

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

Tuesday, 3 May 2011

(9.30 am)

THE CHAIRMAN: Professor, we are treating your affirmation of the last time as simply continuing. So we won't repeat that. Forgive me just a second, Ms Dunlop.
Right.

PROFESSOR CHRISTOPHER LUDLAM (continued)

Questions by MS DUNLOP (continued)

MS DUNLOP: This morning Professor Christopher Ludlam has rejoined us to give his evidence on topic B2 and, professor, we need to start by looking at your CV and your publications because, as I said last time, you were just here to talk about some statistics and we would defer looking at your professional background until May. So that's why we need to do that today.

Firstly, your CV, which is PEN0020650. From that, Professor Ludlam, if we go to the first page in, we can see you have been professor of haematology and coagulation medicine at Edinburgh University from 1999 and other appointments in haematology, including that you have been the director of the haemophilia centre in Edinburgh since 1980 and you are also an honorary consultant to the Blood Transfusion Service, and that's since 1987.

You are a graduate of Edinburgh University, having

1 done your medical degree there between 1965 and 1971.
2 We see you won a number of awards as a student.
3 Then if we move to the next page, you also did a BSc
4 in biochemistry. Is that one of those arrangements
5 where you can do a BSc as you move through your medical
6 degree by taking a year out?
7 A. You take a year out and join the honours class in pure
8 biochemistry. So it was a year's worth of pure
9 biochemistry, which was extremely interesting.
10 Q. And indeed, an interest which has obviously continued
11 until this day?
12 A. I nearly became a biochemist rather than
13 a haematologist.
14 Q. We see that you did your house jobs with
15 Professor Girdwood, whose name is one that we have
16 already come across, and also Professor Woodruff.
17 I take it that was a surgical appointment, was it?
18 A. Yes.
19 Q. You were a senior registrar in haematology in Cardiff
20 between 1975 and 1978, and I take it you worked at that
21 point with Professor Bloom?
22 A. That's correct.
23 Q. If we move to the next page, please, your clinical
24 responsibilities include a general haematology
25 outpatient clinic each week, predominantly for patients

1 with myeloproliferative disorders. Can you give us some
2 instances, please?

3 A. These are a group of related conditions that are akin to
4 a low grade leukaemia and they present with high
5 platelet counts often, splenomegaly. The reason that
6 I have an interest in them is that the principal side
7 effect and complication of the conditions is thrombosis
8 and bleeding. So a lot of these patients actually
9 present with thrombotic problems.

10 Q. Looking at the following page, under a heading
11 "Haemophilia and thrombosis service", we see that you
12 see referrals from other Scottish centres with which you
13 work closely, and there is a, I think, elsewhere, in
14 relation to networking of systems, mention of the East
15 of Scotland. Are you in Edinburgh connected to centres
16 in Dundee and Aberdeen. Is that right?

17 A. Yes, we are the comprehensive care centre for the East
18 of Scotland and so we have some responsibility for
19 helping with the provision of the service and the
20 quality of the service in the other haemophilia centres
21 up the east coast to Dundee, Aberdeen and Inverness.

22 Q. And Inverness?

23 A. Yes.

24 Q. So Glasgow doesn't have a tertiary function in relation
25 to any of the other centres in Scotland, I suppose,

1 apart from Yorkhill?

2 A. There are two centres in Glasgow, the Glasgow
3 Royal Infirmary and at Yorkhill, and those are the only
4 centres for the West of Scotland. So they cover a large
5 geographical area. There is a little bit of overlap
6 between our areas and we are both -- Edinburgh and
7 Glasgow are perfectly comfortable with that. It depends
8 a little bit about where the planes fly to from the
9 outer isles, for example, whether they come to Edinburgh
10 or go to Glasgow, as to where patients are seen or where
11 patients have relatives in the central belt.

12 We are very flexible and patients can choose where
13 they come to, but in general, for administrative
14 reasons, I have responsibility for trying to provide the
15 service in the East of Scotland.

16 THE CHAIRMAN: I wonder if everyone is hearing. Is everyone
17 hearing at the back?

18 MS DUNLOP: Is that a longstanding arrangement that you have
19 additional, as it were, tertiary responsibilities for
20 the centres further north?

21 A. Yes, that's a longstanding arrangement.

22 Q. I noticed too on this page you mention the Scottish
23 Liver Transplant Centre. We did actually notice that
24 you had been involved in looking after the
25 Reverend Black, when we were examining his medical

1 records, and I don't think it's difficult to imagine
2 that liver transplant, particularly in someone with
3 haemophilia, must be quite challenging. The input,
4 I take it, that you are having is particularly in
5 connection with the surgery?

6 A. It is challenging because the patient starts off with
7 having usually severe or moderate/mild haemophilia but
8 once their liver has ingrafted and got a good blood
9 supply, then it is making Factor VIII for the patient.
10 So they no longer in one sense have haemophilia.

11 Q. Right. Does that take a little while after the surgery
12 to begin to work?

13 A. Two or three days.

14 Q. Yes. Can we move on to the following page, please?

15 I notice that you have a subheading "UK
16 haemophilia centre directors' organisation."

17 One of the things that had puzzled us in our
18 preparation for the hearings is whether the "D" stood
19 for directors or doctors. I think actually Dr Hay
20 explained that in association with obtaining charitable
21 status, the "D" was changed from directors to doctors.

22 Is that something you are aware of?

23 A. Yes, I am aware, and I see perhaps it is incorrect on my
24 CV here. Actually the change was made about 15 years
25 ago to encourage other physicians and surgeons who

1 helped look after people with haemophilia, part of the
2 broader team, to come and join our association.

3 Q. Right. So it was about inclusivity?

4 A. Yes.

5 Q. You say you have been a member of the executive
6 committee from 1980 to date. In other words, was the
7 executive committee, from 1980, the group of reference
8 centre directors? Is that ...?

9 A. Yes, it went under a number of different names over the
10 last 30 years, depending upon the exact organisation of
11 the organisation within the UK, because it changed, as
12 you may have seen, on a number of occasions.

13 Q. Yes. So today would the executive committee be the
14 directors of the comprehensive care centres?

15 A. It's actually called the advisory committee. There was
16 a small executive committee, which is the office
17 bearers, but the advisory committee is, as you say, the
18 directors of the comprehensive care centres, who meet
19 three or four times a year, usually in London, to
20 discuss matters of mutual interest.

21 Q. Thank you.

22 On the next page, if we could look at that, please,
23 what caught my eye was a reference to your being
24 co-chairman of the haemophilia directors' committee for
25 Scotland and Northern Ireland, 1987 to date. One of the

1 questions in our minds, as we have prepared for the
2 hearings, has been whether the Scottish directors ever
3 met as a body. Did that happen before 1987?

4 A. The Scottish directors met as a group, I think, from
5 about 1985, and this group in 1987 was set up to bring
6 together the producers of the Factor VIII and the users,
7 and in a sense the funders, the Scottish Government.

8 It was, I think, a very successful enterprise, as is
9 explained in the preliminary report. Dr Stewart was
10 appointed to collect up statistics on Factor VIII usage
11 and production, and it led, over the next three or four
12 years, to the production of a high purity Factor VIII
13 concentrate.

14 A couple of years into the committee's
15 deliberations, it was decided to change the title of the
16 working party because it started out as the Factor VIII,
17 but we then broadened into other clotting factors, so it
18 became the Coagulation Factor Working Party for Scotland
19 and Northern Ireland, and it really formed quite
20 a useful focus for haemophilia-related activities within
21 Scotland, and we used to have a meeting, a fairly major
22 meeting, once a year, to oversee the work of the working
23 party, to give it direction as to where it should be
24 going for the following year and to get some outside
25 help and insight into its activities. So we went to

1 some pains to get eminent individuals, like the chief
2 executive for the NHS in Scotland, to come along and
3 chair the meeting, help us with his insights and perhaps
4 he saw a little bit about what we were doing and trying
5 to achieve.

6 Q. Right. Another grouping, of course, that we have
7 noticed in the 1980s is the grouping immediately above
8 that, the meetings which looked to have been roughly
9 annual meetings, involving the SHHD and the directors of
10 the SNBTS and the haemophilia directors. So did that
11 annual meeting continue alongside the body you have just
12 been describing to us?

13 A. No, I think what happened was in the 1970s there were
14 occasional meetings of haemophilia directors, blood
15 transfusion and Scottish Office, hosted by the
16 Scottish Office Health Department.

17 There was one of those in -- I think the last one in
18 the 1970s was in 1977, and then they were reconvened,
19 I think, in 1981, and then another one was in 1983 and
20 possibly one in 1985, and then it became clear that
21 there were a lot of activities that needed to be looked
22 at and there needed to be more discussions, more
23 meetings, and it was at this point that haemophilia
24 directors started to meet themselves and the Coagulation
25 Factor Working Party was formed, really to take forward

1 more expeditiously the issues under consideration.

2 Q. Right. Can we go to the following page, please?

3 You give us quite a lot of information about the
4 European interdisciplinary working group on haemophilia
5 and it certainly, from your narrative, looks as though
6 you view this as a very positive development?

7 A. Certainly, yes, it was indeed.

8 Q. Not least because you have been able to help some
9 countries where the principles of care might not have
10 been as far advanced as they are, for example, in the
11 United Kingdom. Is that right?

12 A. That's correct, yes.

13 Q. And we see that Professor Colvin has been involved in
14 that as well.

15 A. Yes. He was the lead author and sort of chairman of the
16 group that drew up principles of care.

17 Q. Then on to the following page. You have had involvement
18 in the British Society for Haemostasis and Thrombosis.
19 You have been president in the 1990s, and you then tell
20 us about other national and international organisations.
21 Unsurprisingly they all relate to haematology. Then on
22 the following page, if we look at your research
23 interests, your major research interests, if we go to
24 the next page, please? Thank you. My eye caught what
25 you say under the heading "Hepatitis B virus", where you

1 say that your studies found that HBV replication caused
2 the suppression of Hepatitis C virus in co-infected
3 patients, making it difficult to diagnose infection with
4 the latter virus, that's Hepatitis C, which I suppose in
5 general terms could be described as something of an
6 elusive customer. At first blush, to a layperson, the
7 idea of suppressing the Hepatitis C viruses might sound
8 like good news for the patient. Is that wrong?

9 A. I think it is wrong because this is only observed, as
10 far as I know, in individuals who are replicating
11 Hepatitis B virus.

12 About 5 per cent of people who get infected with
13 Hepatitis B virus continue to produce the virus from
14 within their liver. The other 95 per cent produce an
15 antibody and that eliminates the infection. In about
16 5 per cent of people, they continue to produce
17 Hepatitis B virus and what are called long-term
18 carriers. So the liver is busy making Hepatitis B
19 virus, if you like, instead of Hepatitis C. It's as if
20 it can't do both.

21 Q. I see. But if, through some treatment, the Hepatitis B
22 were to be dealt with, the Hepatitis C essentially has
23 been biding its time and would come back and take over,
24 I suppose, as the dominant form of hepatitis, would it?

25 A. I'm not an expert on hepatitis treatment at the moment

1 but the treatment that there used to be for Hepatitis B,
2 chronic carriers, was very similar, if not identical to
3 what was used for Hepatitis C, in other words,
4 interferon treatment.

5 Q. Yes. Then on to the next page, please. Could we scroll
6 down a little bit under that heading "Hepatitis C
7 virus," you see at the end of the first paragraph:

8 "Our studies have revealed that using second
9 generation RIBAs, all haemophiliacs treated with
10 non-virus inactivated concentrates have been infected
11 with HCV."

12 That's something I think that doesn't come as news
13 to us because we have already been through a lot of
14 evidence about statistics, and it seems to be
15 a reasonable supposition that if someone was treated
16 with concentrates, whether commercial or NHS, before
17 heat treatment that was effective against Hepatitis C
18 came in, that they will have acquired Hepatitis C. That
19 is so, is it?

20 A. That is correct.

21 Q. You also say in the next paragraph that you:

22 "... demonstrated that the predominant circulating
23 genotype could change over time, particularly in
24 HIV-positive individuals."

25 And I suppose, is that because of the immune

1 suppression?

2 A. In HIV-positive individuals, it probably occurs more
3 frequently because they aren't producing as much
4 antibody to suppress the Hepatitis C.

5 Q. Right.

6 A. That's speculation.

7 THE CHAIRMAN: I'm not sure I quite understand that. That's
8 a sort of quantitative answer, "not as much as", but how
9 does that affect the change of genotype?

10 A. I'm getting a little bit out of my depth because I'm not
11 a virologist, but it is possible -- or sometimes
12 possible -- to demonstrate that the antibodies in the
13 circulation are against a particular genotype, and so if
14 there is that genotype present, the antibody against it
15 will be present and may reduce the quantity of virus and
16 that might allow another genotype being latent in the
17 liver to come up.

18 THE CHAIRMAN: So it is not just quantity, the person must
19 be exposed to more than one type, but other factors
20 might affect the extent to which it becomes dominant in
21 the system?

22 A. Yes. And the one that's dominant can change because
23 virtually all patients who have Hepatitis C have been
24 exposed to at least genotypes 1, 2 and 3, because they
25 are widespread in the population, and for reasons we

1 only partially understand, one type tends to
2 pre-dominate for a period of time and then it may
3 change; it may not.

4 THE CHAIRMAN: Yes.

5 MS DUNLOP: So for those patients who have been successfully
6 treated for their Hepatitis C, does it tend to be the
7 case that the treatment works against all the genotypes
8 that have been circulating in them? It is not that they
9 feel they have had successful treatment and then some
10 other genotype comes back?

11 A. My understanding is that the different genotypes have
12 different susceptibility to interferon and ribavirin
13 treatment, as you may have heard, but once an individual
14 has been treated and tested after six months of being
15 off treatment and they don't have the virus in the
16 circulation detectable, then they are thought to be
17 probably cured, and therefore it is likely that the
18 interferon has not only been suppressive in killing the
19 genotype that's in the blood at that moment but any
20 other genotypes that are hidden in residual places like
21 the liver.

22 Q. Thank you.

23 On the next page there is a short reference to
24 Hepatitis A and you say you:

25 "... helped to organise a study to assess the

1 possibility of transmission of Hepatitis A from SNBTS
2 concentrates."

3 I don't know that we need to go into this but are we
4 oversimplifying if we understand that Hepatitis A is not
5 transmitted in concentrates? Is there some evidence
6 that it is?

7 A. It is classical teaching until 1990 that Hepatitis A was
8 never transmitted by blood transfusion. In 1980 --
9 I think it was in Italy -- a number of patients became
10 jaundiced and when they were vetted, it was found that
11 it was recently acquired Hepatitis A infection, and
12 there was a small outbreak of it in Italy and there was
13 one also I came across in South Africa, and possibly one
14 or two other places, and so it was clear that
15 Hepatitis A could be transmitted by clotting factor
16 concentrates.

17 Virally inactivated concentrates probably don't
18 transmit, almost certainly don't transmit Hepatitis A.
19 It's a slightly more resistant virus to inactivation
20 than, say, Hepatitis C or HIV. Of course, a lot of
21 individuals have immunity from an early age to
22 Hepatitis A, they are exposed to it in the community.
23 Or rather they used to be, and what has happened as our
24 environment has got cleaner and cleaner is that fewer
25 and fewer young people get exposed to Hepatitis A and

1 therefore have immunity. It is not quite clear whether
2 one of the possible explanations for this outbreak was
3 that these individuals had not been exposed as children
4 to Hepatitis A and got some immunity.

5 So it was an area of surprise in this field but it
6 seems to have gone away with the viral inactivation
7 arrangements now.

8 Q. Right. Can we skip on, please, to, what is in the hard
9 copy, page 16, and this is under a heading "Regulation
10 of haemostasis", which begins at the bottom of page 15.

11 We shouldn't get sidetracked into going into this in
12 any detail but you have been involved in studies that
13 have revealed that Factor VIII is synthesised in many
14 organs; so it is not just a question of the liver, it is
15 made in other places in the body as well, and you say:

16 "Which is contrary to the popular perception."

17 Where else is it made?

18 A. It is made in endothelial cells, the cells that line
19 blood vessels, and that was a particular interest to me
20 because I have had a long-term clinical and research
21 interest in desmopressin, DDAVP, from when I was in
22 Cardiff, and there is much interest and controversy
23 about its mechanism of action, and this was an
24 observation that has now been confirmed by other more
25 extensive studies and explains, a little bit, I think,

1 why the Factor VIII level rises after giving
2 desmopressin, because the von Willebrand factor and the
3 Factor VIII probably both come out of the endothelial
4 cells.

5 Q. I see. You then list research funding you have had and
6 your teaching commitments. I noticed that, of the
7 haemophilia centre directors elsewhere in Scotland at
8 present, you supervised two of them for their MDs,
9 Dr Watson in Aberdeen and Dr Kerr, I think he is in
10 Dundee. Is that right?

11 A. That is correct, yes.

12 Q. And other activities, scientific journals, organisation
13 of national and international meetings and then
14 professional societies and associations, and then your
15 duties as an external examiner. Then in a separate
16 document, which is PEN0150074, we note your
17 publications, a number of books, four books, and then
18 chapters, reviews and editorials. Again, looking to me
19 as a layperson, pretty much across the whole spectrum of
20 haematology. I notice you contribute to Davidson's
21 Principles and Practice of Medicine?

22 A. Yes.

23 Q. That was, I think, quite a well-known textbook. Is that
24 correct?

25 A. It is, yes.

1 Q. Your work listed by year. If we can just go through it
2 perhaps, without highlighting anything in particular,
3 but have a look on to the next page, 82. Then into the
4 1990s, and then on through the 1990s, the Dr Stirling we
5 see mentioned there, he is the Dr Stirling of "Liver
6 Function in Edinburgh Haemophiliacs"?

7 A. Yes, he is a clinical scientist who works with me and is
8 now responsible for running the molecular genetic
9 service that we provide for Scotland for haemophilia.

10 Q. On to 1995, 1996, so on through the 1990s and indeed
11 right up to 2010. And then after that a list of
12 original articles beginning in 1975, looking, for
13 example, also at areas of orthopaedics; see too from
14 time to time obstetric aspects of haematology. I notice
15 too, 1989, if we can go on to that, please. Yes, Dr Moq
16 (sic), Dr Brettle, other well-known names in HIV studies
17 in Edinburgh. You had worked in vertical transmission
18 of HIV. That is essentially from mother to child, is
19 it?

20 A. Yes.

21 Q. Yes. I noticed also, 1992, one that caught my eye was
22 called "AIDS: The alternative view". What was the
23 alternative view?

24 A. I would need to see -- I'm sorry. I can't remember.

25 Q. Don't worry, professor, it was just a title that caught

1 my eye. That was all.

2 A. I could speculate but I don't think that's helpful.

3 Q. No, let's not bother.

4 Then on to 1997, I saw reflected in an article in
5 1997 a notion which is certainly prevalent in the NHS in
6 Britain, the article is called "Treatment for
7 haemophilia by postcode". I suppose this being 1997,
8 I should ask, at that time did you feel that there was
9 a considerable variation in treatment around Britain?

10 A. Indeed. I think this -- to some extent -- related to
11 the introduction of recombinant Factor VIII, synthetic
12 Factor VIII, which was licensed in about 1993 or 1994
13 but was expensive, and I'm pleased to say that in
14 Scotland we were able to start arranging for it to be
15 made available to patients in 1996 and we had, as
16 I think I have alluded to perhaps earlier in my CV,
17 a committee chaired by the general manager of Lothian
18 Health to oversee the introduction of recombinant
19 Factor VIII, given the strong support by the Blood
20 Transfusion Service, although it was not a blood
21 transfusion product, but I mention this because we had
22 a rolling programme in Scotland that was very much ahead
23 of what was happening in England.

24 In England individual health authorities were
25 deciding whether or not they would spend money on

1 purchasing recombinant Factor VIII. So there was
2 a patchy introduction of a recombinant Factor VIII
3 initially in England.

4 Q. I understand. I noticed too that in 1998 -- and this is
5 actually two pages on -- you had written an article
6 entitled "Funding arrangements for haemophilia within
7 the UK". Perhaps we could just note that for a moment,
8 but I'm going to come back and ask you a little bit
9 about that later in your evidence.

10 Then another tranche of articles, Professor Ludlam,
11 going on from 1999, 2000, 2001, right through the
12 noughties, and indeed the list ends in 2011. And perhaps
13 since this was written, there have been one or two more,
14 I don't know.

15 A. I don't think so.

16 Q. Thank you.

17 Can we put these to one side, please, and approach
18 the substance of your evidence. You have,
19 Professor Ludlam, sent a number of documents to the
20 Inquiry, and indeed there are what I would call four
21 core documents, which deal with many of the same issues.
22 There is quite a lot of overlap between them and I did
23 wonder, sir, what the best way to approach that fact
24 was, and I have decided that it would be of most
25 assistance to the Inquiry, I suspect, if we approach

1 Professor Ludlam's evidence in a topic-based way. So
2 rather than reading systematically through each of the
3 four, we are going to look at what is said on various
4 topics in the different statements. There is no one
5 statement that can be left out because all four of them
6 contain material that I suspect will be of interest to
7 the Inquiry.

8 So just to identify at the outset what the four
9 statements are, they are [\[PEN0150445\]](#), which is your
10 actual draft witness statement to the Inquiry, and then
11 various appendices. We have [\[PEN0150468\]](#), which is
12 a historical summary of AIDS in haemophilia, 1981 to
13 1985. I should say, that was, you say, drafted in about
14 1988. You have also submitted a draft report, which was
15 prepared for an impending litigation in England and
16 Wales in 1990. This was [\[PEN0150385\]](#), and then finally,
17 prepared for this Inquiry, the Edinburgh haemophilia
18 treatment policy, which is [\[PEN0150375\]](#).

