THE TRIBUNAL RESUMED ON MONDAY, 16TH OF JULY, 2001, AT 10:30 A.M., AS FOLLOWS:

MR. FINLAY: Morning, Madam Chairperson. Professor Mannucci, please.

PROFESSOR PIER MANNUCCI WAS SWORN AND EXAMINED BY MR. FINLAY AS FOLLOWS:

THE CHAIRPERSON: Morning, Professor.
A. Good morning.

THE CHAIRPERSON: Thank you for coming.

Q. MR. FINLAY: Professor Mannucci, I think that you are currently the director of the Haemophilia and Thrombosis Centre at the University of Milan, and also, Chairman of the Department of Internal Medicine in the University of Milan?
A. Yes, I am.

Q. Is that correct?
A. That's correct.

Q. Yes. And can you just give the Tribunal some brief outline of your career to date, Professor. First of all, I think, did you qualify as a medical doctor in 1963, I think?
A. That's correct.

Q. And since then, what has been your particular interest as a doctor?
A. I have been always mainly interested in haematology, blood diseases and particularly those related to abnormalities of blood coagulation. So bleeding disorders and thrombotic disorders.

Q. Yes. And I think in fact, since 1970, have you held the position of Professor of medicine of -- of certainly medicine in the University of Milan?
A. Exactly.

Q. And also, since 1970, the position of director of the Haemophilia and Thrombosis Centre in Milan University?
A. Yes, that's true.

Q. I think there is a hospital attached to the university in Milan?
A. Yes, it's called the Maggiore Hospital.

Q. Yes. Now, I think amongst very many other things, Professor, between 1978 and 1994 were you the vice-president, the medical vice-president of the World Federation of Haemophilia?
A. Yes, I was. This is an -- mixed organisation. It's an organisation of patients with haemophilia, but there are also medical officers and I was vice-president medical. I was the main medical officer.

Q. Yes. I think, by tradition, is the president of the World Federation of Haemophilia not a doctor; it's normally a person with haemophilia?
A. It's always been that -- in that way.

Q. Yes. And therefore, the vice-president is a medical person, also by tradition, is that correct?
A. Yes. There is more than one vice-president, but there is -- vice-president medical is the main medical officer, as I said.

Q. Yes. And that position you held between 1978 and 1994?
A. Exactly.

Q. Yes. And I think were you also a member of the International Committee for Thrombosis and Haemostasis between 1979 and 1984?
A. Yes, I was.

Q. And subsequently, I think you have held various offices in that organisation?
A. Yes. The International Committee on Thrombosis and Haemostasis is now called Scientific Standardisation Committee, has changed name; is a working arm of a learned society, the International Society for Thrombostasis and Haemostasis, with a goal of tackling specific issues of standardisation, recommendations, guidelines standards. So it is the working arm of a learned society.

Q. Yes. Now, I think it's quite clear from your published material that you have always taken a very active interest in research and in scientific work, is that correct?
A. It is correct, yes.

Q. And have published very extensively in the field of haemophilia and hepatitis?
A. Yes, I think I did, yes.

Q. Yes. And can you just explain to us, what that was; I mean, what led to you that interest and why did it develop with you?
A. Okay. It's a long story but I will try to make it brief. When I was just graduated I came to the United Kingdom to do some specialisation period, fellowship, partially in London with Professor Ingram at St. Thomas's, and then in Oxford with the -- Oxford Haemophilia Centre at that time was the leading haemophilia centre in the world. I was originally, in principle, more interested in the other part of bleeding thrombosis, so in excess of clotting; but there I did realise how simple it was, in a sense, the treatment of patients with haemophilia. And since in my country there was no organised treatment, when I went back I thought that, as the first thing, I should try to apply the knowledge that I gained, particularly in Oxford but also in London, to those patients, because it seemed to me a relatively simple endeavour, an organisational endeavour. And this coincided with the fact that in the late '60s, after the personal work of Judith Poole, cryoprecipitate became available in my country, as in others, making possible the mode and treatment of haemophilia. So I became interested in that field and I continued to be interested, even though I did something also in the field of the opposite disease, thrombosis.

Q. Yes. Now, I think, Professor, you have furnished the Tribunal with a statement of your proposed evidence, isn't that correct?

