have tried to introduce resources to help them get more control over their lives.

LORD ARCHER OF SANDWELL: So you would deal with each case on its own needs.

DR WINTER: Yes.

LORD ARCHER OF SANDWELL: Yes, thank you very much.

DR NORMAN JONES: I would like to thank Dr Winter for a most illuminating and most moving account.

MS WILLETTS: In January 1992, Professor Bloom, who you referred to, wrote to Haemophilia Centre Directors because of the commercially produced heat treated Factor VIII and there was particular interest there in non-A non-B hepatitis, and I knew you were talking quite a bit about the heat treatment that went on in 1984.

One of the suggestions in here is actually the need to find out the quality and the efficacy of the heat treated product and the suggestion is therefore that studies need to be undertaken in people who haven't been exposed to the pooled source of product before, and I wondered whether you knew any more about that, and how those patients would have been selected, and anything about the trials that were conducted, because clearly there has been some concern expressed that there may have been times when people suffering only from a very mild form of haemophilia may have been exposed to this and people who hadn't been previously exposed may well then have been then exposed and obviously it is very important to find out the results. I wondered if that was anything you could help us with.

DR WINTER: Your comments are accurate. I think they are a reflection of the problem I have outlined to you. You couldn't find out whether your new Factor VIII, whatever it was, was safe or not by using it on people who had ever had it before, because every single previously treated patient, as I have given evidence, had hepatitis. So, I did not get involved in trials, but that was Professor Bloom's dilemma. The only way he could find out is a new Factor VIII safe was to use it on somebody who had never had it before.

These people were called PUPs, "previously untreated patients", and as you are suggesting, they only really fell into two categories: they were children, or they were people with mild haemophilia who had never had Factor VIII who were 35 years old who needed a hip replacement. So that was a particularly sensitive and difficult issue and some doctors accepted, I think, the need for proper controlled studies and other doctors said, "I really don't think it is right to be using a new treatment that may or may not work on a child". So I think that was a particularly difficult issue, and it is a reflection that all previous treatments had infected people and therefore you had no other way of knowing beyond looking at children and mildly infected patients, and that led to a very difficult situation.

MS WILLETTS: And it wouldn't have been widespread at the time for the patient or the parents of the child to be asked "Which way do you want to go on this", presumably.

DR WINTER: My view is it should have been. These were very sensitive matters. I would have certainly felt -- my comments of the then culture not withstanding -- it would have been expected that if you were going to use -- obviously if it was part of a clinical trial the local ethical committee would have been involved and patient consent would have been involved, and even if it was a named patient basis, then you would still have expected, in my view, for the patient to be approached.

MS WILLETTS: Thank you very much.

LORD ARCHER OF SANDWELL: Thank you very much indeed.

MR MEHAN: I have a very quick question. Did the directors have a choice between purchasing UK product over US product, or was it just a question of a request went in and it was sourced by the Centre and by the hospital.

DR WINTER: To my recollection there wasn't enough UK to go round. You were given an allocation and then you topped up from the US. Most people wanted the UK and then they knew that they would have to have additional supplies from the US.

LORD ARCHER OF SANDWELL: And the supplies from the US, would they be dealt with normally by the haemophilia

director, directly with the suppliers, or was there a bulk purchasing?

DR WINTER: No, they would have been individually -- each individual doctor, through his own hospital, or each individual centre, made their own contractual arrangements with one or more of the American companies.

MS WILLETTS: Through the hospital pharmacy?

DR WINTER: The hospital pharmacy in some hospitals got very involved and did it all. In other hospitals the pharmacy were not involved, it was very much kind of at the discretion of the local haemophilia directors. Some directors wanted to do it all themselves because they knew the companies and they could arrange for the Factor VIII to be delivered directly to the haemophilia centre.

Other hospitals, like the Royal Free, I know, it was all handled by the pharmacy; yet again, great variety of practice.

LORD ARCHER OF SANDWELL: And again, the producers were advertising in many cases, were they, so that hospitals and centres over here would receive something through the post saying, "Have you tried our product?"

DR WINTER: It was no different to the marketing, shall we say, of any product. There were four or five American companies and their representatives would come through

the door at contract time with, you know, "Would you like to use our product, how much would you like to use, this is sort of price we could do for you". There was a negotiation that took place at local level with local management.