19 The other device, which I hope to employ to save
20 time, is sometimes to mention documents that we have
21 already looked at without necessarily going to them, and
22 that's, I would suggest, appropriate in one or two
23 instances, where the material is reasonably familiar.

24 THE CHAIRMAN: I hope you will give us a bit of a key
25 because although it may be reasonably familiar now, some

1 time down the line we may need a reminder.

2 MS DUNLOP: I quite appreciate that, sir, and I would never
3 refer to a document just baldly. I will say what it is,
4 but that's a general schematic introduction, as it were,
5 and with that in mind the first of the four I would like
6 to look at is [\[PEN0150385\]](#). This is to look at the
7 background on haemophilia. What should come up, if we
8 look at page 4, is a section entitled "Background to
9 Haemophilia A and B and von Willebrand's disease".
10 There we are, thank you.

11 You tell us Haemophilia A and B, congenital bleeding
12 disorders, and about the prevalence.

13 THE CHAIRMAN: Could I ask just one question about the
14 prevalence point to get it out of the way? The
15 statement is made very generally. Is there any
16 geographical variation or is this standard throughout
17 the world?

18 A. It is standard throughout the world, although
19 individuals with haemophilia tend to -- or used to tend
20 to come to live close to haemophilia centres, so in
21 a particular country there may not be an equal
22 distribution.

23 THE CHAIRMAN: The reason for the question was that
24 Dr Winter explained that his contacts with Pakistan, for
25 example, have related to a population in Islamabad,

1 which he thought could be taken as a general indication
2 of what would have happened apart from treatment. So
3 you and he agree that there is a common prevalence?

4 A. Yes.

5 THE CHAIRMAN: Thank you very much.

6 MS DUNLOP: Thank you.

7 The first thing I wanted to ask you about,
8 Professor Ludlam, is a point that we did also put to
9 Dr Winter. It is just this question of spontaneous
10 bleeding, and I wonder, do you refer here to those
11 people who have severe haemophilia, who experience
12 frequent, often apparently spontaneous haemorrhagic
13 episodes?

14 I think I understood from Dr Winter's explanation
15 some of the things that may cause bleeding in a joint,
16 but if we could focus perhaps more on bleeding into the
17 brain, the background to the question is really that if
18 one has an understanding of haemophilia as a condition
19 in which blood doesn't clot properly, in the sequence of
20 events, the commencement of bleeding seems to be a prior
21 event, and I wonder, with particular reference to bleeds
22 in the brain, why does it start?

23 A. It's likely that there is -- we all have a small amount
24 of bleeding in our brains from time to time. We all
25 have good -- or most of us have good clotting systems

1 and it stops very quickly and heals up. The problem in
2 haemophilia is that once bleeding starts, it takes
3 a long time to stop. You do not necessarily get
4 a greater flow of blood but it just goes on and on and
5 on and on, and if that happens in the brain, then it
6 often has catastrophic consequences.

7 Q. Yes. Thank you.

8 Also covered in this paragraph is a topic we have
9 mentioned before, which is that of gradations of
10 haemophilia. We understand that people are described as
11 having severe, moderate or mild haemophilia, and
12 I notice that the borderlines that you have set out for
13 the divisions between mild and moderate and moderate and
14 severe are 10 per cent and 2 per cent, which is slightly
15 different from what we have in our report, which is that
16 severe would be under 1 per cent and then moderate would
17 be 1 to 5 and mild would be over 5. Yours, I noticed,
18 was the same as what UKHCDO are using in 1983 and
19 that -- sir, this is an example of just an allusion to
20 a document, but we can see that from [\[SNB0017540\]](#), which
21 we don't need to go to. Dr Winter told us that he had
22 taken his -- he was 1 per cent, 5 per cent and then he
23 wanted to go from 5 really up to 50 to cover all those
24 who, even though they are in the 30s and 40s, might
25 still have bleeding problems. I just wondered if you

1 could give us your perspective on where the dividing
2 lines might be?

3 A. The levels of less than 2, 2 to 10 and then above 10,
4 were thresholds that were used in the UK for a long time
5 by UKHCDO. The reason they were chosen, I think, are
6 very good reasons. Less than 2 per cent: If you have
7 less than 2 per cent, you bleed much more frequently
8 than if you have 3 or 4 per cent. People that have less
9 than 1 per cent probably bleed more than people who have
10 between 1 and 2 per cent but if you like, the people who
11 have the most frequent bleeds are those with less than
12 2 per cent. If you have less than 1, you bleed even
13 more.

14 The range from 2 to 10 is what used to be called
15 moderate haemophilia and that includes virtually all the
16 patients who will bleed in relation to minor trauma,
17 twist the ankle walking downstairs, some of them get
18 spontaneous bleeds. Often these people require
19 treatment three or four times a year. There is also
20 a group within this whose Factor VIII level may depend
21 on the particular technique you use to measure it.

22 Those above 10 per cent very rarely bleed, except
23 after major trauma or surgery. That was the system that
24 was in operation until about ten years ago and I think
25 it was a very good system because there were lots of

1 patients with levels up to 10 per cent who need
2 treatment each year. Anyone over 10 per cent had mild
3 haemophilia and needed very occasional treatment.

4 The International Society of Haemostasis and
5 Thrombosis, for reasons that I have never quite
6 understood -- and unfortunately I wasn't at the meeting
7 at which it was discussed -- decided that less than
8 1 per cent would be the definition of severe
9 haemophilia. 1 to 5 moderate and over 5, mild.

10 The reason I don't like that system is there are
11 a lot of patients between 5 and 10 per cent who bleed
12 from time to time in a year. It might be several times
13 a year. And they are categorised with mild -- people
14 over 10 per cent who hardly ever bleed at all. So under
15 the new classification, the mild group is a much more
16 heterogeneous group of patients and so that's why
17 I prefer the previous categorisation but I have to move
18 on with the times.

19 Q. Well, thank you for explaining that to us. I did look
20 at the ISTH website and there certainly does seem to be
21 a bit of controversy about it, with people asking, is
22 this achievable. I don't know quite what that means but
23 also the World Federation of Haemophilia seem to have
24 adopted the 1 to 5 and 5 and up classification, and also
25 I think we found the NHS referring to it as well. So it

1 may be that you are in a minority nowadays, would you
2 accept that?

3 A. I do accept that, yes.

4 Q. Yes. The other point I suppose that I think we all
5 understand is that categorisation isn't always the whole
6 story because, if a patient is bleeding in the way you
7 have described, then something has to be done about it.
8 A patient with haemophilia who is bleeding -- and it
9 doesn't really matter whether their level is 3 per cent
10 or 25 per cent -- something could have caused them to
11 bleed and they will need treatment. Is that
12 a reasonable understanding?

13 A. Absolutely, yes. Could I make it clear that even though
14 I think the previous classification system was better,
15 I fully use the current one. This document was written
16 20 years ago.

17 Q. Yes.

18 A. That's why it is set out in this way.

19 Q. Yes, I appreciate that, thank you.

20 THE CHAIRMAN: Professor, is it entirely a matter of
21 classification, as you have mentioned, or are there
22 financial implications that go with the classification?

23 A. Not in Scotland.

24 THE CHAIRMAN: Not.
25 In Scotland.

1 MS DUNLOP: That is my next question, sir, that noting the
2 article that the professor had written about funding, we
3 had a description from Dr Winter of the sort of
4 capitation arrangement, where a centre that had a higher
5 number of people with severe haemophilia would receive
6 more funding, but that isn't how it works.

7 A. Not in Scotland.

8 Q. Not at all? How is a Scottish haemophilia centre
9 funded? I daresay we could take days on that, but in
10 broad outline, is it to do with the number of patients
11 at all?

12 A. No. Very briefly, it is financed by the local health
13 authority. So Lothian funds the staff and facilities
14 for the centre in Edinburgh, which is at the Royal
15 Infirmary. The clotting factor concentrates, which are
16 the expensive part of the service, are funded through
17 a national arrangement, led by the National Services for
18 Scotland and NSD, in which the health authorities are,
19 I think -- the technical term is "bottom-sliced",
20 a capitation fee, depending on the size of their health
21 authority, and that money is pooled and used to purchase
22 Factor VIII and Factor IX, the other clotting factors,
23 for Scotland on a risk-share basis. It's a good system.
24 I think it should be upheld.

25 Q. Right. This is no doubt stating the obvious but I take

1 it it wasn't much different in the 1980s? Certainly not
2 in the sense of the capitation fee. That wasn't
3 something that Scotland had in the 1980s and has moved
4 away from?

5 A. No, in the 1980s the staff and facilities were provided
6 by the local health board, Lothian Health Board for
7 Edinburgh. Most of the Factor VIII was supplied "free
8 of charge" to the health authority and to our
9 haemophilia centre, and if commercial concentrates were
10 required, they were purchased with -- well in Lothian's
11 case, money from Lothian Health board via the Blood
12 Transfusion Service who actually made the purchase.

13 Q. We want to come back to that and that's on my agenda but
14 quite a long way further down.

15 So moving on to the next page, if we could, please,
16 just a short question, professor. You mention
17 osteoarthrosis; is there a difference between
18 osteoarthrosis and osteoarthritis?

19 A. I'm not an orthopaedic surgeon but I think most of the
20 chronic changes in bones are osteoarthrosis. Arthritis
21 refers more to an inflammatory component. Now, there is
22 an inflammatory component in the changes following
23 bleeding into haemophilic joints but there is also an
24 osteoarthrotic process in the bones. So there is both.

25 Q. Is the arthrotic process where the joint begins, as it

1 were to, seize up. Is that right?

2 A. Yes. It eventually turns into a process that is very
3 like bad osteoarthritis that non-haemophiliacs get.

4 Q. You tell us a bit there, professor, about the natural
5 history of severe haemophilia without treatment, and as
6 the chairman has said, we have had some insight into
7 that from Dr Winter, describing the situation as it
8 currently exists in Pakistan.

9 He also referred to the recent diagnosis of
10 a patient in Cambodia, who I think he said was the first
11 patient diagnosed with haemophilia in Cambodia.

12 Then on to cryoprecipitate. You talk about the
13 revolution in haemophilia care in the 1960s that
14 resulted from the discovery of a technique for preparing
15 cryoprecipitate from plasma. Then on to the following
16 page, please:

17 "When cryoprecipitate from 10 to 15 individual
18 plasma donations was combined and given to the patient,
19 it was possible to raise the Factor VIII levels
20 sufficiently to stop haemorrhage."

21 You say:

22 "During the late 1960s, this treatment became
23 progressively available to haemophiliacs at hospitals on
24 an outpatient basis."

25 At this point I would like to look at another of the

1 four documents, which is your treatment policy, and that
2 is [\[PEN0150375\]](#). This also talks about cryoprecipitate
3 and we can pick it up under that heading. You talk
4 about:

5 "The development of cryoprecipitate in the mid 1960s
6 being a very major therapeutic advance for the treatment
7 of Haemophilia A."

8 We do just need to clarify, Professor Ludlam, why
9 does it not work for Haemophilia B?

10 A. Because it doesn't contain very much Factor IX.

11 Q. Yes. In the process -- I think it is the centrifuge --
12 when the centrifuge is used and the cryoprecipitate is
13 precipitated out of the solution, in very crude lay
14 terms, the Factor VIII is in the powder and the
15 Factor IX is in the solution, in the liquid. Is that
16 right?

17 A. Absolutely correct, yes.

18 Q. I hope that's good enough for us.

19 On to the following page you talk about treatment of
20 an average bleed in an adult patient. I did just
21 notice -- I hope this isn't too pedantic -- you do refer
22 elsewhere, Professor Ludlam, to treatment of an average
23 bleed requiring 10 to 15 packs, and you have here 15 to
24 20 packs. I wondered if we could just go forward with
25 a sort of understanding that around 15 packs would be

1 needed to treat an average bleed. Is that reasonable?

2 A. It depends a bit on the size of the patient.

3 Q. Yes.

4 A. And the amount of Factor VIII you think might be in the

5 individual packs of cryoprecipitate.

6 Q. It was just that in the passage we looked at from the

7 previous statement, you did say cryoprecipitate from 10

8 to 15 individual donations had to be combined and given

9 to the patient, but here it is 15 to 20. So just to

10 assist our understanding, if we think of it as being

11 around about 15, sometimes a bit less, sometimes a bit

12 more?

13 A. Yes.

14 THE CHAIRMAN: Would that do? It does seem to me that from

15 our point of view, what may be important is that when

16 one thinks of cryoprecipitate coming from a single

17 donation, there is only the beginning of the story, and

18 unless there is a measure of the scale of usage,

19 a misleading impression could be given. And I think

20 Ms Dunlop's question is the right one: can we take it as

21 a working hypothesis that 15 would be typical or not?

22 A. I think it depends when and upon the availability of

23 cryoprecipitate. I think latterly we were tending to

24 use 20 packs. It's about 1500 units of Factor VIII,

25 which is a reasonable dose for treating a bleeding

1 episode.

2 THE CHAIRMAN: Yes. So how do we deal with it, Ms Dunlop?

3 A. I'm happy to settle at 15. I don't think there is going
4 to --

5 THE CHAIRMAN: No, I just don't have the feeling that the
6 actual number is as critical as the impression that it
7 takes multiple packs to deal with a bleed.

8 A. Yes.

9 MS DUNLOP: Another point that we need to cover in relation
10 to cryoprecipitate is its potential for home treatment,
11 and you describe for us what happens when a patient is
12 treated with cryo. So the packs are thawed in a water
13 bath -- this is reading from your statement:

14 "... and pooled together before being infused into
15 the patient. This was a messy, wet and time-consuming
16 procedure. The other major disadvantage is that allergic
17 reactions to it were relatively common. Occasionally
18 these reactions could be serious and life-threatening.
19 For this reason cryoprecipitate was not suitable for use
20 by patients at home."

21 Professor Forbes did say that it's possible -- and
22 maybe we should look at a couple of documents at this
23 point. Can we look first at [\[DHF0023406\]](#). Thank you.

24 I think if we go through this, we can see this is
25 a document we have looked at before and it appears to

1 date from the middle of 1974, to have been a paper
2 prepared probably for the Expert Group On the Treatment
3 of Haemophilia. If we go through it, the same sort of
4 reference, paragraph 4:

5 "Cryoprecipitate is tedious and time-consuming to
6 make up."

7 Just at the bottom of that page it says:

8 "Although it has been possible to use
9 cryoprecipitate for home treatment, both storage
10 requirements and the inconvenience of administration
11 make this an unsuitable material."

12 Then the other document was [\[DHF0023161\]](#). And again
13 we need to go through this. We see it's redacted. It
14 is the minutes of the meeting of the Expert Group On the
15 Treatment of Haemophilia in October 1974. Can we go
16 through, please, on to the next page. Further down and
17 then on to following page, please. Then:

18 "Optimum use of Factor VIII preparations."

19 Over to the next page, please. We can see that
20 there was a paper 5. There is a name missing:

21 "... [may have been Dr Biggs] spoke briefly to her
22 paper on home treatment with cryoprecipitate."

23 I appreciate that both these documents date from
24 a long time ago but given that and Professor Forbes
25 saying that it is possible but unsuitable, I wondered if

1 we could ask you just a little bit about what might have
2 been involved or would have been involved for a patient
3 home treating with cryo. I think the first thing we
4 understand is the patient would have to have a deep
5 freeze. Is that right?

6 A. Yes.

7 Q. Right. And then all of this thawing in a water bath,
8 the patient would have to know how to do that?

9 A. He had to have a water bath at 37 degrees to melt the
10 frozen individual units.

11 Q. Right. And I appreciate this is going right back to the
12 beginning of your training but, I mean, are you familiar
13 with the sorts of things that patients using cryo at
14 home had to do?

15 A. Very familiar.

16 Q. So could they do it in their own bath, the thawing.

17 A. It is very important, when you are making up blood
18 products, that it is done in a clean, and if possible
19 sterile environment, and I think I wouldn't be keen to
20 suggest that patients used their baths for warming up
21 packs of frozen plasma, if the water was too hot, the
22 proteins will congeal, a bit like egg white. In the
23 hospitals we have water baths, this sort of size
24 (indicates), a couple of feet across, carefully
25 controlled in temperature and are cleaned regularly and

1 are as sterile as we can make them.

2 Q. So could you just walk us through what the person would
3 have had to do at home. They would, you think, have had
4 to have a piece of equipment, a water bath, and
5 presumably a jolly good thermometer?

6 A. They would have to have a deep freeze, they would take
7 out the deep freeze 15 packs of cryoprecipitate, put
8 them in the water bath. They take about a quarter of an
9 hour to melt. And then each of those packs has to have
10 a tube put into it and the melted cryoprecipitate rolled
11 out. Because they are polythene bags, you can roll them
12 up and squeeze the cryoprecipitate out. You do that
13 repeatedly 15 times, squeezed out into a bigger bag.
14 You would then have to hang that up, connect it to
15 a drip set, like giving a conventional blood
16 transfusion, the patient would then have to put the
17 needle into their vein and connect up the transfusion
18 set to the tubing on the needle. And it would take
19 about half an hour/40 minutes to run in.

20 Q. Yes. And the hypothesis behind home treatment is that
21 this is something carried out by a patient who has an
22 instinct that he is already bleeding or that a bleed is
23 coming?

24 A. Yes.

25 Q. Right. And it could be done, I suppose, by a parent?

1 A. Yes.

2 Q. Dr Winter described to us one indication a parent might
3 look for in a child would be that the child has a very
4 hot knee or something like that, and that could be an
5 indication that a bleed is starting or is about to
6 start?

7 A. Yes.

8 Q. So psychologically, presumably there will have been
9 a pressure of time, but this is a process that takes
10 time, it can't be hurried, but things have to happen as
11 quickly as possible?

12 A. Yes.

13 Q. Right.

14 THE CHAIRMAN: Professor, I'm beginning to form a picture
15 that really is quite concerning in some ways. We must
16 envisage a patient in a relatively remote part of
17 Scotland.

18 A. Potentially.

19 THE CHAIRMAN: With a deep freeze big enough to store really
20 potentially quite a large number of packs of
21 cryoprecipitate. One doesn't know exactly when the
22 bleed is going to come, but they might come repeatedly
23 over a short period.

24 A. Yes.

25 THE CHAIRMAN: So there is quite a large storage problem.

1 A. Yes.

2 THE CHAIRMAN: The next thing is that the Factor VIII
3 content of the individual packs is, within limits, quite
4 unpredictable.

5 A. Yes, and unmeasurable.

6 THE CHAIRMAN: And unmeasurable. And certainly unmeasurable
7 by the patient.

8 A. Yes.

9 THE CHAIRMAN: And did that have an influence on the number
10 of packs the patient would be told to use?

11 A. Yes.

12 THE CHAIRMAN: In order to ensure that one covered the
13 bleed, one would tend towards a larger number rather
14 than a smaller number.

15 A. Yes.

16 THE CHAIRMAN: How on earth did stock control work in these
17 contexts? How did one deal with it?

18 A. The stock control, I think, was fairly straightforward
19 in the hospital.

20 THE CHAIRMAN: Yes.

21 A. But in a home setting, well -- I wasn't prepared to let
22 patients have treatment at home with cryoprecipitate for
23 all these reasons. But perhaps the most important
24 reason, which we haven't dealt with, is the reactions.
25 A lot of patients getting cryoprecipitate, had

1 reactions. Often these were mild and they would take an
2 antihistamine beforehand, but I was looking at some
3 information a day or two ago, suggesting that actually
4 cryoprecipitate should only be given where adrenaline is
5 available, and adrenaline is when you get an acute
6 life-threatening allergic reaction, what's called an
7 anaphylactic reaction. So for these reasons I wasn't
8 keen and I did not have a home therapy programme based
9 on cryoprecipitate. I concede other places did and it
10 seemed to work for them, but it was logistically
11 difficult.

12 MS DUNLOP: Yes, I think we can see that, professor. We
13 need to go back to [\[PEN0150375\]](#), and you do make exactly
14 that point, that allergic reactions are relatively
15 common. We can see that towards the top of the screen:

16 "Occasionally these reactions could be serious and
17 life-threatening."

18 So you say cryoprecipitate was not suitable for use
19 by patients at home. This is obviously a topic that we
20 will come back to about the potential for using cryo in
21 the situation as it developed. Everything can appear to
22 have a nuance. So whether one says it was possible but
23 unsuitable or it was unsuitable but it was possible gets
24 slightly different shades of meaning, but I think we
25 understand that there were significant practical

1 difficulties in using it for home treatment?

2 A. Yes.

3 Q. Then you talk about your clinical experience of
4 treatment with cryo. You say your:
5 "... clinical experience was that a patient who had
6 received very little previous blood product and was
7 treated with cryoprecipitate over a number of days for a
8 bleed or to cover surgery became jaundiced."
9 Are you saying always?

10 A. No, but I was struck when I came here in 1980 that if
11 I gave patients round about 100 or 200 donations of
12 cryoprecipitate over a course of treatment, not
13 infrequently they became jaundiced.

14 Q. And in what situation would they need to have about 100
15 or 200? Each time the patient is receiving about 15
16 bags worth; is that right?

17 A. Yes.

18 Q. So when would they end up having maybe 10 lots of that
19 or ten treatments of that?

20 A. It might be three or four separate bleeds, they might
21 have two or three treatments for each bleed.

22 Q. Then you say:
23 "It appeared to me that the frequency of hepatitis
24 carriage by blood donors was approximately 0.5 per cent.
25 Most of this was due to a putative non-A non-B virus or

1 viruses."