A. Yes, I did.

Q. And you mention at the beginning of your statement on page one, Professor, that you are in a position to give the Tribunal evidence based on published material but also on unpublished information that would have come to you during the time that we are concerned with. Can you just explain how that would have come about, Professor?
A. Well, I will make an example to explain that, an example that I think is quite critical; even though by giving this example I go directly into the problem. The story that -- evidence that the first heat-treated factor concentrate did transmit hepatitis was not published for a number of reasons - that I can explain later - until July 1985. But I knew - being also the coordinator of the study, so that is a special situation - I knew from September 1983 that this transmitted hepatitis. At that time we couldn't give a precise denominator and enumerator. We knew already it was not totally safe. And that was communicated to some colleagues with whom we met in Barcelona, at the meeting of the European Society of Haematology, in September. So that's typical. You see, sometimes a publication of a paper takes some time because you have to organise it in a proper way for publication; also because sometimes you may be lazy in writing it up, even when the evidence is available. But certainly, let us say, that among us there is exchange of information. So sometimes we get to know the information before it is actually published, even though, of course, for the whole community, for those that are less directly involved, one has to make reference to published evidence, because that really is the basis. So that is why I made that comment, to explain a couple of statements that I make here and there.

Q. Yes. Now, I also think, Professor, that you indicate that you think it appropriate to deal with the problem of hepatitis before dealing with the problem of HIV?
A. Yes. For a couple of reasons: The first, that the problem became obvious before -- it was known much earlier than the problem of HIV. We didn't know -- we called Hepatitis non-A non-B what we now call Hepatitis C, but certainly, the problem was known already in the '70s as many papers quoted here witness. And also, I think that the story of hepatitis did impinge upon that of HIV, particularly because of the failure of the early products to transmit the -- the failure to prevent hepatitis, many of us didn't think that a product that was ineffective in inactivating a virus could on the contrary be effective to inactivate another virus. That, as far as we knew at that time, could be -- had to be -- there was no reason to believe that it was a very different term of resistance to inactivating agents than the Hepatitis C virus.

Q. Yes. Now, I think you mention at page two of your statement that there were references to the existence of a problem with Hepatitis B in the literature in 1972. And these were in the nature of anecdotal reports, and I think you give references to two articles, isn't that correct?
A. Yes. It's not only Hepatitis B, there were also some cases in which the only thing that at that time could be seen was an increase in transaminase, which is an index of liver damage of hepatitis in a sense, and also, some jaundice. At that time, even the concept of non-A non-B Hepatitis was not very well-developed. And certainly, one tended to think -- tended to think in terms of Hepatitis B being the major virus transmitted with blood-borne -- transmitted by blood. But the evidence that there were cases of non-B was already available early in the '70s, if not before.

Q. Yes. But I think did your group carry out quite a significant study and publish the results of it in 1975, Professor?
A. Yes. I think that study is quite important, because even though -- it was known that a certain proportion of haemophiliacs - let us say between 10 and 20 percent - became jaundiced, and -- became jaundiced. And so everybody knew that treatment with blood products could be associated with development of hepatitis. The significance of these findings was not well-established. Patients usually did well during the disease, the majority of them at least. They apparently recovered without any obvious consequence. It was certainly not known at that time that severe liver disease, cirrhosis, or hepatocellular carcinoma was a major problem in patients with haemophilia; I mean at that time. And so, when we published in the Journal of Clinical Pathology, 1975, a paper in which we did show a large proportion of multitransfused haemophiliacs had high proportion of elevated transaminases - which are an index of acute liver disease - there was some surprise. You'll notice that, in that paper, we mentioned increase of transaminases but we didn't find - testing the liver in the most comprehensive way as it was possible at that time - we didn't find, really, signs indicating that these patients were having severe liver impairment like cirrhosis and so on, because the tests that are indicative of that type of liver disease were mostly negative. So the thing that emerged more clearly was that there was a high incidence of abnormality of transamination. There is enzymes produced by the liver releasing the serum when the liver is damaged. And it was difficult to interpret those findings. I remember that one of the reviewers of the paper did express the -- did voice the possibility that it could be due to damaged organs other than the liver. Transaminase is not truly specific for the liver. They mention the possibility that it could be due to haematomas, to blood into the muscles, damage of the muscles. And so we contemplated that possibility. But of course, we also contemplated the possibility that it could be due to chronic liver damage. But since the patients appeared well, clinically, very few had liver -- enlargement of the liver, and very few had signs of what one would think portal hypertension, of advanced liver disease, we got the impression that it was a relatively mild disorder, and at that time there was no evidence that a large proportion of patients were affected by severe liver disease, even though we suspected and we voiced the concern that the majority were -- had been in contact with the viruses.