MS WILLETTS: And that would all have been licensed product?

DR WINTER: Yes, that would have been licensed.

MS WILLETTS: By the USA authorities, Federal or State authorities.

DR WINTER: The FDA and then licensed in the UK as well, apart from these unheat-treated were licensed for use in the UK. It was only the initial heat treated that was not licensed.

LORD ARCHER OF SANDWELL: Thank you very much, Dr Winter. You will leave us the publication?

I think it is Sir Joseph Smith now.

SIR JOSEPH SMITH (called)

Thank you very much for coming, Sir Joseph, we are most grateful.

Would you like to make your own presentation, in the same way as the others, and we can intervene if it arises.

SIR JOSEPH SMITH: I hadn't particularly thought to, just a few introductory remarks, if I may, because I assumed you would wish to ask me questions in relation to the

evidence I have presented.

LORD ARCHER OF SANDWELL: It has depended very much on how the witness has preferred to deal with it.

SIR JOSEPH SMITH: Part of my problem, sir, is that my memory of events then is poor, so I have set out --

LORD ARCHER OF SANDWELL: That is a problem which a number of us share.

SIR JOSEPH SMITH: I have set out in the evidence I have submitted what I can remember from my own experience.

I understand from Mr Vijay Mehan that you wish to know something of the work of the PHLS and I have enclosed a photocopy of an extract from the first report I was responsible for when I became director of it, and that sets out, on page 10 and 11, the basic statutory functions.

LORD ARCHER OF SANDWELL: I didn't have -- I am sorry, this is packet I got today.

SIR JOSEPH SMITH: I do apologise, I had a bit of a problem typing.

LORD ARCHER OF SANDWELL: Yes, I see.

SIR JOSEPH SMITH: I am happy to speak to you, if you wish. It will be very brief.

LORD ARCHER OF SANDWELL: Yes.

SIR JOSEPH SMITH: Really the service started out just before the last War because of the fear of epidemics as

a result of enemy action, and it was to make sure that the country could deal as best it could with the bacteriological investigations and support that may be required in an epidemic.

After the War it was thought to be valuable for public health purposes and it remained operated by the Medical Research Council, but then eventually it was transferred to the management of its own board, for which I was responsible, and that was in 1979. Its function then was described, very vaguely, as to provide a bacteriological service for control of infection in England and Wales.

Subsequently, that was extended to allow it to embrace other functions that, within the opinion of secretary of state, could also be taken on board, which allowed the board to assume responsibilities for the former Ministry of Defence unit at Porton Down, the Centre of Applied Microbiology and Research, and that also had the additional function of income generation from the development and sale of biological products through a company with which the board signed an agreement, Porton Products Limited.

This also sets out how it was organised, but it is fairly brief and it may be better that I answer questions. I am leaving a copy of the report for you,

which, if you wish to have a look at sections on PHLS work on AIDS, which relates to 1985/6 and subsequently, and became a very heavy part of the PHLS workload.

It is a bit difficult, because I am not quite sure what you are after about PHLS.

LORD ARCHER OF SANDWELL: I think we are really looking at each of the institutions in turn, to see whether there is anything they might have done and had been expected to do which would have precluded what happened.

SIR JOSEPH SMITH: One of the things that was done very early, I think, and to great credit of Dr Galbraith, the Communicable Disease Surveillance Centre was established -- the exact year I don't know, but it was certainly operating in 1982, when he set up surveillance of AIDS, even though it had only been recognised as a condition in 1981, using at first -- getting reports of opportunistic infections in patients as an indicator of possible AIDS infection, opportunistic infections meaning infections that would not normally attack a healthy person, like (inaudible word) pneumonia, for example.

This was extended quite quickly to ask haemophilia doctors to report cases of AIDS amongst their patients, and this system built up and was then extensively supplemented when AIDS testing came in, firstly on the

basis that Dr Winter talked about, by Richard Tedder and then later in 1984, subsequently, by Dr Phillip Mortimer, at Colindale, which is part of the PHLS.

So it had a heavy involvement in AIDS surveillance, and it had a heavy involvement in other epidemiological activities related to AIDS, such as screening programmes done by consensual anonymous testing in pregnant women and also in virology, to develop and validate AIDS tests for blood tests, which was done primarily in Colindale, and then two years later we established AIDS testing in each of our 52 laboratories where there was a virologist. That extended to about 30 laboratories around the country providing AIDS testing by 1985, on request, to doctors. That was another major part of the activities relating to AIDS.