2 Obviously we are going to come back to that. Can
3 I go on then, please, to the next page? This is still
4 the treatment policy document, and just moving to the
5 following page, to a heading "Factor VIII concentrates",
6 you say that:

7 "Concentrates derived from pools of plasma to which
8 many individual blood donations had contributed, started
9 to be manufactured in the 1970s. Initial pool sizes
10 were small, for example, 500 donations, but the pool
11 size rose so that in the 1980s some manufacturers had
12 pool sizes of many tens of thousands ..."

13 I think the highest number that the Inquiry team has
14 noticed is 30,000, but you think it was beyond that at
15 some points with some manufacturers, or is that round
16 about the highest number you have ever heard?

17 A. I have heard higher numbers, I think.

18 Q. What's your maximum?

19 A. Perhaps 40 or 50. I'm sorry, I don't -- I would rather
20 not say because it's a long time since --

21 Q. It doesn't matter, professor, I'm just interested in
22 getting an idea of the largest pool sizes that may have
23 been used.

24 THE CHAIRMAN: Professor, can I again ask a question at this
25 stage? This is a very general statement about the

1 1970s. I have to say that when the preliminary report
2 was written, I had just discovered but had not really
3 absorbed the papers at a joint symposium held in
4 Edinburgh in 1972 by The Royal Society of Edinburgh and
5 The Royal College of physicians in Edinburgh, which gave
6 rather a clearer insight into what had been happening in
7 Scotland over the previous period and at that time. Are
8 you aware of the history in Scotland in this detail?

9 A. Some of it.

10 THE CHAIRMAN: Have you read the papers of the joint
11 symposium?

12 A. I am afraid I haven't, I'm sorry, no.

13 THE CHAIRMAN: That's the position I was in at the
14 preliminary report, but perhaps we will all catch up in
15 time.

16 A. Yes.

17 MS DUNLOP: These sort of bumper pools of 30,000, 40,000,
18 50,000, these are commercial manufacturers you are
19 thinking of, is it, professor?

20 A. Yes.

21 Q. Yes. One of the questions which has struck us is, on
22 discovering that the first commercial concentrate was
23 licensed in America in 1966, we have wondered why it
24 took until 1973 before the commercial concentrates
25 arrived in Britain. Do you know the answer to that or

1 is that just one of these mysteries?

2 A. I don't, but I would wonder whether it might be that
3 they could only make a limited amount and that was sold
4 and used in the United States.

5 Q. Thank you. Then, just reading down through that, if we
6 go to the foot of that page, you then refer to
7 contamination. You describe viral contamination as an
8 amplification system in concentrates and you say that
9 has been responsible for the early and ready
10 transmission of hepatitis and HIV viruses to patients,
11 with such devastating effect.

12 On to the following page, a comment that the initial
13 clotting factor concentrates were relatively impure and
14 contained large amounts of other plasma proteins. Are
15 we talking about only NHS product here or about
16 commercial product too?

17 A. Commercial product as well.

18 Q. Right. Was that your experience then when you were
19 working in Wales?

20 A. Yes.

21 Q. And was it also your experience when you came to
22 Scotland? I'm just really trying to put a timeframe on
23 this comment about relative impurity?

24 A. Oh, yes, it applied to all clotting factor concentrates
25 around that time.

1 Q. Right. Would you say these early concentrates were very
2 difficult to solubilise. I had to look that up,
3 professor, because initially I wondered whether it just
4 meant dissolved. But my understanding is that's really
5 the stage before one dissolves it: tries to make it
6 soluble and then to dissolve it. Is that what we should
7 understand by the use of the word "solubilise"?

8 A. Perhaps it would be better to say "dissolve".

9 Q. That would cover it?

10 A. Yes.

11 Q. You say:

12 "The volume of reconstitution was relatively large.
13 The early concentrates were only slightly more purified
14 than freeze-dried cryo. The volume of a single infusion
15 might be 200 mls to 300 mls of concentrate, as compared
16 to 1 ml to 5 mls of recombinant factors today."

17 And:

18 "One of the difficulties encountered with the low
19 purity concentrates produced by SNBTS in the early 1980s
20 was that its use to cover major orthopaedic surgery
21 could result in an acquired bleeding state due to its
22 content of non-Factor VIII proteins."

23 I want to come back later in your evidence to
24 notions of purity and potency but for just now I think
25 we need to note that these early products were hard to

1 dissolve and if it was necessary to use the same sorts
2 of volumes of water, then early home treatment must have
3 required the patient also putting himself on a drip. Is
4 that right?

5 A. Or using a large number of 50-ml syringes. For home
6 treatment a patient would make it up with a syringe --
7 into a syringe. He would draw the dissolved clotting
8 factor in the bottle, draw it up into a syringe and then
9 inject it. But, because of the low unitage in the
10 bottles and the large volume of water that had to be
11 added, you could end up with several 50-ml syringes to
12 inject. They were very fine cannulae. So it takes
13 quite a long time.

14 Q. And you keep the needle in and you just change over
15 a full syringe for the empty one. Is that right?

16 A. Yes.

17 Q. Yes. Then can we read down:

18 "1980. A majority of patients in Edinburgh were
19 being treated with cryoprecipitate being prepared by
20 SNBTS from Scottish blood donors. As described earlier,
21 a small number of patients were receiving home therapy
22 with NHS Factor VIII concentrate. The remaining
23 concentrate was used in hospital, either for surgery or
24 for patients who were allergic to all infusions of
25 cryoprecipitate."

1 Then can we go back to [\[PEN0150385\]](#) at page 7? You
2 have a section here, too, professor, on Factor VIII
3 concentrate, covering most of the same ground, but you
4 say:

5 "During the early 1970s Factor VIII concentrates
6 manufactured by the NHS became available in very limited
7 quantities."

8 We have had some discussion in evidence, relating to
9 the Reverend Black, of a treatment he was seen to
10 undergo in 1965. He had four flasks of AHG. We had
11 some discussion then about what that might be, but our
12 understanding is that this is likely to have been a very
13 early NHS concentrate. Does that sound right to you?

14 A. It sounds reasonable.

15 Q. Yes.

16 THE CHAIRMAN: I am, of course, interested in this and
17 slightly concerned about the language. As I understand
18 it from the documents I was referring to,
19 Cohn Fraction 1 was produced in Scotland at the time
20 that Mr Black may have been treated. Is that properly
21 described as a concentrate?

22 A. It's a very low purity concentrate but it is
23 a concentrate, yes; it is a pooled product.

24 THE CHAIRMAN: It's one of these bits of terminology that
25 gets us all wrong-footed, I think, professor.

1 A. No, it's produced from a pool of plasma. The
2 Cohn Fraction 1 was the original purification method for
3 Factor VIII.

4 THE CHAIRMAN: Thank you. Sorry, Ms Dunlop, I'm just trying
5 to get my mind round all the terms and since the
6 chronological sequence has to be taken into account, it
7 becomes quite difficult.

8 MS DUNLOP: I'm also hoping, sir, that Dr Foster will turn
9 out to be a historian of the production of materials in
10 Scotland, so we can ask him too.

11 THE CHAIRMAN: I appreciate that's a possibility but I want
12 to top up as I go, rather than get it all at once.

13 MS DUNLOP: Yes. One of the clinchers for Dr Colvin was the
14 reference to flasks. That, he said, made it much more
15 likely that this was an early form of concentrate rather
16 than, say, cryo.

17 A. Yes.

18 Q. Yes. Just reading down -- we can all read that for
19 ourselves, about the reference to home treatment and the
20 improvement in life expectancy.

21 Then we move to Factor IX concentrates.

22 You say that:

23 "Initially treatment was by fresh frozen plasma."

24 Move on to the next page, please. You refer to the
25 longer survival time in the recipient of Factor IX as

1 compared with Factor VIII. So Factor IX has a longer
2 half life?

3 A. Yes.

4 Q. "In the 1970s treatment with concentrates of Factor IX
5 became available like Factor VIII. These were prepared
6 from large plasma pools prepared from many donors, but
7 chemically they were quite different."

8 I think we can understand that and from what we said
9 earlier, our crude simplification about which way the
10 Factor VIII goes and where the Factor IX is, we can see
11 that from one donation, it is possible to get both the
12 Factor VIII and the Factor IX?

13 A. Yes, and other proteins as well.

14 Q. Well, indeed, yes. Is that partitioning?

15 A. Fractionation.

16 Q. All right. Can we, I think, still talking about
17 Factor IX, go to the document that's 375. That's
18 [\[PEN0150375\]](#). Go to page 7 of that. We can see
19 a heading "Factor IX" again. I'm not going to read it
20 out. It looks as though initial concentrates were known
21 to have other factors in them, II, VII and X, as well as
22 Factor IX.

23 A. Yes.

24 Q. Was that a problem? Is it that that led to the possible
25 thrombosis problem?

1 A. Yes, I think it is. The original Factor IX preparation,
2 manufactured in Scotland, was a four factor concentrate,
3 II, VII, IX and X, and that was superseded by a three
4 factor concentrate, DEFIX, which has II, IX and X in it,
5 not Factor VII.

6 Nowadays we treat patients with a concentrate
7 containing just Factor IX, IX alone. If we have it.
8 And there is a recombinant one available. The reason
9 for this is that these other clotting factors could
10 become a little bit activated during the manufacture,
11 during the separation from the plasma, so that when they
12 are injected into patients, they were a bit
13 thrombogenic, and every now and again that patient
14 actually developed a thrombosis, and particularly if
15 there was some other pre-disposing factor to
16 a thrombosis, then one was more likely to develop.

17 Q. By "activated", do you mean that the factor, rather than
18 going into the patient's body and waiting until it's
19 needed, goes in and immediately begins some kind of
20 clotting process?

21 A. That's correct.

22 Q. Right. And I think we can understand -- and this is
23 simple arithmetic luckily -- that, because the
24 prevalence of Haemophilia B is very much less and
25 because the yield of Factor IX is higher, there has been

1 a more plentiful supply. So in other words,
2 self-sufficiency in Factor IX appears to have been
3 achieved quite early in the story. Is that right?

4 A. That's correct, yes.

5 Q. We then go back to [\[PEN0150385\]](#) and go to page 9. We
6 are on to von Willebrand's factor. Again you explain
7 a bit about that. You say it is due to a congenital
8 deficiency of the von Willebrand factor, and we do
9 understand that both sexes are affected?

10 A. That's correct.

11 Q. So although it is congenital, it is not X-linked?

12 A. That's absolutely correct.

13 Q. Right. You tell us a bit about the symptoms of having
14 von Willebrand's disease, and again if we can just read
15 on to the following page, cryoprecipitate was used in
16 preference to Factor VIII concentrate, partly because it
17 contained a higher concentration of von Willebrand
18 factor and because it reduced the risk of hepatitis
19 transmission as patients with VWD only required an
20 occasional transfusion. So they don't bleed
21 spontaneously. Is that right? Or is that an
22 oversimplification?

23 A. It is a slight oversimplification. Von Willebrand
24 disease is probably the commonest congenital bleeding
25 disorder but it is mild in most patients, and lots of

1 patients live to a ripe old age and are never diagnosed.
2 But we see a steady stream of people with what we call
3 symptoms suggestive of a mild bleeding disorder. They
4 have a tooth extracted and they bleed for three or four
5 days afterwards, or they have very heavy menstrual
6 periods and the gynaecologist can't find any good reason
7 for them, or a mother brings a child because he is
8 always bruising and all her other children don't bruise.

9 So that's the presentation for most patients with
10 von Willebrand's disease. There are a few patients who
11 have what's called severe von Willebrand's disease who
12 have virtually no von Willebrand factor in their plasma
13 and as a result their Factor VIII level is very low
14 because von Willebrand factor is the carrier protein for
15 Factor VIII. So if you lack von Willebrand factor,
16 then, because Factor VIII is unstable in the
17 circulation, its level falls very rapidly after it has
18 been released. So people with severe von Willebrand
19 disease, sometimes known as type 3, actually bleed like
20 a patient with severe haemophilia. They tend to bleed
21 into their joints and their muscles.

22 Q. I see. You have then included a paragraph on DDAVP.
23 This is something that again will crop up later in your
24 evidence. But you give us a useful explanation of what
25 it is. And you say:

1 "Its use in patients with haemophilia and VWD was
2 first reported in 1977 and in the same year it was
3 licensed for use in such patients. When given
4 intravenously, it raises temporarily Factor VIII and
5 von Willebrand factor levels by approximately three to
6 fourfold."

7 And I think we already understand, Professor Ludlam,
8 that DDAVP is not a suitable treatment for an acute
9 bleed?

10 A. It can be if it's a minor bleed, yes.

11 Q. All right. I think we wondered, because of the time
12 that it presumably takes for it to work, if it was
13 adequate for an acute bleed, but you are saying there
14 are circumstances in which it could be used?

15 A. Yes. If a patient has a nose bleed, for example, and
16 comes up to the unit, we might, if their clotting levels
17 are appropriate, give them an injection of desmopressin.
18 We now give it what's called subcutaneously, just under
19 the skin. You can give about 1 ml's worth of injection
20 under the skin. It takes at least an hour to reach the
21 maximum level. It starts working more quickly but it
22 takes a quarter of an hour/20 minutes, to make up
23 a bottle of clotting factor and one wouldn't want to
24 expose them to clotting factor if it's a matter of
25 merely waiting for half an hour for the desmopressin to

1 work.

2 Q. I see. So would you make your judgment as to whether to
3 use DDAVP in a patient with, say, a nose bleed,
4 depending on what their resting level of Factor VIII
5 normally was?

6 A. I would make the judgment on the resting level probably
7 on their von Willebrand factor, not their Factor VIII
8 level, and not all patients respond to DDAVP and so we
9 make it a practice when we see a new patient or diagnose
10 a new patient -- we give them a test dose of DDAVP, to
11 see whether they respond or not and how well they
12 respond and how long the response lasts, because some
13 individuals produce a good response but the
14 von Willebrand factor disappears very quickly from the
15 circulation.

16 Normally it lasts four or five hours and that's long
17 enough to secure a minor bleed, perhaps a nose bleed.
18 But it's only used for minor bleeds in patients who we
19 know will respond or prophylactically. If someone is
20 going to have a tooth out, for example, we might well
21 give them DDAVP first and send them to the dentist round
22 the corner from our unit to have the tooth extracted.

23 Q. Right. We do see in fact you refer to minor
24 haemorrhage. Would it ever be used for a joint bleed?

25 A. Probably not because, if a patient had mild haemophilia

1 such that one might use DDAVP, their basal level of
2 Factor VIII would have to be over about 10 or
3 15 per cent in order to get a rise up to 50 per cent
4 with desmopressin.

5 In mild haemophilia, you do not get a joint bleed
6 until you have had substantial injury to the joint and
7 it's therefore likely -- in fact we know, in mild
8 haemophilia you need actually to give more treatment to
9 joint bleeds because there is a much greater degree of
10 tissue trauma involved. An individual who has severe
11 haemophilia just has to have a minor tweak to the joint
12 and they start bleeding and they continue to bleed. An
13 individual with mild haemophilia who gets a joint bleed
14 has had to get usually a proper sprain -- if I can put
15 it that way -- to the joint and because there is a lot
16 of trauma they require more treatment.

17 One of the difficulties of this situation is that
18 people with mild haemophilia don't bleed very often and
19 they don't appreciate the importance, if they do get
20 a bleed, of coming in for treatment early. So a number
21 of people with mild haemophilia now come in days or even
22 a week or ten days after a bleed has started and they
23 have a very large haematoma and they find themselves in
24 hospital for a protracted period of time, requiring
25 concentrate treatment.

1 Q. I see.

2 THE CHAIRMAN: I think, Ms Dunlop --

3 MS DUNLOP: I'm just at the end of a section. I have been
4 hoping to get to the end of a section before we have
5 a break. Can I ask one more question and then we can
6 move to something --

7 THE CHAIRMAN: It depends whether Professor Ludlam can give
8 you a very short answer.

9 MS DUNLOP: It was just, in assembling a complete picture of
10 treatment, there is also tranexamic acid.

11 A. Tranexamic acid is an interesting, simple molecule made
12 synthetically, it can be given as a tablet and it
13 inhibits the ability of the blood to dissolve clots.

14 Q. Right.

15 A. We believe that in the circulation all the time there is
16 a little bit of clotting going on, a little bit of clots
17 being formed, and that clot is being dissolved and when
18 you get an injury, you get a bit of clotting to stop the
19 bleeding, but after a little while you don't want that
20 clot any more and it is dissolved. Otherwise, you would
21 be covered in scars the whole time. And this medicine,
22 tranexamic acid, inhibits the breakdown of the clots,
23 what's called fibrinolysis. So the clots stay a bit
24 longer. If the clots are a little bit friable because
25 you have a bleeding disorder, then it helps strengthen

1 concentrates, and I suspect that's due to the fact that
2 the commercial concentrates contained more Hepatitis C
3 virus in the bottles than NHS concentrates. Therefore
4 you got a worse acute episode and you became jaundiced
5 and sick and unwell. Whether that led to worse chronic
6 liver disease I think is not at all certain. I don't
7 think there is evidence that liver disease following use
8 of commercial concentrates is worse than liver disease
9 following hepatitis exposure from NHS concentrates.

10 Q. Right. The next sentence reads:

11 "It was also considered that the chances of an NHS
12 concentrate transmitting hepatitis was rather less than
13 a commercial one."

14 If we confine ourselves to the 1970s, I suppose
15 particularly the very early days of commercial
16 concentrates, when there are references to NHS
17 concentrates being made from 100 or 200 donations pooled
18 together, that may have been true in those early days,
19 may it?

20 A. I think so, yes.

21 Q. Then you say:

22 "There was also some evidence that commercial
23 concentrates might contain at least two viruses
24 responsible for non-A non-B hepatitis."

25 Was that true?

1 A. There was evidence for there being more than one type of
2 non-A non-B virus, and actually some of the evidence was
3 from studies done in the early 1980s on NHS
4 concentrates, but I think looking back, yes, it was all
5 Hepatitis C.

6 Q. So it was a bad question. The statement, I would hope
7 it's true, but in effect once the virus, Hepatitis C,
8 had been found, it turned out to be the culprit.

9 A. For the majority of cases of non-A non-B hepatitis, yes.

10 Q. Yes. Then:

11 "Furthermore, it was not clear whether the hepatitis
12 caused by NHS concentrates was the same or different
13 from the causative agent in commercial concentrates."

14 What about that?

15 A. Well, I think that was perhaps based on the experience
16 of the Bournemouth outbreak, if I can call it that,
17 where commercial use was followed by a lot of malaise,
18 more so than NHS. So was this a different virus or was
19 it a different quantity of virus? And I think
20 probably -- I have not asked a virologist -- I suspect
21 it's because the quantity of the virus in the commercial
22 concentrates.

23 Q. That's just the empirical finding you referred to
24 a moment ago, that people seemed to be more sick, as it
25 were, immediately after the commercial concentrate had

1 been administered?

2 A. That is one of the take-home messages from the
3 descriptions that have been written up of the
4 Bournemouth and associated hospitals outbreak.

5 Q. Yes. Our understanding, Professor Ludlam, is that
6 ultimately -- and by "ultimately" I mean the early
7 1980s -- it appeared that whether a patient had received
8 commercial or NHS concentrate, they generally acquired
9 non-A non-B hepatitis?

10 A. Yes.

11 Q. Much of the work in this area appears to have been
12 carried out or at least co-ordinated by Dr Craske.
13 I presume you worked with Dr Craske?

14 A. Yes.

15 Q. And knew him quite well?

16 A. Yes.

17 Q. We have had him described as "tireless". I take it you
18 would agree with that?

19 A. He was a great enthusiast for what he was doing, yes.

20 Q. Indeed. I don't need to take you to this but
21 Dr Boulton's note of the UKHCDO meeting on
22 17 October 1983 -- and for the record, that is
23 [\[SNB0017535\]](#) at page 4 -- contains a note by Dr Boulton
24 to the effect that you had said confidentially to him --
25 that may have been confidential then but it isn't now --

1 that the report of the hepatitis working party was
2 largely a solo effort by the chairman. Do you want to
3 see that?

4 A. No, I saw it in some of the papers. No, he led the work
5 of the hepatitis working party. He did a lot of, if
6 I can put it, the background work, the designing of the
7 forms, writing out the protocols and really keeping the
8 projects rolling.

9 Q. You say:

10 "My predecessor, Dr S H Davies ..."

11 That's Dr Howard Davies; is that right?

12 A. Yes.

13 Q. "... had a policy of not using commercial concentrates
14 because of the uncertainty about hepatitis viruses in
15 the concentrates derived from plasma collected in the
16 United States and elsewhere."

17 So that's your predecessor as director of the
18 haemophilia centre at Edinburgh Royal, is it?

19 A. Yes.

20 Q. In fact, if we look at [\[SNB0072254\]](#) -- we have seen this
21 letter before -- maybe you haven't but we have. This is
22 a letter from Howard Davies to Dr Cash in December 1975
23 and we can see that he was wanting to get home treatment
24 up and running, and I suppose what's interesting to the
25 Inquiry about the letter is that he is wanting to get

1 home treatment up and running with NHS concentrates.

2 A. Yes.

3 Q. One of the thoughts I had about Dr Davies' policy was
4 that it might date from the television programme but of
5 course, this is a full year before the television
6 programme was shown, so his reservations about the
7 commercial products pre-dated World in Action?

8 A. Yes.

9 Q. Do you remember the World in Action programme from 1975?
10 I think you would be a senior registrar in Cardiff at
11 that point. Do you remember it being on?

12 A. I just moved to Cardiff about a month before, a month or
13 two before the programme was shown, and I was still
14 settling in there. And I was still getting familiar
15 with my colleagues and the patients. I don't know
16 whether it was shown in Wales but I don't recall there
17 being discussion about it. There was lots of discussion
18 about the Bournemouth outbreak but I don't recall
19 discussions about the programme. Whether it was shown
20 in Wales or not, I don't know. I may not have had
21 a television at that time.