Q. Yes.
A. Sorry, this is quite a crucial paper so I think it is --

Q. I understand that. If we could look briefly at the paper. I think in your book of references, it's at page 51, the -- the paging up on the top right-hand corner, the black letters.
A. Yes.

Q. And in your synopsis, you conclude, the synopsis: "All patients were asymptomatic and only a minority showed clinical signs of liver involvement. These data suggest that in haemophiliacs, repeated and prolonged contact with the agents responsible for post-transfusion hepatitis may cause chronic liver damage not associated with overt illness."
A. Mm-mm.

Q. And I think in the discussion, Professor, if we turn to pages -- to page 55, there are two paragraphs where you discuss the consequences of your findings or -- three paragraphs. First of all, there is paragraph dealing with the possibility that analgesic drugs might have played a role in the transaminase findings. You thought that was unlikely, would that be correct?
A. Yes. Certainly it was a concern, because before the advent of large pool concentrates and the modern treatment of haemophilia, patients were always living in agony and with frequent haemarthroses, very painful. So they did use a large amount of analgesic drugs. Not so much, I would say, as far as I know at least in my patients, but there was problem also, some problem of addiction of -- due to the repeated use of this product. As I mentioned here, the best analgesic I would say to my patients is replacement therapy, raising the factor. And so with the advent of concentrates, I think it was logical to assume that very few were using the concentrate because as soon as you give the injection, the pain disappears, so -- at least attenuates rather dramatically.

Q. Yes. And then in the next paragraph, which I think perhaps is at the heart of your comments: "The clinical and prognostic significance of the observed abnormalities is presently unknown and the lack of liver biopsies renders the task of clarifying them rather difficult. The great majority of the patients were completely asymptomatic and free of physical signs of liver involvement. It is possible that constant exposure to the infective agent induces a general immunological intolerance conditioning an attenuated pattern of chronic hepatitis." You give a reference there. "It also seems reasonable to suggest that antibody to Hepatitis B Surface Antigen occurring in haemophiliacs may offer protection." And there is a reference to Hollinger. I think the hypothesis there in that article, Professor, would have been a relatively optimistic hypothesis: If that had been correct, the problem would not have been very significant?
A. No, that -- you are right in saying that it was an optimistic statement. But as I told you, now of course with the retrospective evidence, everything looks silly; but at that time, I told you, we knew that they developed jaundice in a sizable proportion of patients. But as a clinician -- I mean, I am an internist, you see, so I'm actually -- in our unit, one of the reasons why we did tackle this problem extensively -- because in my medical unit, there are -- let us say the expertise other than haemophilia and thrombosis is liver disease. So I think we are quite -- Professor Colombo, which is mentioned in many of the papers, is a leading haematologist. I think we are in a good position to tackle the problem, because we are quite expert.

Q. Yes.
A. And we knew that there was jaundice, but the patients seemed to be well; they had no enlarged liver. We couldn't do any biopsy, and it was not just the -- until our study there was no evidence of transaminitis, as you want to call it. So, it was a hypothetical; this is all speculation. Also, I would say that at that time, quite frankly, the natural cause of the Hepatitis non-A non-B, that we now call Hepatitis C, was not known. It was not known what is known now; that the disease is a long-lasting disease with a very long disease-free interval before the development of complication. They still develop; not in all patients, thank God. They don't develop in all, even though, I mean, there is a sizable proportion of patients that develop cirrhosis as a consequence of -- cirrhosis, hepatocellular carcinoma. But the natural history of

Hepatitis non-A non-B was not known. It was more known at that time that Hepatitis B was more aggressive and we were actually very concerned with Hepatitis B.

Q. Yes.
A. But there was a relatively small number of patients here affected with Hepatitis B, as you can see, from the test of HBV, even though the majority had been exposed to the virus, but the majority didn't -- did develop a protective antibody.