Then CAMR also played an important part in manufacturing HIV virus, which it provided to the Welcome laboratories for manufacture of AIDS testing kits.

At the time in question, when the 1983 meeting of the biological subcommittee was held, I was then director of the National Institute for Biological Standards and Control, and I am happy to say something about this if you wish it.

LORD ARCHER OF SANDWELL: I would be grateful. We have

heard a little now about this, but I think this is something which we would regard as of great importance.

SIR JOSEPH SMITH: Well, it was created two years before I came director in 198 -- I am just trying to remember the year -- 1985 -- I am sorry.

LORD ARCHER OF SANDWELL: I think you were on the committee from 1978, were you.

SIR JOSEPH SMITH: The committee?

LORD ARCHER OF SANDWELL: Yes, the Committee of Safety in Medicines.

SIR JOSEPH SMITH: From my appointment, yes, 1976, was it?

LORD ARCHER OF SANDWELL: I think you said 1978 in your paper. It may not matter greatly.

SIR JOSEPH SMITH: Yes, there was probably a delay after my appointment before I became a member of the Committee on Safety in Medicines and a further delay before I was appointed Chairman of the Subcommittee on Safety of Medicines and Biological Products.

The Institute was concerned with the potency and purity of biological products. These are products which cannot be prescribed by physical and chemical means really by weighing. One would prescribe aspirin really by weight of the aspirin used. Such products embrace vaccines, blood products, antibiotics, hormones, and the only way of prescribing these in a dose which is

meaningful and reasonably constant is to create a yardstick, which Sir Percival Hartley developed this concept. This is how he described it:

"As we use a yardstick for measuring length, we need a yardstick for measuring the potency of biological products."

This essentially means laying down a batch of the product which is carefully characterised and preserved by freeze drying, so that you have a large batch of ampoules which serve as either the national or the international standard for that product, so there is an international standard for penicillin, which meant that penicillin was prescribed in units, rather than by weight, which would be so variable, and you would test a batch of a product in the same test against the potency of the batch of the standard with which you were provided, which we provided them. And we also served as a World Health Organisation international laboratory for biological standards.

LORD ARCHER OF SANDWELL: Just help me on this.

SIR JOSEPH SMITH: I beg your pardon.

LORD ARCHER OF SANDWELL: What I was going to ask, we had been told, this afternoon, I think, by Dr Winter, when it became clear that AIDS was a viral condition. That was before you joined the committee, is that right?

SIR JOSEPH SMITH: I joined the committee in about 1978.
LORD ARCHER OF SANDWELL: 1978.
SIR JOSEPH SMITH: No, I don't think so, sir. It was suspected when these first cases appeared in 1981 and 1928 that a new virus cause was one of the likely possibilities.
LORD ARCHER OF SANDWELL: Yes, I see.
SIR JOSEPH SMITH: And indeed by the end of 1982 my own view was that that was almost certainly the explanation.
LORD ARCHER OF SANDWELL: And that was really the point at which you became involved in prevention and cure.
SIR JOSEPH SMITH: No, our remit was in relation to licensed products and looking at the data concerning applications for clinical trial certificates or product licences.
LORD ARCHER OF SANDWELL: And that wasn't primarily or certainly not wholly to do with viral infections.
SIR JOSEPH SMITH: No, by no means, sir. There were many other questions as well: reactivity, contamination and so on.
LORD ARCHER OF SANDWELL: Of course.
SIR JOSEPH SMITH: It only became clear that AIDS was a viral disease, due to a new virus at the end of 1983, when Montagnier in France isolated a virus, and that was confirmed in early 1984 by Gallo in the United States and it rapidly became clear that that was the primary

cause, although there could well be contributing causes, such as -- one possibility was always that the immunological challenge of giving Factor VIII itself might raise sensitivity to becoming infected by the AIDS virus.

Now, our concern, then at NIBSC, was with advising the committees of the CSM and the biological subcommittee in particular in relation to the evaluation we would do on licence applications for clinical trial certificates or product licences, or variations in product licence.