22 Q. Certainly one would speculate that a programme like
23 that, featuring some of the big names of the day, would
24 have been a major talking point. So you are telling us
25 you don't even remember that? Even if you didn't see,

1 it, you don't remember people saying there was an
2 amazing documentary on on Monday or anything like that?

3 A. No.

4 Q. No. Right. You have seen it now, I think, haven't you?

5 A. Yes.

6 Q. What's your reaction to it?

7 A. I think it confirmed a lot of my pre-conceptions, except
8 that I think the plasma collection facilities were
9 rather worse than I thought they were. They did not
10 have a good reputation but I was appalled by the
11 conditions.

12 Q. We need to go back to [\[PEN0150375\]](#). Having referred to
13 Dr Davies' policy you say:

14 "I did my utmost."

15 I'm guessing that most of these statements were not
16 typed by you, Professor Ludlam. Is that correct?

17 A. I'm not a good proof reader. No, this is professional
18 typing.

19 Q. Right. Yes, there are a number of others, but anyway,
20 you did your utmost to continue this policy when you
21 became responsible for the service in 1980. Just on
22 that point, your becoming responsible for the service.
23 I would like to look firstly, please, at a document
24 [\[LOT0032997\]](#). And this is the minutes of the ninth
25 meeting of the reference centre directors, held at

1 Oxford on 15 October 1979. We can see that you are
2 there, Dr Forbes is there as well, and interestingly we
3 can see from page 2 that you seem to have been on the
4 agenda. This is the whole question about process, and
5 I think really in a nutshell who should be approving
6 your appointment as Dr Davies' successor at Edinburgh
7 Royal:

8 "Dr Davies thought the appointment of his successor
9 should be approved by both the SHHD and the haemophilia
10 reference centre directors. Dr Davies had contacted
11 SHHD about this matter but had received no reply.
12 Officially there were no reference centres in Scotland
13 although unofficially the Glasgow and Edinburgh centres
14 acted as haemophilia reference centres."

15 This point, professor, if it is big enough even to
16 be considered a point, but the fact that there wasn't an
17 official designation does crop up in quite a lot of
18 minutes over the years. Do you remember that being
19 a topic at various meetings?

20 A. I do. And I think a great deal was made out of it for
21 very little. We were keen that Edinburgh and Glasgow
22 were seen as reference centres. We were part of a UK
23 arrangement for overseeing haemophilia treatment. Our
24 colleagues in the other centres in Scotland were very
25 happy for Edinburgh and Glasgow to be recognised as

1 reference centres. They didn't feel they wished to bid
2 for that status. The Scottish Home and Health
3 Department was a little hesitant and when I enquired
4 a little further, it seemed they were a bit afraid there
5 might be some financial implications of so designating
6 us. But as you will have seen from some of the
7 documents, bit by bit approval was given, and certainly
8 from when I took up my appointment -- in fact, this
9 meeting is before I took up my appointment -- I have
10 always been part of the reference centre directors'
11 committee.

12 Q. Yes. You will appreciate, Professor Ludlam, that coming
13 to the issue cold, the Inquiry team was concerned to
14 discover if the lack of the formal designation had ever
15 meant that the directors in Glasgow and Edinburgh and
16 therefore in Scotland were out of the loop in some kind
17 of way?

18 A. No, we were in the loop.

19 Q. Yes. Perhaps the only other thing to notice about this
20 particular set of minutes is that, if we look at
21 page 11 -- that's [\[LOT0032997\]](#), page 11 -- there was
22 a report from Dr Craske's hepatitis working party and
23 some question about how data was to be collected.

24 For completeness, sir, I should say that the
25 report -- although I'm not completely certain -- from

1 the hepatitis working party appears to be [\[SNB0017207\]](#).
2 If we could just quickly look at that, and in particular
3 if we can look at page 3, which is SNB0017209, there is
4 one of really quite a large number of pieces of
5 information about the NHS commercial comparison. We see
6 that just under the table 2 it says:

7 "Patients treated with NHS and commercial
8 Factor VIII concentrate showed no significant difference
9 in their liver function tests."

10 Do you see that?

11 A. Yes.

12 THE CHAIRMAN: Could we scroll down a little bit please? We
13 don't have that.

14 MS DUNLOP: Sorry. There it is.

15 It really looks as though Dr Craske studied this
16 subject more or less without ceasing from about 1975,
17 certainly well into the mid 1980s.

18 A. I think he is a great credit to his endeavours and to
19 studying hepatitis in a systematic way, which, as far as
20 I know, was hardly happening anywhere else in the world.
21 This was sort of world-leading research.

22 Q. Could we go back, please, to [\[PEN0150375\]](#).

23 You are talking here about home treatment, and we
24 can see about halfway through this paragraph reference
25 to the delay in introduction of home treatment for many

1 eligible patients.

2 Just on that point, professor, we have seen some
3 references from the early 1970s, particularly at the
4 point where the commercial concentrates are arriving in
5 Britain, to ideas of home treatment being confined to
6 people who lived a long way away from the
7 haemophilia centre. Even if that was someone's
8 expectation or someone's hope, it doesn't appear that
9 that was ever translated into practical policy. Do you
10 remember that being a sort of caveat about home
11 treatment, that it was only for a small group of
12 patients who couldn't get to the centre?

13 A. No, each patient was considered individually. There
14 were patients who travelled very long distances and who
15 had severe haemophilia, and I can think of one or two
16 patients that I tried to help, because they were coming
17 so frequently, by putting them on to home treatment.
18 But home treatment, when there is a plentiful supply of
19 Factor VIII, is for anyone who is competent to give it
20 to themselves and bleeds sufficiently frequently that
21 they need it.

22 Q. I suppose it would have been a way of limiting
23 expenditure when the commercial concentrates became
24 available in the early 1970s?

25 A. I see -- I don't think it was ever a way of rationing

1 treatment.

2 Q. When you arrived at Edinburgh Royal in 1980, what was
3 the system for patients who realised that they were
4 having a bleed? We had Dr Forbes on Thursday describing
5 the system in Glasgow and he laid out for us a sort of
6 open-access policy. I wonder if you can describe what
7 the system was in Edinburgh around this time?

8 A. Certainly. This is for a patient who needs to come into
9 hospital for treatment?

10 Q. Yes.

11 A. Yes. They would phone up in the morning, usually the
12 morning, to order an ambulance to bring them to the
13 haemophilia centre. So the patient would wait for an
14 ambulance. The ambulance would bring them, sometimes
15 a considerable distance, from West Lothian or Fife or
16 down in the borders. They would come to our
17 haemophilia centre, which in those days was a single
18 room attached to ward 23 in the hospital. One of us,
19 either myself or my registrar, would go and see them and
20 by the time we went to see them, often several patients
21 had accumulated so we would go round with our notebook,
22 noting what was the trouble, where the bleeds were and
23 we would order up the cryoprecipitate, although we did
24 encourage patients, when they phoned in advance, to say
25 they were coming, to let us know, so we could get the

1 cryoprecipitate sort of thawed out in advance. We then
2 had to put the request to the blood transfusion who were
3 50 yards down the corridor. They conveyed the
4 cryoprecipitate up to our haemophilia room. The
5 infusion would have to be set up. Some patients could
6 set their own infusions up. Others had to wait for
7 a doctor to come and do it. The infusion would take
8 about half an hour/three quarters of an hour to run
9 through, at which point the patient was free to go. The
10 only thing was that they often had a bleed in their knee
11 or elbow, so it was difficult for them to get around and
12 they would wait for an ambulance to take them home.

13 The ambulance might come at the end of the morning
14 or the early afternoon and they would be home by about
15 four o'clock.

16 Q. Did that system operate well during working hours? Was
17 that a kind of nine-to-five system?

18 A. That's how it worked during the working day. Patients
19 could come up at any time of the day or night. It was
20 an open-access service. So we had to respond to
21 patients whenever they came.

22 Q. So what about a patient who felt they were starting
23 a bleed at nine o'clock at night or on a Sunday at 11
24 am. What would happen to them? Would they have to go
25 to casualty?

1 A. No, they came up to the haemophilia room and usually the
2 doctor on call for the ward would see them and ring one
3 of us up and we would make some recommendations about
4 their treatment, and the ward doctor would give the
5 treatment and the patient would go away again.

6 Q. So help was available really 24/7?

7 A. Absolutely.

8 Q. Just moving through this part of the statement,
9 professor, you refer to the driver for collection of
10 plasma being obviously the need to produce more
11 Factor VIII concentrate. You say:

12 "One of the disadvantages of Factor VIII concentrate
13 was the yield of Factor VIII from starting plasma is
14 substantially lower compared to plasma being converted
15 to cryoprecipitate. The demand rose sharply in
16 Edinburgh after 1980 because I wished to use more
17 Factor VIII concentrate to treat the patients."

18 Then an interesting paragraph about patients having
19 a card. You say that:

20 "Patients were individually told to request either
21 cryoprecipitate or an NHS concentrate and to avoid
22 a commercial concentrate if possible. To emphasise the
23 importance of this, each patient was supplied with
24 a small statement to this effect which was placed in
25 their haemophilia card, which could they could show to

1 get treatment at another centre."

2 When did you initiate this system, or was it
3 something Dr Davies had done?

4 A. I think I initiated it, very shortly after I arrived.
5 Because patients would obviously travel and they might
6 go down to England and, as you know, in England there
7 was much more commercial Factor VIII used. So if
8 a patient turned up as a visitor there was a possibility
9 they might get an injection of commercial concentrate.

10 Q. Right. So did every patient with haemophilia have
11 a little card like a sort of bank card or a little
12 cardholder?

13 A. Every patient we diagnosed with haemophilia or other
14 congenital bleeding disorder is given a card stating
15 what the condition is, what is the level of severity of
16 the condition, which haemophilia centre they are
17 registered with, where to phone in an emergency.

18 Q. Right.

19 A. They are invited to carry these with them wherever they
20 go.

21 Q. Has that been the system for as long as you have worked
22 in haemophilia care?

23 A. It has been the system since the 1970s.

24 Q. This issue of patients needing treatment in another
25 place, or indeed even when they are in Edinburgh, being

1 on home therapy, I wanted to ask you how they actually
2 physically got the product, the medicine. I suppose
3 people who arrive at hospital because they think they
4 are having a bleed, that's all done from the hospital
5 pharmacy, is it?

6 A. With the Factor VIII concentrate.

7 Q. Yes.

8 A. No. The Factor VIII concentrate was stored by a blood
9 bank in the hospital and the blood bank was
10 overseen/managed by the Blood Transfusion Service.

11 Q. So it doesn't form part of the pharmacy set-up in the
12 hospital at all in fact at this point?

13 A. Not at this point, no.

14 Q. Right. And for patients on home therapy, how did they
15 get their material?

16 A. They would phone up and say that their stocks were
17 running low, could they have some more. We would phone
18 the blood bank and ask them to make up a package which
19 the patient would come and collect, often in the early
20 evening on their way home from work or a relative would
21 come.

22 Q. I see. You go on to say that:

23 "Because of the relative scarcity of NHS Factor VIII
24 concentrate during 1981 and 1982, a small amount of
25 commercial concentrate was purchased but it was

1 purchased for treating a small number of patients with
2 specific haemostatic therapeutic difficulties."

3 There are really two propositions rolled into that,
4 professor. I wasn't sure whether you were saying that
5 some commercial concentrate was purchased in 1981 and
6 1982 because there wasn't enough NHS concentrate, or
7 some commercial concentrate was purchased because it was
8 necessary for patients for whom NHS concentrate wasn't
9 suitable?

10 A. Mostly the latter.

11 Q. Mostly the latter, right. So there were occasions when
12 you had to supplement your NHS concentrate with
13 commercial material just because there wasn't enough
14 NHS?

15 A. I have set out in one of the documents -- I don't know
16 your number --

17 Q. We are going to that later.

18 A. Okay.

19 Q. You have set out a very detailed account of the
20 individual patients for whom commercial concentrate was
21 used and why.

22 A. Yes.

23 Q. You have. So if I say that we will come back to that,
24 but this point about relative scarcity, perhaps it is
25 just very difficult to remember, and we appreciate it's

1 30 years ago, but do you think there was ever a time
2 when you had to buy commercial because there just wasn't
3 enough?

4 A. There was at least one patient who I put on to home
5 therapy with commercial because of the distance he lived
6 from the hospital and because his brother was also going
7 to go on to it because he had started, if I can call it,
8 for clotting reasons.

9 No. If I had been anywhere else in the UK in these
10 circumstances and had not inherited this situation where
11 commercial concentrate had never been used, then I would
12 have been going to my health authority and saying,
13 "Look, we need much more commercial concentrate to allow
14 these people to go on to home treatment". Because that
15 is what had happened five years earlier or four years
16 earlier, in England. So a lot of my patients couldn't
17 get home therapy because there wasn't an adequate supply
18 of concentrate. And I wasn't prepared to take the risk
19 of giving patients cryoprecipitate at home.

20 Q. You see, that was interesting, professor, because you
21 are saying that really the reason why you didn't try to
22 get a large number of patients or a large increase in
23 the number of patients on home therapy by going to
24 commercial product, to make up any shortfall, was that
25 you wanted to maintain Dr Davies' policy but you

1 yourself must have reached a clinical judgment as to
2 whether it was a good policy or not.

3 A. It was very difficult. As you see, there is much more
4 literature. A great deal of interest and concern about
5 hepatitis, non-A non-B hepatitis and what it was and
6 what it meant, and I took the view that here are a group
7 of patients who had not been exposed to commercial
8 concentrate and maybe it was worth trying to preserve
9 that in these very difficult times of supply, so that at
10 least we had a group of patients that we could see what
11 happened with NHS concentrates because the majority of
12 patients being treated in England were treated with
13 a mixture of NHS and commercial.

14 Q. So there was at least, to some extent, an interest in
15 monitoring what was going to happen if you had this
16 group of patients treated purely with NHS product. You
17 are nodding?

18 A. Yes.

19 Q. The last paragraph on that page, you talk about a batch
20 dedication system -- and I appreciate we are jumping
21 into 1984 but just because it is there. I think if we
22 look at a letter, which is [\[SNB0074755\]](#), this is
23 actually from Dr Perry to Dr McClelland, and if we go
24 down to paragraph 2. It takes a minute but when you
25 first see this letter you don't appreciate the

1 difference but there is a difference between dedicating
2 a batch to a patient and dedicating a patient to a batch
3 and it looks as if it was mooted, certainly in 1984,
4 that each patient would have, as it were, their own
5 batch but because that would have led, as I understand
6 it from this letter, to a degree of wastage because the
7 batch would outdate perhaps before the patient had got
8 through it, the system that was introduced was actually
9 the other way round, so that the batches were dedicated
10 to the patients. I think that's when you describe in
11 your statement?

12 A. Yes.

13 Q. If we go back to that then, please, that's [\[PEN0150375\]](#)
14 at the bottom. You say:

15 "There were three parallel batches of Factor VIII
16 concentrate. Patients received from a particular batch
17 based on their surname."

18 Do you know if that operated elsewhere in Scotland
19 or indeed in Britain?

20 A. Yes, it was a Scottish initiative, as part of our
21 collective activities. I think it operated in Glasgow.
22 It was started at about the same time. The reason why
23 it came in rather later than it might have done is
24 because you need to have a larger stock of Factor VIII
25 available actually to run a system like this. You have,

1 in a sense, to have three times the stock level. Where
2 there was a paucity of Factor VIII concentrate, then it
3 made it difficult to run a system like this. So this
4 became available -- or we did this when there was more
5 Factor VIII available.

6 Q. I see. Then on to the following page, you actually talk
7 about heat-treated product being issued
8 in December 1984. But we don't need to go into that
9 just now.

10 I would like to move from here to page 8 of this
11 document. If we look at the first paragraph you talk
12 about:

13 "In the 1980s commercial fractionators moved towards
14 manufacturing clotting factor concentrates of higher
15 purity, which is more units of Factor VIII per
16 milligramme of protein in the final vial."

17 You say:

18 "This was important for the treatment of babies in
19 whom it can be difficult to give injections of clotting
20 factor concentrate because of the small veins buried in
21 chubby arms. Higher purity products were also less
22 likely to give rise to allergic reactions ..."

23 We are going to go on to look at purity and potency
24 but just because you mentioned children here, I wanted
25 to ask you in general terms, from your arrival in 1980,

1 how children were cared for, children with haemophilia,
2 particularly were they on home treatment and so on?

3 A. When I arrived, there weren't actually many very small
4 children with haemophilia but I was responsible for
5 looking after them as well. Previously, some of them
6 had been looked after by paediatricians in other
7 hospitals in the city, and they continued to be so even
8 after I arrived for a spell and so I would find myself
9 advising about their treatment, as it were, by proxy.
10 But eventually, as part of the "centralisation of
11 services" I became responsible for about a 13-year
12 period.

13 Q. Right. Did you move to introduce home treatment for
14 children?

15 A. Yes.

16 Q. From what sort of age of child?

17 A. Oh, it is very variable. It depends on the child and
18 the parents. It could be done from the age of
19 four/five/six/seven. It very much depends on the child.

20 Q. The reference to babies; do babies tend to need much
21 treatment for haemophilia or is it really only once
22 a child is ambulant that they are more at risk of
23 bleeding problems?

24 A. A child with severe haemophilia usually starts to bleed
25 about the age of nine months when they start to crawl

1 around and walk and fall over. And so to begin with,
2 they only get occasional bleeds, perhaps every month or
3 so, and so they need treatment and the baby is
4 distressed from the pain of the bleed and that makes
5 their veins constrict a bit. They have very small
6 veins, they may have chubby arms, and it is not easy to
7 treat small babies, give them an intravenous infusion of
8 anything. The clotting factor concentrate is of some
9 volume and therefore it can be very traumatic for
10 everybody, treating very small babies.

11 Q. Nonetheless, you managed to maintain Dr Davies' policy
12 of using NHS material, even though you had
13 a constituency of children in your haemophilia patients
14 in Edinburgh. Is that right?

15 A. Yes, I did not have, as I say, many small babies when
16 I arrived, actually. I don't know why that was, except
17 that one or two of them were looked after by
18 paediatricians, who would have done some of the therapy.

19 Q. What about school age children? Did you have a group of
20 them?

21 A. Yes.

22 Q. And so notwithstanding the difficulties of possibly
23 having to use quite a large infusion -- we discussed
24 earlier about maybe 200 or 300 mls -- you did manage to
25 treat the children as well without resorting to

1 commercial product?

2 A. Yes.

3 Q. I suppose for the home therapy, you had some sort of
4 training programme for parents, did you?

5 A. Yes.

6 Q. The rest of that statement, I think we can put to one
7 side, save perhaps to notice that I think on the
8 following page it says "iron" when it should say "ion".
9 I just wanted to correct that one in case we became
10 confused. You see in line 3:

11 "It was agreed to develop a high purity iron
12 exchange concentrate."

13 I think that should read "ion"?

14 A. The "R" should be removed.

15 Q. The rest of this section is dealing with events rather
16 later than we are focusing on, at least in this topic.

17 Can we go next, please, to [\[PEN0150445\]](#) at page 15?
18 This is, as promised, purity and potency. Just to be
19 sure that we understand this, professor, looking firstly
20 at paragraph 51 you say:

21 "Purity is defined as unit clotting factor per
22 milligramme of total protein in the reconstituted vial."

23 Then:

24 "Potency is the concentration of clotting factor in
25 the reconstituted vial, international units per

1 millilitre."

2 Given that the former one is international units per
3 milligramme, would we be losing anything if we thought
4 of your definition of "purity" as being units of
5 clotting factor per milligramme of the solid, as it
6 were? I appreciate, the solid is dissolved but ...?

7 A. You would need to ask the protein fractionators. That
8 is milligramme of protein. In the freeze-dried keg in
9 the bottle, there may be some salts solution and
10 stabilisers. So they will be, if you like, additional
11 weight and are not part of the purity definition.

12 Q. Yes. I suppose there is the water as well. This is an
13 international or a conventional understanding, is it?

14 A. Yes.

15 Q. Well, we should probably stick with that. So purity is
16 unit clotting factor per milligramme of total protein in
17 the reconstituted vial and potency is the concentration
18 of clotting factor in the reconstituted vial and the
19 former is expressed in international units per
20 milligramme and the latter in international units per
21 millilitre. Then we have a definition of purity.
22 That's another one that has three gradations, and you
23 say:

24 "The definition of purity changed in the 1980s but
25 for the purposes of this statement the above categories

1 are used."

2 It is interesting to note that -- and this is line 4
3 of that paragraph beginning "Factor VIII" -- that:

4 "Factor VIII protein represents about 1 to
5 2 per cent of the protein in the concentrate."

6 So there is an awful lot of other stuff in there as
7 well?

8 A. It is probably less than 1 per cent, actually. Yes,
9 most of the protein is not Factor VIII in these low and
10 intermediate purity concentrates.

11 Q. Then you explain that:

12 "From a manufacturer's perspective, a low purity
13 product usually maximises the yield of Factor VIII. It
14 is highly relevant when trying to reach
15 self-sufficiency. But purity is important to
16 a physician and patient for the following reasons: one,
17 lower purity products are usually slower to dissolve.
18 There is a greater chance of aggregates remaining in the
19 solution."

20 I was wondering -- obviously the answer to this must
21 be that it does matter but if you were trying to
22 dissolve and there is other stuff there that you don't
23 want, it doesn't just sink to the bottom. It is not as
24 simple as that?

25 A. Well, you want to make sure that you have dissolved, if

1 you like, all the Factor VIII.

2 Q. Yes.

3 A. So we teach people that they should wait until the whole
4 of the keg is dissolved. It is actually drawn up out of
5 the bottle through a filter needle, which filters out
6 big aggregates of proteins -- probably non-Factor VIII
7 proteins, like immunoglobulins and fibronectin -- so
8 that when the solution is injected into the patient,
9 they don't actually get aggregates, or as many
10 aggregates, as they might otherwise.

11 Q. Then the second point you make is that:

12 "Lower purity products are more likely to result in
13 'allergic' reactions because there are more
14 'contaminant' proteins ..."

15 Then over on to the next page:

16 "Lower purity concentrates may contain anti-blood
17 group A and B antibodies, which can react with the
18 recipient's red cells ..."

19 Then fourthly:

20 "The contaminant proteins may accumulate in the
21 recipient pre-disposed to a haemorrhagic state."

22 So it does look, professor, as though there is an
23 inevitable tension between the manufacturer, who wants
24 as big a yield as he can, for which there may be
25 a purity cost, and the physician and patient, who would

1 like as pure a product as possible but for which there
2 would be a yield cost. Is that accurate?

3 A. Yes, at that time.

4 Q. At that time.

5 A. What transpired -- and I'm sure Dr Foster will be able
6 to speak much more eloquently to this than I can -- is
7 that when we came to develop, or they developed the high
8 purity Factor VIII concentrate in the early 1990s, the
9 yield in making that was actually quite high, and
10 I remember during the 1980s there was -- because of
11 events in protein fractionation technique -- the ability
12 actually to increase the yield at a higher purity.

13 Q. Right. Pleasing both sides of the tension?

14 A. Absolutely.

15 Q. Then reading on, paragraph 54:

16 "Purity became a particular issue in the 1980s."
17 And you explain that. You say:
18 "In the early days of AIDS it was considered that
19 a large amount of these proteins might pre-dispose to or
20 be the cause of AIDS."
21 Were the commercial products at that time not much
22 more pure?

23 A. Yes.

24 Q. Right.

25 A. In general. It was an evolving scene, and can I draw

1 your attention, if I may, to Peter Foster's witness
2 statement, in which he gives a table of many of the
3 commercial concentrates prepared in the 1970s and the
4 1980s, and he gives their physical characteristics
5 including their purity.

6 Q. Right. Thank you. But then you say:

7 "There was a possibility that the contaminant
8 proteins might be beneficial. Beneficial by modulating
9 the immune system and reducing the development of
10 antibodies to the transfused Factor VIII."

11 Then:

12 "Anti-Factor VIII antibodies arise in about 25 per
13 cent of small children with severe haemophilia and are
14 currently the most feared and severe complication of
15 haemophilia."

16 Anti-Factor VIII antibodies are much more of a
17 problem for young children than for older people,
18 I suppose, because they have come through the stage of
19 being exposed to the other products. Is that right?

20 A. Having an inhibitor at whatever age greatly influences
21 what treatment you give and the response to it. Whether
22 you are a child or an adult, if you have an inhibitor,
23 it is much harder to treat the bleeds. But the
24 inhibitors mostly -- not exclusively at all -- arise in
25 children with severe haemophilia within the first ten or

1 20 injections of concentrate. So by the time the child
2 is two or three, a quarter of them have these
3 inhibitors.

4 Q. If you were able to extract a sample of pure Factor VIII
5 from everybody in this room, would it be the same
6 substance?

7 A. Probably not completely identical because there are some
8 polymorphisms in it.

9 Q. I just wondered why, if people have a small amount of
10 Factor VIII circulating in their body, they would
11 develop an antibody to Factor VIII?

12 A. Oh, but individuals with severe haemophilia don't have
13 any Factor VIII.

14 Q. Right. I understand you mention elsewhere that you can
15 get a gene deletion. So that would be an example of
16 somebody who wouldn't have any Factor VIII. Is that
17 right?

18 A. Yes, but you can get other genetic abnormalities
19 resulting in no production of Factor VIII.

20 Q. Right.

21 A. So those individuals see Factor VIII as a foreign
22 protein, like a flu virus, and they make an antibody
23 against it. There are other people who have
24 a Factor VIII with reduced activity, in mild
25 haemophilia, say 10 per cent activity of Factor VIII.

1 If they receive large doses of Factor VIII, particularly
2 under particular circumstances, they are actually only
3 tolerant to their own Factor VIII. They recognise their
4 slightly abnormal molecule as their own. So when you
5 transfuse them with Factor VIII to treat their bleed,
6 that Factor VIII is structurally slightly different from
7 their own Factor VIII. They then may make an antibody
8 against that so it neutralises the transfused
9 Factor VIII. And to complicate matters further, that
10 antibody may then cross react with the patient's own
11 Factor VIII and reduce the basal level to nought. So
12 a mild haemophiliac suddenly turns into an individual
13 with severe haemophilia and severe haemophilia with an
14 inhibitor.

15 Q. Right. So it is not just people with no Factor VIII who
16 can develop inhibitors?

17 A. That's correct.

18 Q. Yes, it is people with abnormal Factor VIII. Is there
19 any other group of people who can develop inhibitors?

20 A. They can arise spontaneously. It tends to be in older
21 people, with an instance of about 1 in 1 million. We
22 see about one patient a year with acquired haemophilia
23 and they can be very difficult to treat.

24 Q. So when a patient has developed inhibitors, is that it
25 as far as concentrate treatment is concerned? You have

1 to think of something different?

2 A. There are two things. One is how we treat a bleed in
3 someone who has an inhibitor, and that depends on the
4 level of the inhibitor. If it is a very low level
5 inhibitor then you can give large doses of Factor VIII
6 and as it were, neutralise the inhibitor. If it is what
7 we call a high level inhibitor, then however much
8 Factor VIII you give, it is immediately neutralised.

9 So we use currently two other medicines. One is
10 called FEIBA and one is called Recombinant 7A. Both
11 those are effective in stopping bleeding in inhibitor
12 patients. It is not as good as treating a patient with
13 haemophilia who doesn't have an inhibitor with
14 Factor VIII but --

15 Q. FEIBA has been around a long time.

16 A. FEIBA has been around for a long time but you are then
17 left with the other problem in a child who has an
18 inhibitor, of trying to get rid of that inhibitor, and
19 what emerged from studies in the Bonn haemophilia centre
20 is that if you treat these children with huge doses of
21 Factor VIII, sort of industrial doses of Factor VIII
22 each day, after about a year or two, in about
23 80 per cent of children the inhibitor actually
24 disappears and the patient then responds to Factor VIII
25 normally.

1 Q. Right. If I'm following -- this is a dangerous question
2 because I may not be -- this description of inhibitor
3 formation would make it seem as though inhibitors are as
4 likely to develop, or were as likely to develop whether
5 the concentrate used was commercial or NHS.

6 A. That's correct.

7 Q. Right. But of course, there are other immune responses
8 which might happen in a recipient which are due to the
9 material other than the Factor VIII, and that would
10 depend, I suppose, on how pure the product was.

11 A. That's also correct. I should perhaps qualify my
12 previous answer, when you asked the difference between
13 NHS and commercial. Commercial includes recombinant
14 Factor VIII these days, and there is an important
15 question before the haemophilia community at the moment
16 as to whether inhibitors arise more frequently in
17 patients treated with recombinant Factor VIII.

18 Q. All right.

19 A. The supposition being that maybe some of the contaminant
20 proteins, the non-Factor VIII containing proteins in
21 plasma-derived concentrates, may actually be beneficial
22 and suppress the development of inhibitors.

23 Q. And that's the point I think you make in the second
24 bullet there, is it?

25 A. The one that ends with the Sippet.org.

1 Q. Yes?

2 A. That's the study that's being mounted by
3 Professor Mannucci in Milan.

4 Q. I guess that's a current major "trial" rather than
5 a current major "trail", is it?

6 A. Trial, yes.

7 Q. Going on to the next page, you talk about potency. And
8 there is obviously a huge difference between the early
9 Factor VIII concentrates and currently available
10 products?

11 A. Yes.

12 Q. The corollary being that you need very much less in your
13 syringe with the modern product?

14 A. Yes.

15 Q. And you say that purity and potency are bound up
16 together because lower purity concentrate requires
17 a larger volume of diluent for a reconstitution and that
18 gives you a lower potency product. Then you go on to
19 instance a particular difficulty and we will come back
20 to that because it links in with your use of commercial
21 product.

22 Having looked at purity and potency, can we move to
23 page 14 of this same document, please. "Home therapy".
24 Again you give us quite a lot of information, professor,
25 and a table showing the UK as a whole in 1980 and then

1 Edinburgh in 1979 and 1980. Large use of commercial.
2 Edinburgh in 1979 under Dr Davies' stewardship, no
3 commercial product. Then 5 per cent of the product used
4 in 1980 was commercial. We worked it out to be slightly
5 higher than that but I'm not going to get bogged down in
6 single figure percentages. You refer back to the
7 historical policy. At the beginning of 1980, this is
8 reading from this paragraph, you say:

9 " There were only six patients on home treatment out
10 of a population of 187 patients registered with
11 Haemophilia A."

12 Do you think the patients felt that they were in
13 a very backwards centre because they heard of people in
14 the rest of Britain on home treatment and they weren't?

15 A. There was a lot of enthusiasm for home treatment and
16 I was being continually asked about it.

17 Q. And we have heard that there are weekends organised by
18 the Haemophilia Society. That must have been a big
19 topic for discussion when patients met people with
20 haemophilia from other parts of Britain?

21 A. Indeed.

22 Q. You have set out for us how the number on home treatment
23 increased from 1976.

24 Can we go to [\[PEN0150385\]](#) at page 11 and also
25 [\[PEN0150468\]](#) at page 1. Maybe if we could juxtapose

1 them.

2 This document that's coming, Professor Ludlam, is
3 really more of a timeline or a chronology, and we see
4 that you drafted it in about 1988. So we accept that
5 it's not a recent piece of work. Your timeline begins
6 in June 1981, like many we have seen, with that
7 reference to the MMWR. I don't need to go to it but
8 I did want to ask, when you move into 1982, about
9 a symposium that took place in Stirling in June 1982.
10 Its full title is:

11 "The second international symposium on infections in
12 the immuno-compromised host."

13 We have been told that it actually occurred in
14 Stirling in June 1982. Were you at that?

15 A. No.

16 Q. No. Does it ring any bells? Do you remember --

17 A. No.

18 Q. No, right. It was actually Professor Hann who drew our
19 attention to it. So I think we will save that for him.

20 Then you refer to the publication in July 1982 in
21 MMWR, three patients with haemophilia who had
22 pneumocystis pneumonia. And you paraphrase that for us.

23 There is also perhaps to be inserted in 1982 -- and
24 I suppose we should have put it above the July
25 reference -- a reference [\[LIT0010566\]](#). This is another

1 MMWR. It's 11 June. This one we refer to in the
2 preliminary report but you will see from the first
3 paragraph, Professor Ludlam, that:

4 "Of the 355 reports that had been received at CDC,
5 79 per cent were homosexual or bisexual men, 12 per cent
6 were heterosexual men, 6 per cent were men of unknown
7 sexual orientation and 4 per cent were heterosexual
8 women. This proportion of heterosexuals is higher than
9 previously described."

10 So we can see that even by June 1982 it was evident
11 that people who were heterosexual were being affected.
12 I suppose we can see that there has been a search for
13 the best way in which to classify people who were
14 getting this new disorder and one approach seems to have
15 been in terms of sexuality, and that's reflected here.
16 But I suppose there was no one obvious way in which to
17 classify people. When you are looking for the aetiology
18 of a new syndrome, it may depend on all sorts of things
19 and the classification you choose may be completely
20 misconceived, I suppose. Is that right?

21 A. I think so, yes.

22 Q. But nonetheless it's evident that by this stage it has
23 been noted that some people who are getting this,
24 whatever it is, are heterosexual. So it is not confined
25 to those of homosexual orientation. The other thing

1 that we can see from this particular report, if we go
2 down, is that in the mind of the writer or writers the
3 question of intravenous drug use is featuring. So is it
4 reasonable to say that even by June 1982, those in the
5 CDC were very much thinking about transmission and
6 possible roots of transmission? So that would be why,
7 looking at intravenous drug use would be of interest?

8 A. Yes.

9 Q. Yes. Can we go back to that statement, please? That's
10 [\[PEN0150468\]](#). We can close down the MMWR for just now.

11 You say that:

12 "During 1982 it became apparent that fatal
13 Pneumocystis and Kaposi's sarcoma were spreading
14 epidemically in homosexual populations. Homosexuals
15 were also noted to be at risk of a syndrome of
16 Persistent Generalised Lymphadenopathy."

17 Then you mention non-Hodgkin's lymphoma. It looks
18 in fact as though it was a particular form of
19 non-Hodgkin's. It was diffuse undifferentiated
20 non-Hodgkin's lymphoma that was particularly striking
21 people. I don't know if you recall that, but that's
22 what's mentioned in the MMWR you refer to.

23 A. Yes, okay.

24 Q. Right. It seems that the syndrome at that point was
25 being described, at least by some people, as KSOI

1 syndrome. So that would be Kaposi's sarcoma
2 opportunistic infection syndrome, would it?

3 A. Yes.

4 Q. In fact I had hoped that we had the 4 June 1982. We do
5 have it in hard copy, the MMWR, but we don't have it on
6 the screen. But, sir, I think we will arrange for it to
7 be available in the court book. Simply, at least, note
8 that what it seems to be saying, as a kind of
9 conclusion, is that these particular patients are
10 suffering from very unusual tumours and opportunistic
11 infections. I suppose that fits with calling it KSOI
12 syndrome.

13 Then going back to that timeline, if we go down
14 a little bit further, you say:

15 "September 1982 AIDS diagnosed in drug addicts."

16 First date. At this point, because we are
17 in September 1982, I just wanted to mention the UKHCDO
18 meeting on 13 September 1982. We have a note -- and I'm
19 not going to go to it because we looked at it last
20 week -- that was prepared at that meeting by Dr Boulton
21 who was one of those who attended from Scotland, and he
22 has written down in his note that the cases in the
23 people with haemophilia -- that is the three people
24 whose cases are reported in the July 1982 edition --
25 were possibly associated with parenteral drug abuse. We

1 have looked at the MMWR and not only is there no
2 reference to these patients using intravenous drugs, it
3 actually says there is no history of intravenous drug
4 use. I just wondered, do you have any idea how it could
5 be being said in September 1982 that there might be this
6 association?

7 A. I wonder whether Dr Boulton misheard what was being
8 said.

9 Q. The other point I suppose that strikes us when we look
10 at the actual minutes of the meeting is that what's
11 referred to as a possibility that blood products may be
12 involved in the MMWR report in July becomes a remote
13 possibility in the minutes of the UKHCDO meeting. What
14 do you think would be the explanation for that?

15 A. Only that this was three out of 20,000 people with
16 haemophilia.

17 Q. Right. Do you think it is possible that the tone of the
18 discussion in September 1982 led to a sort of
19 understatement of the possible connection because
20 haemophilia clinicians would very much not want there to
21 be a connection?

22 A. No, I don't think so. I have vague recollections of the
23 meeting and it was brought up towards the end of the
24 meeting, as I recall, and possibly even "under any other
25 business", and it was, "There has been this report.

1 What should we be doing about it? What do people know
2 about it?" This was only two months or so after the
3 MMWR report. I should say that the MMWR report is not
4 something that we all read every week, or took. It's
5 a minor publication that most of us had never seen until
6 HIV and AIDS came over the horizon. It was filed away
7 in a discrete part of the library. It really didn't
8 cross our horizons at all because we weren't, apart from
9 hepatitis, in the infectious diseases business and
10 that's what a lot of the MMWR reports are about.

11 Q. So I suppose, even though it is American, people in the
12 United Kingdom in the infectious diseases world would be
13 much more interested --

14 A. I'm sure they would read it. It would also have to come
15 by airmail so although it is dated, whenever it is
16 in July -- 16 July -- it would take a month or so to
17 come.

18 Q. I think our impression is that PFC also took the MMWR,
19 but we can certainly ask them.

20 Then you mention December:

21 "An additional four cases of AIDS in haemophilia.
22 No common batches identified."

23 Common batches of concentrate were identified and
24 then the first case of transfusion-associated AIDS in
25 California, in a 20-month old infant after multiple

1 transfusions. We can look in more detail at that
2 shortly.

3 Then, January 1982, first reports of two cases of
4 AIDS in female sexual partners of IV drug addicts with
5 AIDS. So just that last reference, the January 1983 one
6 about AIDS in female sexual partners of IV drug addicts,
7 that points clearly in the direction of something that's
8 sexually transmissible, does it?

9 A. It is suggestive, although I presume that there was
10 absolutely no evidence of even a single injection in
11 either of these women from their partner.

12 Q. Right. Can we look at the other side, the left-hand
13 side, please? We see the same reference to the report
14 in June 1981, a reference to non-Hodgkin's, and if we
15 just go slowly down that, we see you discuss, a little
16 bit, PGL. You say:

17 "It was difficult to reconcile this evidence
18 indicating an apparent active immune state with the
19 subsequent development of clinically profound immune
20 deficiency."

21 Over on to the next page, please:

22 "The aetiology of AIDS was unknown and was the
23 subject of much speculation."

24 We are going to come to look at that in a little
25 more detail, all of that paragraph. You say:

1 "During 1982 it also became apparent that AIDS was
2 occurring with increasing prevalence in intravenous drug
3 abusers in the USA."

4 That's another MMWR reference. You have a table,
5 which we will come to look at later. You say:

6 "It is pertinent to note the relatively high
7 prevalence of AIDS in the USA, compared with most
8 countries in western Europe in 1982 to 1984. Although
9 the first AIDS cases were reported in the USA in 1981,
10 it was not until 1983 that a small number in England
11 were identified."

12 There is, of course, the case that was mentioned in
13 the Lancet in 1981. We discuss that in our preliminary
14 report, paragraph 8.8. Perhaps we could just have
15 a look at that briefly, if we could. That's page 188 in
16 the hard copy and [\[LIT0012479\]](#), page 3. Towards the end
17 of paragraph 8.8 there is this reference to the person
18 who had been treated at the Brompton Hospital in London
19 and the hospital in Bournemouth. Actually, Dr Winter
20 was working in London at the time. He could recall this
21 being a talking point.

22 So there was that one in the UK, and then we also
23 noted, if we could just look at the following page,
24 please, paragraph 8.13, that the BMJ of 3 July 1982 had
25 an article about severe Acquired Immuno-deficiency in

1 European homosexual men, and that was describing four
2 Danish men with KS or opportunistic infections. Three
3 of them had never been to the United States of America.

4 So I take your point, Professor Ludlam, that the
5 numbers are very different as between western Europe and
6 the United States, but it had happened in Britain and it
7 had happened in Denmark as well in individuals, three of
8 whom had never been to America.

9 Can we go now, please, to [\[PEN0150445\]](#)? This is
10 back to your statement. So, having dipped into the
11 chronology up to a certain point, we now look at this
12 section in your statement on page 2 entitled, "Potential
13 causes of AIDS".

14 Actually, I wonder, sir, this is quite a big chunk.
15 Maybe it would be better to start it after lunch.

16 THE CHAIRMAN: I think so. Are you going to raise with the
17 professor the history given by Professor Forbes?

18 MS DUNLOP: You mean the Ratnoff and Menitove paper?

19 THE CHAIRMAN: Yes.

20 MS DUNLOP: Professor Ludlam has a copy of it, which I gave
21 him this morning, sir, and I have said to him that I'll
22 give him time and I'll ask him about it tomorrow. Is
23 that adequate?

24 THE CHAIRMAN: That's adequate. What I'm interested in, of
25 course, is not just the paper but whether, within the

1 haemophilia doctors circle, if I can call it that, there
2 was any dissemination of the information that
3 Professor Forbes had, so if you could cover that as
4 well. I'm happy to leave it.

5 MS DUNLOP: Thank you.

6 (12.54 pm)

7 (The short adjournment)

8 (2.00 pm)

9 THE CHAIRMAN: Yes?

10 MS DUNLOP: Yes, sir.

11 Professor Ludlam, although we were at a certain
12 point in your statement, when we stopped for lunch,
13 before we go back to that, I think it is probably useful
14 to ask you a couple of questions, which relate to 1981
15 and I'm going to ask you to have a look at a couple of
16 documents.

17 The first is a minute of the meeting of the
18 directors of SNBTS and the haemophilia directors in
19 St Andrew's House on 30 January 1981, and actually you
20 mention this in your evidence, that there was one of
21 these larger meetings in January 1981. The reference
22 for it is [\[SNB0015055\]](#).

23 For what it's worth there is quite long paragraph in
24 this about recognition of Glasgow and Edinburgh as
25 reference centres. That's paragraph 9. But that wasn't

1 why I wanted you to look at it. It was because of the
2 reference to commercial purchases of Factor VIII. You
3 see at the bottom of the first page -- this is really
4 paragraph 3(c) -- it says that:

5 >Data provided for 1979 and 1980 showed that a
6 significant and apparently increasing quantity of
7 commercially produced Factor VIII was being used. The
8 reasons for this were discussed. Sometimes only
9 a commercial product was available."

10 Said somebody:

11 "There were also occasions when, for clinical
12 reasons, a high purity product was required."

13 If we could just go back to the first page of that
14 again. This is during Dr Willoughby's time at Yorkhill
15 but we can see from the minutes of that meeting that
16 Dr Pettigrew, actually, subbed for him at that meeting.
17 And you were there.

18 Then at more or less the same time, March 1981, if
19 we go to another document, please, [\[SNB0015064\]](#). This
20 is the working group, which is meeting on 4 March 1981.
21 So really only about five weeks after the meeting we
22 just looked at, and you were on the working group at
23 that point as well.