One other factor which I don't think Dr Melling mentioned was that it was quite possible for manufacturers to apply for a variation of licence on the basis of evidence they would provide, and that was done subsequently for heat treated products. They could apply for a variation in their product licence, based on data showing that their heat treatment provided a product which was safe and might well be effective.

LORD ARCHER OF SANDWELL: Yes.

SIR JOSEPH SMITH: The only other factor I think I wanted to make by way of introduction was to mention that the concern we had was a very serious concern. This was obviously a very worrying development, that we may actually be having a licensed product that was

transmitting infection, and I think the background in which we had the 1983 meeting of the biological subcommittee is put well by Dr Fowler, who wrote the Department of Health's Medicines Division evaluation of the problem, which you may have.

LORD ARCHER OF SANDWELL: Which we have.

SIR JOSEPH SMITH: You do have it?

LORD ARCHER OF SANDWELL: Yes.

SIR JOSEPH SMITH: And it shows the sort of background to the case at which we were looking.

I think many of us would have approached that meeting with concern, that knowing the source of the US Factor VIII, from donors who were prisoners, who would include drug addicts, and knowing homosexuality was common in prisons, and that the bulk of the AIDS had then been seen in homosexual persons, that was a very poor source to use for blood products, and that if we possibly could it should be stopped. And it was against that background that I think we approached it.

The other background point is that we had considerable expertise in infection, and in relation to both virology and clinical care, and also in epidemiology and blood and blood products generally, but we didn't have any expertise specifically in AIDS, although I think my clinical colleagues,

Professor Harold Lambert and David Tyrrell, would have been pretty well up on haemophilia, but we needed added expertise, and we were fortunate in securing the input of considerable additional expertise, including Professor Bloom, who chaired the Haemophilia Centre Directors Committee, Dr Craske, who we have heard of from Dr Winter, and Dr Galbraith, who was head of the Communicable Disease Surveillance Centre at the PHLS, and Harold Gunson who was head of the Regional Transfusion Centre. Also Phillip Mortimer, who is an outstanding virologist, head of virology in the Health Authority Service.

There are minutes, which tend to be written without talking much about the discussion. The practice in Medicine Division is to write pretty succinct minutes, and there may be questions there which you have which I will do my best to answer, sir.

LORD ARCHER OF SANDWELL: There is one question which is in my mind about this: presumably when an application for a licence is made, part of the information is, in this case, how the plasma was gathered, how the donors were selected, so that would be known to the committee?

SIR JOSEPH SMITH: Yes, I think so, sir. I cannot remember specifically, but I don't think at the beginning blood products, Factor VIII preparations, were subject to stop

orders which Dr Fowler mentions, where you can require, or the Department of Health can require, every batch of the product to be submitted to NABLC(?) for its independent valuation, and we then would advise the Department of Health (Medicines Division) whether or not we advise that it should be released. It is up to Medicines Division then to decide whether to take our advice.

On that stop order, that could require information about its source, but for the product licence application it would certainly consider and include information --

LORD ARCHER OF SANDWELL: It would automatically?

SIR JOSEPH SMITH: Yes.

DR NORMAN JONES: Sir Joseph, two questions, if I may. At the rather momentous meeting in July 1983 of the CSM, to which your subcommittee of which you were chairman reported, obviously the CSM was faced with a very difficult situation.

SIR JOSEPH SMITH: Yes.

DR NORMAN JONES: And had to make a very difficult situation. Do you have any recollection of how closely the decision taken was subsequently followed up? In other words, how closely it was revisited and reviewed, how frequently?

SIR JOSEPH SMITH: I tried to get hold of minutes of subsequent meetings and I failed. I am told that they were in the -- the Department had sent them all to -- there is a depository, presumably, and they were able to get the minutes of the 1983 meeting for me, but those are the only ones I have been able to get hold of. So I have not been able to look up -- I am pretty sure that it was constantly on our minds and constantly discussed, and I have looked on the Web, for example, and I have found evidence that we did look at product licence applications for products in 1948 and granted a licence for one of them, and also that in that year the CSM pressed the Licensing Authority to prompt applications for product licences or variations of licences to permit heat treated products. But that is not my direct memory, sir, that is by looking up other sources.

DR NORMAN JONES: Thank you very much.

One last question, if I may. On the third page of your written submission, item 13 -- shall I just read it:

"The subcommittee strongly supported the aim of reaching UK independence from imported Factor VIII and from the discussions I gained the clear impression that UK self-sufficiency was expected soon."