24 Paragraph 6, which is on the second page:

25 "Concern was expressed at the level of commercial

1 material being purchased. It was agreed that the aim
2 must be for the NHS in Scotland to be self-sufficient."

3 I suppose it is very unlikely you remember either of
4 these meetings as meetings, Professor Ludlam, do you?

5 A. Just a little bit. Not very much.

6 Q. Right. Do you remember round about the spring of 1981,
7 quite a focus on how much commercial material was being
8 bought and why?

9 A. I don't think I can answer that question actually. From
10 my recollection of the discussion, I obviously read here
11 ...

12 Q. It looks, professor, as though around about that time,
13 the explanation for the large amounts of commercial
14 material being purchased must have been largely The
15 Royal Hospital for Sick Children in Glasgow. Do you
16 remember that?

17 A. Well, I remember that but I also remember there was
18 a substantial shortage of NHS Factor VIII concentrate.

19 Q. You see, I just wondered, Professor Ludlam, in light of
20 what you were saying this morning about the patients in
21 Edinburgh using only NHS material and about how your
22 group included some children, there was obviously
23 a difference of practice between Glasgow and Edinburgh
24 at that time, and Dr Willoughby, in particular, as far
25 as we can make out, seems to have been very keen to

1 introduce home therapy and to use commercial product.
2 What can you tell us about that?

3 A. I can tell you that he was a very good, enthusiastic
4 paediatric haematologist and he was, I think, wanting to
5 treat his patients almost certainly more aggressively
6 that I was able to. I read recently that he was
7 introducing prophylactic treatment. That was very
8 go-ahead for the UK at that time. Clearly, the type of
9 therapy he was wanting to give needed to be concentrate
10 rather than cryoprecipitate, and I imagine he had had
11 difficulties in getting sufficient supply of NHS
12 concentrate that he thought was of a suitable quality to
13 give to small babies, small children.

14 Q. Did you ever have any conversations with him about it?

15 A. No.

16 Q. What was the atmosphere of the time? I don't mean to be
17 disrespectful but was everybody really doing their own
18 thing, as between Glasgow Royal Infirmary, Edinburgh
19 Royal Infirmary, Yorkhill?

20 A. We were working much more independently as separate
21 units than we did from, shall we say, the mid 1980s,
22 onwards, where the directors of all the centres would
23 meet regularly to promote the service in a unified way
24 across Scotland. Before that, they were more separate
25 institutional activities.

1 Q. Do you have any knowledge about the establishment of
2 Yorkhill as a separate haemophilia centre?

3 A. No.

4 Q. Right. Just the other thing before we leave these
5 minutes that we see in front of us, to look at
6 paragraph 7 onwards, the chairman, and that was
7 Dr George McDonald, who was from
8 Glasgow Royal Infirmary:

9 "The chairman invited Dr Cash to comment on the
10 proposal that freeze-dried cryoprecipitate be produced
11 with a view to studying, on a multi-centre basis, its
12 role in home therapy."

13 Then Dr Cash appears to have gone on to speak in
14 favour of cryoprecipitate, paragraph 8. Interestingly
15 perhaps in light of what we have recently seen, the last
16 sentence of paragraph 8:

17 "The majority of home therapy patients had no
18 problems when using cryoprecipitate and in Belgium it
19 was used extensively. The chairman suggested it could
20 be an R and D project, research and development.
21 Dr Foster said PFC didn't have resources. There was
22 a study being undertaken in the West of Scotland ...
23 which was being extended to include children with the
24 help of Dr Willoughby. Dr Ludlam expressed his interest
25 in the treatment of children, particularly the need to

1 protect them from the problems of liver disease and
2 hepatitis."

3 So should we take it from your evidence this morning
4 that you would not have been at all enthusiastic in this
5 discussion about the proposals to consider more
6 cryoprecipitate use?

7 A. There was a project -- I'm just seeing whether it was
8 referred to here -- in the West of Scotland to produce
9 small pool cryoprecipitate and that never really got the
10 resources to get off the ground, and it is not an
11 approach that has received much support elsewhere.

12 I think I was, as you see, interested in the use of
13 small pool treatment if it was convenient and suitable
14 for children. There was a number of different ways
15 actually of making cryoprecipitate which would alter the
16 purity of it and therefore the propensity to reactions.

17 Q. Right.

18 A. I accept that there is a spectrum of opinion, both in
19 how children should be treated and in whether or not
20 cryoprecipitate is suitable to use at home, and you have
21 seen some of the spectrum from me today.

22 THE CHAIRMAN: Professor, were you aware of any particular
23 preference for the use of cryoprecipitate in the West of
24 Scotland, leaving Yorkhill aside?

25 A. No.

1 THE CHAIRMAN: That never came to your notice?

2 A. A preference for cryoprecipitate?

3 THE CHAIRMAN: Yes.

4 A. I can't recall it and at one of these meetings we
5 considered the Council of Europe recommendations on
6 self-sufficiency, and in that one of the recommendations
7 is that cryoprecipitate should only be used if
8 a concentrate is not available.

9 MS DUNLOP: To reassure you I should let you see the next
10 page, to show that that was the end of that particular
11 discussion.

12 There doesn't really seem to be anything else about
13 cryoprecipitate use, at least in those minutes.

14 Right. We can put the 1981-minutes aside now, thank
15 you, and go back to your statement, [\[PEN0150445\]](#). If we
16 could go to page 2, please. Just at that numbered
17 heading, "Two potential causes of AIDS". You say:

18 "In the earlier 1980s there were many potential
19 aetiological agents which were considered to be possible
20 causes of AIDS."

21 Then you list the groups of individuals in whom the
22 occurrence of the syndrome had been noted. Then you
23 list some possible aetiological agents:

24 "1. An AIDS-causing virus."

25 Which I take to mean a new virus, in essence,

1 compared to what you go on to say?

2 A. Yes, I think so.

3 Q. So an AIDS-causing virus:

4 "What was it and where had it come from? If so, why

5 had no haemophiliacs in Germany, where large amounts of

6 US commercial concentrates were used, developed AIDS by

7 1983.

8 "2. A previously known virus which had mutated to a

9 virus which caused immune suppression, for example

10 Hepatitis B.

11 "3. A virus known to cause immune suppression, for

12 example CMV or EBV, cytomegalovirus."

13 What's EBV again?

14 A. Epstein Barr virus.

15 Q. That's a glandular fever type illness?

16 A. Yes.

17 Q. Which may have become more virulent. Just at that

18 point, professor, having noted that the first three

19 suggestions are all viruses in the early 1980s, when

20 patients with haemophilia were receiving concentrates,

21 whether NHS or commercial, does it follow that as well

22 as hepatitis, which we know a bit about, there must have

23 been quite a lot of other viruses being transmitted in

24 the concentrates as well?

25 A. Yes.

1 Q. Right. And you have mentioned CMV, EBV and in your
2 curriculum vitae you mention other viruses that you have
3 researched. So I suppose some of these viruses, the
4 only reason we are not having an Inquiry about them is
5 that they didn't really cause much by way of symptoms?

6 A. There were some that were transmitted that appeared to
7 cause no harm. There were some that we appear all to
8 have and to live happily with. There are some, and one
9 in particular is parvovirus, which is a small DNA virus
10 that in small children causes a mild erythematous
11 condition, sometimes called slap cheek condition, which
12 about a third of children get at nursery school when
13 they come into contact with other small children.

14 But a goodly number of people do not get infected as
15 children and this virus is not really susceptible to the
16 solvent detergent technique or heat treatment, and
17 therefore can be transmitted by plasma-derived
18 concentrates.

19 Into adults, who are susceptible, that can cause
20 quite an unpleasant condition of arthropathy,
21 generalised arthritis. It can cause the death of
22 a foetus in pregnancy and it can cause the bone marrow
23 problems in someone who has what we call a haemolytic
24 anemia.

25 That's all well-known. The reason that I think it's

1 an important virus is not for the damage that it does at
2 the moment, but we know it can be transmitted by
3 plasma-derived concentrates. Were that virus or one
4 like it to come into the plasma supply, then we might
5 have an outbreak of some other infection. West Nile
6 fever has been in the news and has been considered in
7 relation to blood safety. It was very fortunate that
8 that was a lipid-coated virus that was sensitive to the
9 solvent detergent technique and heat treatment. Had it
10 not have been, then it might well have been spread by
11 plasma-derived concentrates.

12 So parvovirus is a very valuable, in one sense,
13 model virus. I mean, it has mutated in dogs to a more
14 virulent form and caused an outbreak around the world of
15 a dog infection porcine infection, that was much more
16 fatal.

17 So that is why there is an interest in small DNA
18 viruses.

19 Q. The fourth --

20 A. And one of these could have caused, obviously, immune
21 suppression.

22 Q. The fourth candidate cause, if we go on to the next
23 page, we can see is antigen overload. You say by way of
24 example, semen in the rectum of homosexual men and
25 non-Factor VIII or IX proteins in clotting factor

1 concentrates used to treat haemophilia. I just
2 wondered, professor, I hadn't actually seen antigen
3 overload advanced as a possible explanation for the
4 immunodeficiency in homosexual men. Was that actually
5 a theory that had much currency in the early 1980s?

6 A. I think it had some and potentially exposure to white
7 cells and their antigens in the rectum of men,
8 particularly if there was any mucosal injury and these
9 could be antigenic.

10 Q. Your fifth suggested cause is recreational drugs. For
11 example, amyl nitrate and isobutyl nitrate. But both
12 number 4 and number 5, professor, are surely much less
13 likely, particularly as soon as you had, on the one
14 hand, the three people with haemophilia reported
15 in July 1982, who were all reported as heterosexual
16 individuals, they were 62, 59 and 27 in terms of their
17 age, and also in the December of 1982 the report of AIDS
18 in an infant. Surely both of number 4 and number 5 are
19 much less likely as soon as those events had occurred?

20 A. That is making the assumption that the AIDS in people
21 with haemophilia was of similar aetiology to the AIDS in
22 the other groups, and we know that clinically they were
23 different and so we considered the possibility that
24 actually they had arisen simultaneously, or nearly
25 simultaneously, but were of different aetiologies.

1 Q. I think we will come on to look at how different they
2 were, but you go on to say that:

3 "Even after there was general agreement that
4 HTLV-III was the probable cause of AIDS, there was very
5 considerable uncertainty as to how to interpret an
6 anti-HTLV positive and negative result in an individual
7 person."

8 Then you say:

9 "There was also doubt as to whether this virus was
10 the sole cause. Even up to 1996, reputable scientific
11 and medical journals were giving publication space to
12 non-viral pathogenesis for AIDS."

13 I wanted just to carry on with this theme by looking
14 at [\[PEN0150385\]](#) at page 13, if we could, please. Just
15 looking down through that you mention in this statement
16 as well the report in July 1982 in the MMWR. You say:

17 "These haemophiliacs denied homosexual activity or
18 intravenous drug abuse."

19 If we look at the actual report. That's
20 [\[LIT0010559\]](#). You see in the very first paragraph, when
21 talking about the three people concerned:

22 "All three were heterosexual males, none had an
23 history of intravenous drug abuse."

24 I have seen the form of words that you used,
25 professor Ludlam:

1 "These haemophiliacs denied homosexual activity or
2 intravenous drug abuse."

3 Why do doctors sometimes feel it necessary to say
4 that the patient denied drug abuse, rather than that
5 just simply the patient didn't have a history of drug
6 abuse?

7 A. Well, one is an absolute state of affairs and the other
8 is what you are told by the patient.

9 Q. So do you tend to opt for the form of words that the
10 patient denies something rather than saying -- we can
11 see the MMWR for example, they went for the absolute
12 form. They said:

13 "All three were heterosexual males and none had
14 a history of intravenous drug abuse."

15 A. It's a matter of words. I'm happy with what's here but
16 that presumably is what these individuals -- whoever
17 took the history for this was --

18 Q. It is just a matter of impression, professor. It is
19 just that where you see the words "the patient denied
20 homosexual activity or intravenous drug abuse", and
21 I quite accept that doctors sometimes use those words,
22 but where you see them there is a slight suggestion of
23 doubt which you do not get from the MMWR.

24 A. Well, there are instances where people will have had
25 homosexual activity or used intravenous drugs and who

1 won't want to admit that to the doctor.

2 Q. So can we go back to the statement, please, and just go
3 down through that page. That's 0385. Thank you.

4 You are making a reference to a reference centre
5 directors' meeting on 22 September, and of course we
6 have already looked at the UKHCDO meeting on
7 13 September. But the conclusion of this paragraph is
8 that Dr Craske as chairman of the hepatitis working
9 party had been asked at the meeting to investigate and
10 keep directors informed, which would seem to be what was
11 said on 13 September, but you are telling us there was
12 also a meeting on the 22nd, was there?

13 A. I think it unlikely. I think this must be a mistake --

14 Q. All right. Then:

15 "Haemophilia treaters in the United States were also
16 quick to appreciate that if AIDS was due to a virus, it
17 might be transmitted by Factor VIII concentrates ...
18 This body, The National Haemophilia Foundation Medical
19 and Scientific Advisory Committee ..."

20 We have seen them referred to as MASAC. I suppose
21 an acronym is always handy, isn't it?

22 "... recommended in January that individuals at
23 higher risk of AIDS should be excluded from blood
24 donation."

25 You presumably now know, Professor Ludlam, that

1 there was quite a contentious meeting in America on
2 4 January 1983? Yes?

3 A. Yes.

4 Q. Yes, you are nodding. Dr Evatt was there, as was
5 Dr Aledort, and there was a bit of a difference of view
6 there. We have, I think, already noted that it's set
7 out in considerable detail in Douglas Starr's book
8 "Blood". I don't know, have you read Douglas Starr's
9 book?

10 A. I haven't, no.

11 Q. Right. Well, certainly I think those of us who are lay
12 have found it a good read. Did you hear about this
13 meeting at the time?

14 A. No.

15 Q. Right. If you look at an article that appeared around
16 that time [\[LIT0011589\]](#), we have looked at this before.
17 This is a piece from Science, which I understand to be
18 an American periodical. Did you ever look at it or was
19 it not something that you would be picking up in the
20 Royal Infirmary?

21 A. Science is a reputable scientific journal, like Nature.

22 Q. Do you think you might have seen this at the time?

23 A. I think it unlikely.

24 Q. Right. In fact this is actually describing the meeting
25 on 4 January 1983. Do you see firstly on the left-hand

1 side, Bruce Evatt is mentioned. He told the workshop
2 that AIDS was the second leading cause of death for
3 haemophiliacs in 1982:

4 "Eight haemophiliacs, who had none of the other
5 known risk factors, died from AIDS, compared to some 40
6 who died of bleeding. James Curran ..."

7 Presumably another very well-known name,
8 James Curran?

9 A. Yes.

10 Q. "The sense of urgency is greatest for haemophiliacs.
11 Suspicion has been cast on blood products in addition to
12 clotting factor, however ..."

13 Going on to refer to the infant -- and we will look
14 at the situation pertaining to the infant in a moment.
15 In the middle column we can see some easily achieved
16 consensus about some preventative measures but the
17 seriousness of the threat of AIDS -- and this is looking
18 at the bottom:

19 "The threat of AIDS transmission by blood products
20 and what, if anything, ought to be done in the current
21 state of uncertainty, remain thorny issues. Not
22 everyone agrees with the conclusion, accepted by CDC
23 officials and many other investigators, that AIDS is
24 caused by an infectious agent, presumably a virus, which
25 could contaminate blood products."

1 And then a reference to Dr Aledort. Really,
2 I suppose, two things that are striking, one -- and you
3 rejected this when I put it to you earlier but I'll
4 suggest it again -- that haemophilia clinicians found it
5 particularly difficult to really look at the possibility
6 that blood products were transmitting this infectious
7 agent. I think this is an example of it here, with
8 Dr Aledort, is it?

9 A. I think for Dr Aledort, yes.

10 Q. Right. So he was one of those in the group of
11 haemophilia clinicians internationally who found it
12 particularly difficult to accept?

13 A. I think so, yes.

14 Q. The other thing that's striking is the notion that
15 haemophiliacs -- and this is reading from the last bit
16 of the middle column:

17 "... because they are exposed to a great number of
18 foreign antigens, experience a high degree of antigenic
19 stimulation that effectively wears out their immune
20 system."

21 What's striking about that is that if that were the
22 explanation, that would not really be reassuring, would
23 it?

24 A. No.

25 Q. Then if we turn to the next page, so LIT0011590, we can

1 see mention of Oscar Ratnoff who has featured in our
2 evidence of the past day or two, a haemophilia
3 specialist from Cleveland, proposing that patients with
4 haemophilia might minimise their risk of AIDS by using
5 clotting factor cryoprecipitate. You yourself do come
6 on to mention Oscar Ratnoff and his particular practice.

7 Going back to your statement, please, 0385, and
8 looking where we were, we find your reference to the
9 infant. I think just for clarity, professor, there seem
10 to have been the two reports, one in the MMWR
11 in December 1982, and then it seems to have been written
12 up in the Lancet by Ammann -- I think it's the Lancet --
13 in 1983, but it does appear to have been the same child.

14 I don't know if that has struck you since you wrote
15 this. Perhaps if we just have a quick look first of all
16 [\[LIT0010405\]](#). That's the Lancet piece, 30 April 1983.
17 If we look at the summary, we can see that what had
18 happened was that this child had become ill with various
19 different infections and because he had received
20 multiple transfusions, some research had been done and
21 one of the blood donors, who was well at the time of
22 blood donation, had died 17 months later, apparently of
23 AIDS. But just to link it to the other report, if you
24 look at the case report, where it says the mother was
25 29. This is San Francisco. The infant weighed 2.85

1 kilos at 33 weeks gestational age. History of rhesus
2 sensitisation.

3 If we look at [\[SGH0085105\]](#). It is just so that we
4 are clear. I think there was only one case, although
5 you say an additional infant. If we look at
6 [\[SGH0085105\]](#). If we can go forward to 5108, I think we
7 can see it's the same child, isn't it, professor?
8 A history of rhesus sensitisation, 33 weeks gestation,
9 the infant weighed 2.85-kilos and so on.

10 A. Yes, I'm interested in the title of both these. It says
11 "possible transfusion-associated". It's not saying it's
12 a definite, and I wonder whether, as I'm sure you are
13 aware, children occasionally are born with congenital
14 immune deficiency. An area I have no expertise in. But
15 I just wonder whether there is a possibility that this
16 child could have had a congenital deficiency of
17 immunity, notwithstanding there was also this donor as
18 well.

19 Q. Well, I guess in medicine, professor, it can be very
20 difficult to rule anything out absolutely, but would you
21 agree that on any view in the unfolding story of
22 Acquired Immunodeficiency Syndrome, this was
23 a significant event?

24 A. I think it's a significant event. I don't think it's
25 a clinching event.

1 Q. Right. Can we go back to where we were, please. That's
2 back to 0385 at page 14. Thank you.

3 Pick up the narrative in January 1983:

4 "Two haemophiliacs with PGL ..."

5 You go on to say:

6 "In summary, evidence accumulated from June 1982
7 onwards that AIDS and probably PGL were caused by an
8 agent that could be transmitted by blood. Although it
9 became apparent in the latter part of 1982 that
10 haemophiliacs may have been at risk of AIDS, this did
11 not appear to be substantial as, by January 1983, only
12 eight cases out of a total haemophiliac population of
13 approximately 20,000 in the USA had developed AIDS."

14 Then you talk about the total number of reported
15 cases increasing in 1983?

16 A. Could I just interject that in the second line it says:

17 "Seven had received blood components other than
18 Factor VIII concentrate."

19 So they might have received an infectious agent from
20 those units of blood.

21 Q. Right. But certainly -- and I think this is really what
22 you are saying yourself, aren't you -- the evidence is
23 leading one away perhaps from possible causes 4 and 5,
24 the antigen overload, and the recreational drugs, as far
25 as an explanation for the syndrome in the various people

1 who have developed it is concerned?

2 A. I'm not sure that it moves us away from the -- if I can
3 call it this -- antigenic overload theory. I think
4 that's still on the table.

5 Q. All right. We will come back to that too. Then the
6 mention of Europe. You say:

7 "In the UK the first suspected case was identified
8 in May 1983."

9 And there is a reference again to Germany. We will
10 develop that. But to do so we need to go to your
11 timeline again, [\[PEN0150468\]](#). And pick up the narrative
12 at the bottom of page 1. We had gone before lunch just
13 to that one in January 1983, which was actually the end
14 of volume 31, I think, of the MMWR. Just because you
15 made the point, professor, before lunch about the female
16 sexual partners that, as you pointed out, it would be
17 relevant to know whether these ladies, who were the
18 partners of intravenous drug users, were themselves drug
19 users, and we checked the MMWR over lunch and if we can
20 go back to the context. It is the latter form of words,
21 if you like, in that, that they are said to have denied
22 intravenous drug use.

23 So it certainly looks as though, from the point of
24 view of the CDC, that they had considered, well, was
25 there an alternative explanation than sexual

1 transmission for these ladies acquiring the syndrome,
2 and they, at least on the say-so of the ladies, could
3 rule out that they were also drug abusers.

4 Two cases of PGL in haemophiliacs. This is actually
5 a report from Margaret, is it Ragni or Ragni?

6 A. Ragni.

7 Q. You say that on the next page, if we turn over, staying
8 in January 1983:

9 "There was a meeting at Heathrow Airport
10 in January 1983 ..."

11 You say in your other statement you actually don't
12 remember it but just for our narrative, could we look at
13 the preliminary report at paragraph 8.19. This is
14 page 191. It will be [\[LIT0012479\]](#), page 6. The format
15 looks to have been, professor, arranged with Immuno, an
16 Austrian drug company; is that right?

17 A. Yes.

18 Q. And they were keen to talk about their research into
19 methods of reducing or eliminating the risk of
20 transmission of NANB. So their note of the meeting
21 didn't mention AIDS very extensively, but in the
22 afternoon Dr Craske spoke to the assembly and we quoted
23 what he said. So he seems to have imparted further
24 information on 24 January 1983. There are now 800
25 people reported as suffering from AIDS in the

1 United States. With a 45 per cent mortality. 10
2 haemophiliacs in the United States have been infected
3 and five have died. The youngest was aged 7. All cases
4 have had prolonged treatment with Factor VIII. Then
5 there is the mention of the 20-month old child as well.

6 Although you were there, you do not really remember
7 this meeting, I gather?

8 A. I have seen the minutes from it. I can quite believe
9 I was there but, I'm sorry, I don't remember it.

10 Q. So we can put the preliminary report to one side then,
11 thank you, and go back to your timeline. [\[PEN0150468\]](#)
12 at page 2. You refer to the editorial in the New
13 England Journal of Medicine, questioning whether it
14 would be prudent to switch to cryoprecipitate. We
15 mentioned this last week too. I think in fact
16 Professor James researched afterwards Dr Desforages and
17 ascertained that she was a haematologist as well. You
18 knew that, did you?

19 A. I did a little research to try and found out whether she
20 had switched her practice and I couldn't find Ragni
21 follow-up to this. I have to say she is not a name that
22 I recognise as being in the haemophilia community of
23 treaters but clearly she did have a practice and this
24 was her suggestion, but nowhere has she, as far as
25 I could ascertain, published how successful she had been

1 in changing.

2 PROFESSOR JAMES: She was the head of the haematology
3 laboratory and haematology department, I think at Tufts,
4 one of the Boston medical schools. So I don't think she
5 ever was a treater of haemophiliac patients. She was
6 also an associate editor of the New England Journal. So
7 probably she had been asked as a haematologist rather
8 than a haemophilia practitioner.

9 MS DUNLOP: You cover this editorial in a little more
10 detail, Professor Ludlam, in your statement, properly
11 so-called, which is [\[PEN0150445\]](#) at paragraph 15. You
12 discuss that in a bit more detail. You say that
13 Dr Desforges seems to have been partly basing her
14 proposal:

15 "... on the fact that the immune system of
16 recipients of cryo appear to be normal compared to
17 concentrate users but we now know that the immune
18 changes are not a good reflection of the presence of
19 infection by HIV."

20 Would it be correct to say, professor, if one were
21 using immune changes as a marker for infection by HIV,
22 that this would be a sort of marker where you would get
23 a lot of false positives? But the false negative rate
24 would be very low, would it not?

25 A. No, the false negative rate might be significant in

1 early HIV infections.

2 Q. Right, in the window period?

3 A. Even for the first year or two perhaps. Because these
4 immune tests have quite large normal ranges and
5 therefore it may be difficult. To say that a patient is
6 outwith the normal range, they may have to be quite
7 a long way outwith what might be their basal level. We
8 know the levels from the studies we have done are
9 relatively constant without HIV, and therefore if you
10 have someone who has a high level and they get HIV
11 infection, it may be a long time before it reaches the
12 bottom end of the normal range.

13 Q. Right. Okay. We can go back, I think, to the timeline.
14 That is 0468.

15 Moving through March. Also the reference to the
16 Annals of Internal Medicine. We have looked at that as
17 well. Perhaps we should just quickly look again at
18 [\[LIT0010047\]](#). Actually, professor, from your reference
19 I think you are looking at an editorial which appeared
20 on 403, whereas we looked last week at the one which
21 began on 401, which is in front of you now. This is
22 introducing an issue which appears -- and if you look at
23 the third paragraph -- to have contained six articles,
24 all of which lent further support to the transmissible
25 agent hypothesis. Annals of Internal Medicine. Would

1 that be something that you would have read at the time?

2 A. It wasn't one of the regular ones but I could easily
3 have had access to it if it had been referred to
4 somewhere else.

5 Q. Certainly it is striking for the figures it gives about
6 how many donors, as it were, a person with severe
7 haemophilia might be exposed to in a year. I think
8 actually from the figures given towards the bottom of
9 the page, one can easily rack up a total of not just, as
10 the editorial says, tens of thousands of donors a year
11 but even hundreds of thousands of donors per year. And
12 a given donor potentially exposing approximately 100
13 people.

14 Then at the bottom of the left-hand column on the
15 second page, the comment:

16 "Among patients receiving blood products, those with
17 haemophilia will continue to be at highest risk."

18 Unfortunately, as I say, we don't have the whole of
19 the White reference, which is the one you make, but if
20 we look at page 3, LIT0010049. It's the page 403 in the
21 actual journal.

22 I think that must have been the particular editorial
23 that you were referring to, Professor Ludlam. You say
24 that the author is White:

25 "Had reduced surgery and switched a few patients

1 from Factor VIII concentrate to cryoprecipitate."

2 Can we go back then to the timeline, back to
3 [\[PEN0150468\]](#) at the second page?

4 You then refer to an editorial in the Lancet
5 in April, which itself referred to the New England
6 Journal of Medicine and the Annals of Internal Medicine.
7 Do you know who wrote this editorial in April 1983?

8 A. No.

9 Q. Right. And similar sorts of questions indeed to those
10 I think you have posed yourself, about why German
11 haemophiliacs hadn't got AIDS, they being heavy users of
12 American concentrate:

13 "No strong argument for a change of treatment
14 policy."

15 You refer also to this in your other statement,
16 [\[PEN0150445\]](#) at paragraph 20. How did the Lancet
17 recruit individuals to write its editorials? Was there
18 a panel of people who wrote them or were people from the
19 particular field invited to come?

20 A. I think the editor tries to find someone who is
21 particularly knowledgeable and writes a begging letter.

22 Q. Right. I see.

23 A. I don't think they have a panel. I think it depends on
24 the subject. They look for the best person who can
25 provide them with an article.

1 Q. Right. Can we go back to the timeline? That's 0468,
2 please, just to note the bottom of that page. We are
3 in April 1983. Then there is a reference to an article
4 suggesting that:

5 "Alloantigens in Factor VIII concentrate induce
6 immune changes."

7 What's an alloantigen?

8 A. It is an antigen that an individual may not have but
9 another person does have so that, when they are
10 transfused with it, they may develop an antibody to it
11 or at least some immune reaction.

12 Q. Then can we move to the next page, please? There is
13 a reference to the work of Barre-Sinoussi and others.
14 And further report of immune abnormalities in
15 haemophiliacs. This is May 1983.

16 I thought at this point, professor, we could try to
17 get to the bottom of the British people with haemophilia
18 who were thought to have AIDS in 1983. Because I think
19 it's possible to get a little confused. In the first
20 place can we look at [\[DHF0014328\]](#). Sorry, I think it
21 has another reference. Oh, yes. First of all, do you
22 see, if we go right to the top, I think we can get
23 a date, yes, 2 May 1983, and if we look particularly at
24 the Daily Mail, which is on the left, we can see:

25 "Government health experts have begun investigating

1 the possibility that Britain is importing blood products
2 from America contaminated with the killer homosexual
3 disease, AIDS. The action follows the discovery that
4 two men given routine blood transfusions for haemophilia
5 are now seriously ill, apparently suffering from the
6 disease. Disclosure of the men's illness and their
7 treatment at hospitals in Cardiff and London was made
8 exclusively yesterday in the Mail On Sunday."

9 So that's one reference. Can we go to [\[PEN0150244\]](#),
10 please? This is a CDSC report. Have you seen this
11 before?

12 A. Yes, I have. But I'm not sure of the date. It has been
13 scored out.

14 Q. The week ending 6 May 1983.

15 A. Right.

16 Q. We can just see that. I think there is a piece of
17 highlighting unfortunately that goes right across the
18 date but it's 6 May 1983.

19 A. Yes.

20 Q. We can see Acquired Immunodeficiency Syndrome, Cardiff.
21 This is said to be the first report of AIDS in a patient
22 with haemophilia in the United Kingdom known to CDSC.
23 This is a 20-year old man in fact.

24 A. Sorry, does oral oesophageal candida put someone in the
25 AIDS category? I'm sorry. I have forgotten from the

1 classification that was around at the time.

2 Q. I'm deferring to Dr Galbraith here, Professor Ludlam.

3 He has certainly put this patient in the category.

4 That's certainly a matter we can put to other witnesses.

5 A. It is easy enough to check up afterwards.

6 Q. That's a puzzle. Certainly at the time it looks as

7 though some people at least were treating this as

8 looking like the first report of AIDS in a patient with

9 haemophilia in the UK.

10 A. I may be wrong. As you know, there are very stringent

11 criteria for indicating that an individual had AIDS at

12 that time.

13 Q. Yes. And then --

14 THE CHAIRMAN: Had a formal definition been developed by

15 this stage?

16 A. 1983 -- May 1983? Yes. It was a clinical definition if

17 you got an opportunistic infection like pneumocystis or

18 Kaposi's sarcoma, for example, as a tumour. That put

19 you in the category of having AIDS.

20 PROFESSOR JAMES: I think I agree with you. At that time if

21 you just had oesophageal candidiasis, I don't think you

22 would have been classified as having AIDS without

23 something more than that.

24 A. It will be easy enough to check.

25 PROFESSOR JAMES: Yes.

1 A. -- out and the relevant literature is in your court
2 book.

3 MS DUNLOP: Yes. I'm sure of that, professor, but I'm
4 really more interested in the way that these cases were
5 seen at the time, and certainly by CDSC, who are
6 operating more in the realm of infectious diseases than
7 in virology or haemophilia treatment, it looks as though
8 they were treating this as a possible case at least of
9 AIDS in person with haemophilia.

10 The other case we can see referred to on
11 [\[DHF0015006\]](#). That article "US blood caused AIDS",
12 seems to refer to the other person. You see:

13 "The British haemophiliac who died from AIDS, almost
14 certainly caught the disease from contaminated supplies
15 of the blood clotting agent."

16 This looks to have been a patient treated in Bristol
17 and this is somebody who was written up in the Lancet.
18 I think we have worked out before that this seems to
19 be November 1983. Just to establish, professor, that
20 the two men referred to in the newspaper cutting appear
21 to have been, one, a patient in Cardiff and, two,
22 a patient in Bristol. That looks to have been the
23 situation, doesn't it?

24 A. At very different times. Six months apart.

25 Q. Well, yes, but if the Daily Mail was able to refer to

1 two people, it does look as though there were people in
2 Bristol and Cardiff. We can see that reference in the
3 Guardian which also mentions the patient in Cardiff.

4 A. Yes, I mean, I think the Bristol one was diagnosed with
5 AIDS earlier than November 1983.

6 Q. Right. When we look at what was said in relation to the
7 Council of Europe report, which also gives us some
8 information on how many patients with haemophilia in the
9 United Kingdom seemed to be developing AIDS at this
10 time. We can look at [\[DHF0014394\]](#). I don't imagine you
11 had seen this before, Professor Ludlam?

12 A. Yes, I have.

13 Q. You have? Right. When did you first see it? Recently?

14 A. Recently, yes.

15 Q. You see, it's a report for the committee of experts on
16 blood transfusion and immuno-haematology for their
17 meeting in May 1983, and the actual date of it is
18 28 April 1983. It is narrated as information on the
19 present situation in Council of Europe member states and
20 in other countries represented on the committee. But
21 the information that appears to have been supplied for
22 Germany in this is that there were two people with
23 haemophilia. Could you turn to page 4, DHF0014397. You
24 see that reference there, that the Federal Republic of
25 Germany appeared to have sent a report that they had two

1 patients with haemophilia who had AIDS.

2 Just looking, Professor Ludlam, at all that was
3 happening around about this time -- and there certainly
4 seems to have been a great deal happening --

5 A. I'm sorry, could I interrupt?

6 Q. Yes.

7 A. Go back to this document. I think if you go on through
8 several pages, you will find the questionnaire that
9 John Craske had developed for investigating patients
10 with haemophilia who might present either with AIDS or
11 with AIDS-like -- that's it, thank you -- which I think
12 is further evidence of the fact that Britain was well
13 organised compared with many other countries in relation
14 to this particular difficulty.

15 Q. Yes. Indeed. We can certainly see reproduced in full
16 the UKHCDO hepatitis working party surveillance form.
17 That, as you say, appears from page 9 onwards. It's
18 also worth noting that actually in the entry for the
19 United Kingdom, which is the page before that, so if we
20 look at page 8, 4401, whenever this return was made from
21 the UK, it certainly said there had been no reports of
22 AIDS syndrome following the transfusion of blood or
23 blood products.

24 So it looks as though, as far as we can judge after
25 this passage of time, whenever the return was

1 sent, April perhaps, no one was saying that anybody with
2 haemophilia in Britain had suspected AIDS but by May
3 that situation looks to have been changing.

4 I think we should just ask you, Professor Ludlam,
5 about the Professor Bloom letter, or the letter which
6 has a part drafted by Professor Bloom, which is
7 DHF0030738 [sic].

8 THE CHAIRMAN: Can we get it into the transcript, Ms Dunlop?

9 MS DUNLOP: Yes, it is [\[DHF0014474\]](#). This letter is dated
10 4 May. We can see that from the bottom if we just
11 quickly look at the bottom. It has a date, 4 May 1983,
12 and then the introduction:

13 "In view of the unduly alarmist reports on AIDS
14 which appeared in the press over the weekend, we are
15 writing to reassure members of the Society. We have
16 been in touch with Professor Bloom, chairman of the
17 haemophilia centre directors, senior member of our own
18 medical advisory panel and a member of the Central Blood
19 Laboratories Authority, who has kindly written to us all
20 as follows."

21 Let's take Germany first. He does say:

22 "Neither have any cases been reported from Germany."

23 I suppose it must have been very, very difficult at
24 this time, Professor Ludlam, but, of course, no evidence
25 that X is the case is not the same as evidence that X is

1 not the case?

2 A. I appreciate that but Professor Bloom had written round
3 to haemophilia centres in Europe, asking about whether
4 they had seen patients with AIDS or with AIDS-like
5 syndromes, and he must have got reports because there is
6 a number of large centres in Germany. When he received
7 those replies, there weren't any cases of AIDS.

8 Q. Right.

9 A. So he had very positively attempted to find out.

10 Q. And do you remember then talking to Professor Bloom
11 around about this time about the steps he had taken?

12 A. Yes, because I got a copy of the questionnaire as one of
13 the many centres in Europe.

14 Q. Right. What about the sentence before:

15 "In spite of inaccurate statements in the press, we
16 are unaware of any proven case in our own haemophilic
17 population."

18 Do you think it is the word "proven" that's crucial
19 there, Professor Ludlam?

20 A. I think it possibly is and, as I mentioned a few minutes
21 ago, because there was not a laboratory diagnostic test
22 for AIDS and because a lot of other conditions could
23 mimic the early symptoms of AIDS -- they are very
24 non-specific, like weight loss and sweats and, to some
25 extent, lymphadenopathy -- the criteria for AIDS were

1 well circumscribed into either unusual opportunistic
2 infections or Kaposi's sarcoma or lymphomas.

3 THE CHAIRMAN: Professor, I find some of this quite
4 difficult. If the interpretation one placed on cases
5 that some people thought were AIDS had been that, in
6 treating haemophilia patients over a significant period
7 of time, there was a well documented and established
8 incidence of similar circumstances, similar signs,
9 similar symptoms, one might have expected to see that
10 writ large across the United Kingdom literature. I'm
11 not sure I have.

12 A. No, you see, because early HIV infection is mostly
13 asymptomatic and so people didn't present often until
14 they got what we call an AIDS-defining illness, the PCP
15 or the Kaposi's sarcoma, and that our patients, like
16 other individuals in the general community, would turn
17 up with weight loss or night sweats which could have
18 been due to anything, we weren't seeing a lot of
19 patients, for example, with night sweats or weight loss
20 in our community. Does that ...?

21 THE CHAIRMAN: I'm not sure that helps me. You see, if the
22 position were that in general practice these signs and
23 symptoms were not being seen, but they then emerged,
24 it's quite difficult to step from that point to say, oh,
25 well, when they emerged, they might just have been

1 typical of other signs and symptoms and other conditions
2 that were already well established. That doesn't seem
3 to me to fit as a logical explanation of the response.
4 Maybe I'm getting it wrong, professor. I'm quite
5 capable of doing so.

6 A. I'm sorry, I think I have misunderstood.

7 THE CHAIRMAN: You see, what I had noted you as saying -- I
8 don't want to go back to the transcript -- that the
9 conditions were not diagnostic because other conditions
10 could mimic the early stages in HIV infection. If there
11 were other circumstances, other diseases, other
12 conditions, that were producing the same range of signs
13 and symptoms, then what appeared to me to be a possible
14 response, when it was alleged that AIDS had been
15 identified, was that the medical profession would say,
16 "No, come on, now look, we know these signs and
17 symptoms, we have seen them in the past and indeed
18 probably before AIDS emerged, they are not diagnostic."
19 But that seems to be missing. So why one would construe
20 the emerging signs and symptoms as being attributable to
21 a different condition I'm not quite understanding, but
22 it may be, as I say, I'm not getting it right.

23 MS DUNLOP: It may help, Professor Ludlam, also to look at
24 [\[DHF0017178\]](#). This is another Dr Craske document and
25 it's possible to demonstrate that it was sent to the

1 DHSS, presumably who wanted to know about it. It's
2 dated March 1st 1983. It is quite interesting to look
3 at page 7183. This is Dr Craske's survey.

4 Actually, Professor Ludlam, you were referring to
5 Professor Bloom's survey. I think we will come to this
6 but I think Professor Bloom didn't send out his survey
7 until December 1983. But we will look at that later.

8 This is Dr Craske's survey and this is March 1983.
9 He looks to be casting his net pretty wide actually. He
10 is asking haemophilia doctors to send him a form if they
11 see any of really quite a long list of conditions. So,
12 rather than expecting people to go through a very
13 specific and precise assessment of whether their patient
14 fulfils all the criteria set down perhaps by CDC or
15 something, Dr Craske is asking for, as it were, possibly
16 over reporting rather than under reporting, just to be
17 sure that he gets a complete picture. Is that not how
18 it looks?

19 A. No, the heading, "1. Diseases specific for AIDS."
20 These are what are called AIDS-defining illnesses, and
21 I note here, going back to our discussion of ten minutes
22 ago, that under "fungal", oesophageal thrush would
23 appear to be an AIDS-defining illness. So, I'm sorry,
24 I misled you earlier.

25 Q. It's all right, I don't carry these things in my head.

1 I thought it might be here.

2 A. This is the --

3 PROFESSOR JAMES: I think the point is it's a necessary but
4 not a sufficient condition.

5 A. Is it not actually a sufficient condition? Can you move
6 the screen up? It doesn't actually say whether these
7 are AIDS-defining conditions but I think most of them
8 are.

9 PROFESSOR JAMES: Yes.

10 THE CHAIRMAN: Could I come back to my question, which
11 clearly wasn't terribly well expressed, against this
12 background: one might look at the words "diseases
13 specific for AIDS", and read it as being something that
14 is, as Professor James said, associated with AIDS but
15 any one of them might not of itself be diagnostic.

16 But if one were to dismiss it on the basis that all
17 of these conditions are known, and particularly all
18 known in haemophilia, then what I was suggesting was
19 that perhaps when these were listed or when this was
20 examined, clinicians would be saying, "Come on, we have
21 had a long history of these conditions, we know them.
22 They are prevalent in the haemophilia community." And
23 it's that that I don't see anywhere.

24 A. No, these aren't. Yes. No, no.

25 THE CHAIRMAN: So the question then becomes: when they do

1 begin to emerge in the haemophilia community, would it
2 be right that one couldn't say, "Oh, well, we do know
3 them, we can dismiss the possibility of AIDS"?

4 A. That's right, yes.

5 THE CHAIRMAN: And that rather leaves one with them as being
6 fairly diagnostic if they happen in the haemophilia
7 community.

8 A. Yes.

9 THE CHAIRMAN: And that, I think, brings us back to --

10 A. I'm sorry if I have misled you.

11 THE CHAIRMAN: Don't worry about that. We are all capable
12 of misleading each other here, professor.

13 MS DUNLOP: Yes.

14 A. These are all evidence of immune suppression. Part of
15 the definition of AIDS is the appearance of one of these
16 conditions which reflects immune suppression for which
17 there is not another obvious cause. In other words, the
18 patient hasn't had chemotherapy, for example, for
19 malignancy, as perhaps the other commonest cause.

20 Q. I don't think the Cardiff case was written up,
21 professor, or at least if it was, we haven't found it
22 and we have a very big database. But I think we can
23 perhaps just note that there were certainly two
24 different cases being discussed at about this point in
25 1983 in the United Kingdom. And, you know, whether on

1 close examination they ticked all the right boxes at all
2 the right times might be another exercise, but they
3 certainly were cases that people were talking about.

4 Just if we go back, please, to 0468. Just read down
5 1983. I don't think there is anything else particularly
6 that I want to take you to, except to say that that
7 reference you make in November, "first UK AIDS case in
8 haemophilia reported", I take your point that that's
9 what, no doubt in medical circles, is a proper report,
10 it's in the Lancet, but there certainly was mention of
11 that case and another case in May.

12 December, there is a total of 21 cases of AIDS in
13 haemophilia in the United States and then seven from
14 outside. Can we go from there to [\[PEN0150385\]](#) at
15 page 16, please -- sorry, it is being suggested to me
16 that we should be having a break because it is 20 past
17 three.