SIR JOSEPH SMITH: Yes, that was the impression I gained,

sir.

DR NORMAN JONES: As it turned out, it took a long time. Do you have views on why it took such a long time?

SIR JOSEPH SMITH: I can't explain it. It seems to me very, very bad and I can't see why it wasn't acted upon back when the department were tasked with trying to get that achieved, I think it was 1977, and -- but it seems to me extraordinary that there were obstacles -- I had the impression, I have the impression from when I was in post, and on the committee, that the licensing authority staff were frustrated that the action was so slow, but I go back to the point, if I may, that to have as a source material blood taken from that sort of donor as a source, even when heat treatment comes along, is very unsatisfactory, because if you can get as clean as source as possible it gives you an extra safety margin, should there be a slight hiccup with the heat treatment process applied to any batch.

I don't know why it was so late and it was not good.

LORD ARCHER OF SANDWELL: One reason that seems to have been suggested is that the initial demand for the product was grossly underestimated; there was quite an escalation in the demand for the product; that would be something to do with it, would it?

SIR JOSEPH SMITH: That could well be so, sir. I have

sometimes speculated in my mind whether the development and introduction of heat treated Factor VIII may have taken some of the keenness of the Department of Health to get its act together, perhaps, in late 1984, early 1985. I have no evidence of that, sir, but even so, in my own view, still from the source material, I think we should still get as clean a product source as possible. So I think it still was an objective, but it took an unconscionable time in my view.

LORD ARCHER OF SANDWELL: Thank you very much.

MS WILLETTS: Sir Joseph, along similar lines, Dr Galbraith, actually just shortly before the meeting in July 1983, in May, wrote to the Department of Health, expressing serious concern about imported product, and he came to the conclusion that all blood products made from blood donated in the USA after 1978 should be withdrawn. This was in specific relation to the Action on AIDS report that he brought together.

He actually comments in this, and I wonder whether it was something you had any recollection of, he is proposing that this is discussed at subsequent meetings. He says that he is:

"... most surprised that the USA manufacturers of the implicated blood products have not informed their customers of this new hazard."

He goes on to say:

"I assume no official warning has been received in the United Kingdom."

I am quite interested in this area -- and I appreciate it is rather a long time ago -- do you have any recollections of discussions about warnings or action that the US suppliers perhaps should and did make, and indeed whether anything official may have come into the department or into the committee or the subcommittee that you chaired?

SIR JOSEPH SMITH: If I say by way of comment, I have only, as far as I know, seen Dr Galbraith's letter recently. It is a very good letter. But so far as I remember it didn't come to the Committee on Safety of Medicines, although we had Dr Galbraith at the meeting as one of our expert advisers.

LORD ARCHER OF SANDWELL: At that meeting we are talking about?

SIR JOSEPH SMITH: Yes, he was there. As about 50% of the material used in the UK was imported, it was not possible to do that. As far as I remember, he went along with that. I have no memory or recollection of warnings, although it is probably not an area I would have been involved with anyway.

I certainly have no recollection, I am afraid of it.

That doesn't mean to say it wasn't considered, but I do not remember, I am afraid.

MS WILLETTS: It is the sort of thing I would sort of expect may well come up at something like the CSM, I am somewhat surprised --

SIR JOSEPH SMITH: With hindsight I don't disagree at all, yes.

MS WILLETTS: I think what we need to do if we can is to find out, if we can, what the response of the DHSS was to this letter.

SIR JOSEPH SMITH: Then I had very little contact with the rest of the DHSS. My contact was with the Licensing Authority (Medicines Division), except I was also on the Joint Committee on Vaccination, but that was only with the field of vaccination.

MS WILLETTS: I think Galbraith asks an important question and we should see whether it was answered.

SIR JOSEPH SMITH: Yes, I very much agree, yes, yes, yes.

MS WILLETTS: Thank you.

LORD ARCHER OF SANDWELL: Thank you very much, Sir Joseph, most helpful, we are most grateful.

That concludes our evidence for today.

We will be taking evidence tomorrow but also, I think, on 19th September.

MS WILLETTS: That will be 30th August and 19th September.

(3.10 pm)

(The hearing adjourned until 11.30 am the following day)