18 THE CHAIRMAN: I'm sorry, I was just far too fascinated to
19 notice the time. We will have a break.

20 (3.22 pm)

21 (Short break)

22 (3.40 pm)

23 MS DUNLOP: Can we start with [\[PEN0150385\]](#) at page 16.

24 Thank you.

25 Professor Ludlam, this is quite a lengthy section in

1 your 1990 report, and we can see it's headed "Immune
2 studies in haemophiliacs". Just to give everybody
3 a moment to look at that page ... (Pause)

4 Just a couple of points, I think, for our
5 understanding, professor. This is a description which
6 you are giving us of the attempts that were made to
7 investigate these immune abnormalities, patients with
8 AIDS, very many of whom in the early days, as we have
9 seen, were homosexual men. The first is the ratios. It
10 was noticed that there was a decrease in CD4 numbers.
11 These are the helper cells. Is that right?

12 A. That's correct, yes.

13 Q. And the CD8s are the suppressor cells?

14 A. That's correct.

15 Q. In a couple of sentences can you just tell us about
16 helpers and suppressors. It doesn't have to be two
17 sentences. That was just a rough guide.

18 A. The immune system is immensely complex and I'm not an
19 expert but it is made up of white cells, lymphocytes,
20 some of which are called B cells, which make antibodies
21 and some are called T cells, that regulate the process
22 of antibody development. These cells work together in
23 a network with other cells like dendritic cells, which
24 take up foreign matter into them and process them and
25 pass them to the T cells for further processing, either

1 activating a further set of cells called T killer cells
2 or producing antibodies through the B cells.

3 My understanding, which is far from complete, is
4 that in a sense the CD4 cells promote this activity and
5 the CD8 cells suppress it. Having said that, it's
6 actually immensely more complicated than that, in that
7 I think you can nowadays get CD4 suppressor cells.

8 Q. Perhaps we can do a little at a time, and given that we
9 have Professor Lever coming, he will be able to advance
10 our understanding in a couple of weeks' time, but it
11 was the ratios that I understand were particularly
12 significant, and you say:

13 "Sometimes the reduced ratio was due to a lowered
14 CD4 count, sometimes it was due to an increased CD8
15 count and yet other times it was due to both a lowered
16 CD4 count and an increased CD8 count."

17 So I think we can all understand that, at least at
18 a superficial level.

19 The other thing on the page was the very end, that
20 there were other aspects of the immune system which were
21 impaired. These included a reduction in lymphocyte
22 response to phytohemagglutinin and other mitogens."

23 Can I put brackets around "a reduction in natural
24 killer cell activity"? The reduction in lymphocyte
25 response to phytohemagglutinin and other mitogens is

1 a reduction of natural killer cell activity, isn't it?
2 I think that's the sense of the sentence?

3 A. No. I think not.

4 Q. It's the way the sentence read. It looked as though
5 that phrase, "a reduction in natural killer cell
6 activity", was meant to be an explanation of what had
7 gone immediately before.

8 A. I'm sorry, I should perhaps have worded it differently.
9 There was a reduction in the way in which lymphocytes
10 responded to phytohemagglutinin. Quite separately there
11 was a reduction in natural killer cell activity.

12 Q. Right, okay.

13 A. As well as a third thing, which was an increase in
14 immunoglobulin levels, which is evidence of immune
15 stimulation, because I think one of the paradoxes of HIV
16 infection is you get both immune inhibition, if you
17 like, and immune stimulation.

18 Q. I see. Go to the next page, please. It says that
19 people with haemophilia were studied. The results that
20 emerged during 1983 and 1984 demonstrated a range of
21 immune disturbances. And you quote a number of those
22 who published in this area, including yourself:

23 "Reduction in CD4 count, CD4/8 ratio and other
24 immune abnormalities was observed in asymptomatic
25 haemophiliacs. There is much speculation as to the

1 cause of the immune abnormalities in haemophiliacs."

2 You then go on to list for us some of the
3 possibilities:

4 "1. A previously undescribed feature of
5 haemophilia:"

6 I think you mention that so that we can now ignore
7 that. Is that right?

8 A. Yes, but at the time we just wondered whether it could
9 be.

10 Q. Right. Next possible cause: chronic liver disease. And
11 then third possible cause: blood products given for the
12 treatment of haemophilia contain large amounts of plasma
13 proteins other than Factor VIII or IX, which constitutes
14 less than 1 per cent of the total protein, and I think
15 we established earlier today that that statement about
16 large amounts of plasma proteins would be true of
17 commercial products as well as NHS.

18 A. Yes, less so for most of the commercial products at this
19 time.

20 Q. Then you say in a sentence at the end of 3:

21 "The evidence for the immune abnormality being due
22 to blood products and not a virus are (a), many
23 haemophiliacs exposed to blood products had abnormal
24 immunity."

25 You say:

1 "Some studies indicated that cryoprecipitate use was
2 associated with less immune disturbance. This was
3 almost certainly because patients receiving
4 cryoprecipitate were moderate and mild haemophiliacs who
5 only required occasional treatment compared with
6 concentrate users, who tended to be clinically severe
7 ..."

8 I think we have seen this on a number of occasions
9 but any one administration of concentrates could have
10 been exposing a patient to approximately 1,000 times
11 more donors than an administration of cryo?

12 A. Yes.

13 Q. Then:

14 "(b), recipients of Factor IX concentrates had fewer
15 abnormalities than those treated with Factor VIII ...
16 Studies in haemophiliacs treated exclusively in 1983 by
17 blood products manufactured from local blood donors in
18 AIDS-free areas, for example, Scotland, demonstrated
19 that the patients had similar immune abnormalities,
20 compared with patients treated with commercial
21 concentrates manufactured in North America."

22 Then we are still in the paragraph dealing with why
23 immune abnormalities in patients with haemophilia could
24 be due to blood products and not a virus. You have
25 said:

1 "(d), some haemophiliacs who had received massive
2 doses of Factor VIII concentrate and other blood
3 products apparently had normal immune function. If
4 a putative AIDS virus was present in even a minority of
5 batches of Factor VIII/IX concentrate, patients in
6 receipt of these very large doses would have been
7 expected to be infected."

8 Professor, (d) would have been a puzzle if repeated
9 antigenic stimulation was the explanation as well, would
10 it not?

11 A. Not all patients we believe respond similarly to
12 infusion of Factor VIII concentrates. There may well be
13 genetic differences between people in the way they
14 respond.

15 Q. Right. But at the time, if you were considering the
16 competing theories, you would have had to explain why,
17 if antigenic stimulation was the cause, it happened to
18 some people but didn't happen to other people who had
19 received massive doses. You would have had to come up
20 with an explanation for that as well, wouldn't you?

21 A. It could be an observation and I think some of our
22 studies actually supported that.

23 Q. Right.

24 A. That there was a genetic element.

25 Q. You see, where you say:

1 "If a putative AIDS virus was present in even
2 a minority of batches, patients in receipt of these very
3 large doses would have been expected to be infected."

4 That could have depended on how new the virus was
5 and really how small the minority of batches was, could
6 it?

7 A. I suppose it could have done. I'm just laying out the
8 possibilities.

9 Q. Right. Then (e):

10 "In patients who had received Factor VIII or IX
11 concentrate, there was no relationship between the
12 degree of CD4 concentration or CD4/CD8 ratios and the
13 total annual use of the concentrate. This argued in
14 favour of an all or nothing response, some patients
15 being more susceptible to immune change following only
16 small amounts of concentrate."

17 Then:

18 "(f), if AIDS was due to a virus transmitted by
19 blood products, why had so few patients with haemophilia
20 out of many tens of thousands developed AIDS in 1983?
21 It was not proved until later, when anti-HIV testing
22 became available, that the latency between infection and
23 the development of AIDS could be many years."

24 But even in 1983, there were a number of people who
25 suspected that, were there not, Professor Ludlam? For

1 example, Dr Galbraith's paper. We will have a look at
2 that in due course. Dr Galbraith suggested that the
3 latency period could be up to four years. So even at
4 the time, some people were thinking there could be
5 a very long latency period?

6 A. Yes.

7 Q. Then you say:

8 "The immune changes could have been due to
9 a putative AIDS virus".

10 And:

11 "The evidence for this was ..."

12 You list in the same manner various factors, which
13 we can see for ourselves.

14 THE CHAIRMAN: Before we go through the list, if one looks
15 at this presentation of the possibilities, is this
16 something that has been developed over time or are these
17 the possibilities that a clinician in your position
18 would have acknowledged at the time and set out in this
19 way?

20 A. Very much at the time. The reason I put in this
21 document to the Inquiry is because I was encouraged to.
22 As you see, it was written 20 years ago. So this was
23 written, if you like, shortly -- relatively shortly,
24 after AIDS had arrived, and so it perhaps reflects more
25 the way of thinking at that time, the processes we had

1 been through, and I fully accept that, you know, we have
2 just been through all the non-viral possibilities that
3 were considered and these were very real, particularly
4 in 1982/1983/1984.

5 THE CHAIRMAN: If we turn to the next set, are they in the
6 same position?

7 A. Yes.

8 THE CHAIRMAN: Yes, Ms Dunlop. Sorry for interrupting you.

9 MS DUNLOP: Thank you, sir.

10 This was actually written for a litigation in
11 England and Wales, wasn't it?

12 A. It was a background document for that, yes.

13 Q. Was it written for any particular group? Who asked you
14 to write it?

15 A. The solicitors acting for the NHS authorities, health
16 boards.

17 Q. Just looking at your paragraph number 4, the same
18 exercise, looking at the subparagraphs which are marked
19 by letters and perhaps on to the next page, thank you.
20 Where you say in (d):

21 "Other blood products, for example platelets, had
22 been implicated in the transmission of AIDS, and by
23 implication Factor VIII or IX concentrates might also be
24 infectious ..."

25 That immediately makes us think of the infant at

1 whose case we looked before our break. That infant had
2 received platelets and the donor from whom the platelets
3 had been taken had gone on to develop AIDS. I just
4 wondered, how would the antigen overload or the
5 antigenic stimulation hypothesis have explained the case
6 of the infant?

7 A. Well, the infant had had actually many transfusions.

8 Q. Right.

9 A. About 20 or 30 different transfusions.

10 Q. I think it was 19?

11 A. 19, all right, 19. Still a considerable number for an
12 immune system in a baby, which is ill-formed, it is
13 still developing.

14 THE CHAIRMAN: I'm sorry, but looking at the coincidence of
15 the emergence of these things, by now, when you are
16 writing this, or the period by reference to which you
17 are writing it, there had in fact been a reasonable
18 history of the use of concentrates. So patients might
19 have been developing abnormalities. Could you have
20 written this list, let's say, ten years earlier, sorry,
21 with reference to a period ten years earlier, when there
22 had been a much shorter exposure to concentrates?

23 A. No, I mean, I think one of the things that we were just
24 wondering -- and it goes back to what I was trying to
25 say earlier -- was that maybe the AIDS in people with

1 haemophilia was actually of a different aetiology from
2 that in gay men; that was it possible that AIDS was
3 arising in haemophiliacs because during the 1970s there
4 was increasing use, massive increasing use of
5 Factor VIII concentrates.

6 I mean, I calculated that at least using SNBTS
7 concentrates, that in an average lifespan, you gave out
8 a kilogramme of protein intravenously in an average
9 severe haemophiliac. We are not designed to accept
10 proteins in that magnitude intravenously. So one
11 possibility was that actually -- as we hinted earlier --
12 maybe haemophilia as a whole was sliding into AIDS
13 because of all the concentrate we were using. Quite
14 separate from HIV or a putative virus.

15 THE CHAIRMAN: Just looking on AIDS almost as an end stage,
16 as it were, in the progressive demolition of the immune
17 system?

18 A. From Factor VIII concentrate per se or the proteins, the
19 contaminant.

20 THE CHAIRMAN: And on any view, that would have required
21 a significant period of time to develop and you just
22 happened to have a coincidence in time of the two
23 situations that required resolution.

24 A. Yes. And also the AIDS in haemophiliacs was clinically
25 different.

1 Q. It had no Kaposi's --

2 A. It had no Kaposi's sarcoma which was a puzzle for a long
3 time.

4 THE CHAIRMAN: I'm just trying to understand it, Ms Dunlop.
5 Anything that can contribute is welcome.

6 MS DUNLOP: You have mentioned that before,
7 Professor Ludlam, but apart from the absence of
8 Kaposi's sarcoma, what were the other differences
9 between AIDS in homosexual men and AIDS in patients with
10 haemophilia?

11 A. I think that was the main one but a very significant
12 one.

13 Q. Well, did anyone speculate then as to why
14 Kaposi's sarcoma might be occurring in homosexual men
15 and not in patients with haemophilia?

16 A. Well, we now know it's due to HHV6 or 8, but it was
17 a puzzle for a little while.

18 MS DUNLOP: Yes. Professor Lever, I think, is going to
19 explain that to us more fully, sir, about the aetiology
20 of Kaposi's sarcoma?

21 THE CHAIRMAN: Right, yes.

22 MS DUNLOP: Which has obviously been, as Professor Ludlam
23 says, a bit of a puzzle.

24 Professor, I did actually also want to take you to
25 an article by Drs Tedder and Barbara on this whole

1 theme, and I take it it's an article with which you are
2 familiar. You know the article I'm meaning? We refer
3 to it in our preliminary report.

4 I'm going to take overnight because I don't have
5 a hard copy of it with me today, and I would prefer to
6 do it with a hard copy of it. So we will look at that
7 tomorrow.

8 But just to carry on with this recital of the
9 different reasons in favour of each hypothesis. We are
10 still looking at pieces of evidence, if you like, that
11 might favour a virus as the explanation. You say:

12 "(f), the clinical epidemiology of AIDS was very
13 similar to Hepatitis B, a virus known to be transmitted
14 by blood products."

15 Then:

16 "Of the four principal possible causes for immune
17 modulation in haemophiliacs ..."

18 By four principal possible causes, I think we mean
19 an incident of haemophilia, liver disease, antigenic
20 overload; to use a shorthand, or a virus. That's what
21 you are referring to as the four principal causes. It
22 is the ones you have sketched, I think, earlier:

23 "... there was general agreement it was due, at
24 least in part, to the extraneous non-Factor VIII
25 proteins in the concentrates. Some of the immune

1 disturbance might in addition be due to the presence of
2 a putative AIDS virus."

3 Then:

4 "The reason why it was possible that both the
5 extraneous proteins and the virus gave rise to similar
6 immunological changes is because the immune system only
7 has a limited repertoire of responses when challenged by
8 foreign substances."

9 Perhaps we can just read for ourselves on to the
10 next page. (Pause)

11 Then you do say at the very end, professor, that as
12 it turned out, the immune abnormalities which people had
13 found in patients with haemophilia under their care,
14 were not all early indicators that those individuals
15 were going to develop AIDS. Is that correct?

16 A. Yes.

17 Q. Right. So as it turned out, this finding, immune
18 abnormalities in people with haemophilia, in some
19 instances was associated with the development of AIDS
20 and in other instances was, as it were, free-standing.
21 Is that a reasonable view?

22 A. Yes.

23 Q. Right. The analysis of all of this material is
24 complicated, Professor Ludlam, because on any view, it
25 must have looked around this time as though it was

1 certainly something about the blood products, something
2 about the concentrates in particular, did it not?

3 A. Yes.

4 Q. Yes. I suppose lawyers are particularly interested in
5 not necessarily going straight to getting the right
6 answer but getting the right question first as well,
7 because that always helps you to get the right answer if
8 you have the right question. But if the question was
9 seen as whether the abnormalities were due to antigen
10 overload and only antigen overload, was there anything
11 that pointed in the direction of antigen overload being
12 the explanation for all the cases, including people who
13 had gone on to develop, and in some instances, die from
14 AIDS?

15 A. Could you repeat the first part of the question?

16 Q. Yes, sorry. I'm really trying to focus on antigen
17 overload and only antigen overload.

18 A. Yes.

19 Q. For our purposes, I'm actually putting to one side the
20 first two of your four possible causes; that is that
21 it's just a complication of haemophilia per se or that
22 it's to do with the liver disease, and I'm looking at 3
23 and 4 and for shorthand, if we think of 3 as antigen
24 overload, as I have seen it referred to colloquially,
25 and 4 as a virus, was there anything that could make

1 physicians examining the problem then think that antigen
2 overload was not just a bit of the explanation but the
3 whole explanation?

4 A. I think that became increasingly less tenable with the
5 unfortunate case reports of a spouse and a child of
6 a haemophiliac developing AIDS.

7 Q. Right.

8 A. Because that was evidence of a presumed sexually
9 transmissible agent, furthermore, sadly being passed to
10 the child.

11 Q. That's the Pitchenik article, is it?

12 A. I forget the author.

13 Q. If I'm pronouncing that correctly. We do have that in
14 our preliminary report as well. But that would put your
15 sense of when the antigen overload theory became less
16 likely quite late, because I think that's not until
17 1984. Perhaps we can give you the reference for that
18 tomorrow rather. Yes, January 1984. It was an article
19 in Annals of Internal Medicine entitled "The acquired
20 immune deficiency syndrome in the wife of
21 a haemophiliac."

22 A. Yes, that's the article.

23 Q. That's chapter 8, paragraph 68 of the preliminary
24 report.

25 A. Yes.

1 Q. You see, I wanted just to put to you one or two passages
2 from Dr Winter's evidence, if I might. You might want
3 to have it in front of you. That might be easier. Could
4 we go to day 1 of Dr Winter's evidence, which was
5 26 April. Page 114. The version I have is a different
6 page 114, I think unfortunately. It's the more fully
7 spaced version. That's it. 114.

8 Yes. You see the question, Professor Ludlam, the
9 question is posed as at July 1982 and I'll give you
10 a minute to read the answer. (Pause)

11 Do you disagree with that answer, professor?

12 A. It is very difficult looking back 30 years, to think
13 about the exact balance. Clearly, after the report
14 in July 1982 in MMWR, a viral aetiology had to be
15 a possibility.

16 Q. Yes. The next one, if we can do this from 27 April, so
17 the following day, pages 7 and 8. Here I do have the
18 four pages to a page version, if that helps. About line
19 9 on page 7. If we think of this report about the
20 infant, now this question is in the context of
21 a discussion of Koch's postulates, with which you will
22 be very familiar, I'm sure.

23 Actually Koch originally was involved in research
24 into tuberculosis. Is that right?

25 A. Yes.

1 Q. So infectious diseases research generally. But looking
2 at line 9 and reading on right down the right-hand side
3 of what's on the screen, if you would, please. (Pause)
4 You need to go down the page.

5 A. If you want me to comment on the 1 to 3 of Koch's
6 postulates or ...?

7 Q. By all means, professor. It was suggested to Dr Winter,
8 after his explanation of Koch's postulates, albeit that
9 2, the second link in a Koch chain, as it were, was
10 missing, links 1 and 3 were there because the recipient
11 had developed AIDS, or appeared to have developed AIDS,
12 and the donor had developed AIDS. Did you want to say
13 something about that?

14 A. Right. I wasn't quite sure in what order the three --
15 because in fact there were four component to Koch's
16 postulates.

17 Q. What's the fourth? I think we have maybe missed the
18 fourth.

19 A. I think you have to culture the organism.

20 Q. Right. I thought that was the second. That you could
21 isolate the organism from a sample.

22 A. You have to show that an organism causes the disorder
23 and then transmit the disorder with the organism and
24 show that it develops the same condition. I can't
25 remember what the fourth thing is.

1 Q. Right.

2 THE CHAIRMAN: I think Ms Dunlop, if we are having different
3 approaches to Koch's postulates, we have to try and get
4 the basic criteria fixed and we are getting on a bit.
5 Perhaps, Professor Ludlam, you can think of it overnight
6 and let us have your four criteria. I have to say, if
7 culturing it is an essential pre-condition, then that
8 might introduce quite a different level of test, as it
9 were.

10 MS DUNLOP: I suppose another thing that's troubling me
11 slightly, sir, is how you would ever do that, because
12 that presupposes some sort of process in which you
13 culture the organism and give it to someone.

14 THE CHAIRMAN: Or something.

15 MS DUNLOP: Or something. Certainly nowadays I can't quite
16 envisage how that would happen. That was the other
17 section, and by all means, Professor Ludlam, if you want
18 to finish reading that whole section, that whole answer,
19 on to page 8 and indeed on to page 9. If you want to
20 think about that overnight and perhaps we can begin
21 tomorrow morning by asking you if you want to make any
22 particular response to what Dr Winter is saying.

23 THE CHAIRMAN: And make arrangements to get hard copies
24 provided to cover that. Just how many pages would you
25 like the professor to have?

1 MS DUNLOP: That's it. I suppose we should start with page 6
2 then, on to 7, 8, 9 and 10.

3 THE CHAIRMAN: I don't think that's too much of a challenge
4 overnight for us.

5 MS DUNLOP: No, I certainly don't think we need a treatise
6 on Koch's postulates.

7 THE CHAIRMAN: I don't want that. All I want to know --

8 MS DUNLOP: We are trying to look at the big picture here.

9 THE CHAIRMAN: All I want to know at the end of this is
10 whether you are looking at the same factors that
11 Dr Winter was looking at. Where they come in the
12 enumeration is far less important to me, but I would be
13 interested to know if he has omitted anything of
14 significance that you consider to be important, for
15 example. But otherwise, so long as you know what he is
16 talking about, you can give us your observations on what
17 he has said.

18 A. I'll try and do my best.

19 MS DUNLOP: Right. Thank you.

20 THE CHAIRMAN: How are we doing, Ms Dunlop, for progress?

21 MS DUNLOP: Yes, I think we are on schedule.

22 THE CHAIRMAN: That's fine.

23 (4.22 pm)

24 (The Inquiry adjourned until 9.30 am the following day)

25

1	
2	PROFESSOR CHRISTOPHER LUDLAM1
3	(continued)
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	