Q. Yes. I think at the next paragraph, Professor, you refer to the possibility of the outcome being less good than the previous paragraph. You go on: "However, the evidence accumulated with the investigation of asymptomatic carriers of Hepatitis B Surface Antigen suggests that these humoral abnormalities are not entirely benign since they may be associated with structural changes of the liver similar to those occurring in patients with chronic hepatitis."
A. As I said, this was referring particularly to the Hepatitis B virus that, at that time, was really the only one, apart from Hepatitis A, well-known. There was already some information on hepatitis due to non-B non-A /non-A non-B viruses. But the main thrust at that time was Hepatitis B. So the discussion here is heavily influenced by the knowledge at that time.

Q. Yes. And then you go on to say, your final conclusion is that: "In haemophiliacs, an answer to these problems can be given only by a long-term prospective evaluation of any possible relationship between the observed abnormalities and the development of overt hepatic dysfunction. We recommend, therefore, that complete liver function tests should be carried out at regular intervals for early detection of any abnormal evolution, the latter requiring the establishment of a therapeutic programme which appears unjustified in the great majority of these patients at the present stage of our knowledge."
A. Yes. I think is -- I think it's self-explanatory, and again, reflects our knowledge at that time.

Q. Yes.
A. The thing that certainly occurred is that after that study,
now in our centre, and I suppose in many other centres, patients were seen at regular intervals - once a year or every six months - to be tested for transaminases and also to be followed clinically. And that's how we and others obtained some information about the persistence of abnormal transaminases which was because -- because this was a snapshot, in a sense.

Q. Yes.
A. It was only one sample. So the -- probably the first thing was to understand whether there was persistent elevation of transaminases. Because now we know very well in Hepatitis non-A non-B, or C as you want to call it, there is this fluctuation. This has been established in some subsequent studies that are mentioned by us and others, that there was some fluctuation. Some patients remain always with very high levels; others went back to normal levels, because there are some patients that get rid of the virus and have abnormal transaminases in which the antiHCV only represents immunity without disease. So, in a sense, was a programme for what was not known at that time but became known in the next few years.

Q. Yes. I think returning to your statement, Professor, at page three of your statement, in the second paragraph you -- you refer then to a study which was carried out in 1977 and was a joint American and English study, which is your reference 4 at page 56, reported by Peter Levine and others.
A. Yes.

Q. Is that correct?
A. Yes. That was a nice study done in a centre in Worcester, Massachusetts, and the Royal Free Hospital in London. And basically that study confirmed our study; it was done, I think, independently. It was published only a few months afterwards, it only -- only a different year, but I think it was done independently. And the results are really very, very similar to ours. They found probably more increase, slight increase in the size of the spleen than we did; but they didn't -- for the same reason that we did, they didn't attribute that to severe liver disease. And they thought it was the continuous bombardment - they used this expression - with plasma proteins; not foreign, but certainly different from what our indigenous plasma protein could induce - stimulation of the macrophages of the cells of the spleen. But basically the results were very, very similar.

Q. I think if we look at that in your references at page 56. I think there was a contrast: The American patients were receiving concentrate?
A. Mm-mm.

Q. And the English patients were I think receiving cryoprecipitate, isn't that correct?
A. Yes.

Q. And in the American patients, the level of problems was 68 percent; whereas in the English patients receiving cryoprecipitate, it was 48.5 percent. So, there was a difference, but perhaps not an enormous difference, between the patients who were receiving concentrate in America and the patients who were receiving cryoprecipitate in the London Hospital?
A. Okay. This opened a completely new problem: Whether cryoprecipitate made from single donations and usually from voluntary donors was really better than large pooled concentrates made from thousands and thousands of donors. My comment would be, first, that this difference may be statistically significant. I don't remember whether they did a test of statistical circumstances, but certainly it's not impressively different; but it's still very, very high, the prevalence of -- in patients with cryoprecipitate. So it's not -- what I would say, certainly doesn't tell us that, by using cryoprecipitate, you are on the safe side. It's telling us even in large proportion of patients with haemophilia, treated with cryoprecipitate, would develop transaminitis. And this is not surprising, because even though it has been established in the United Kingdom, very clearly, that when you give the concentrate, usually to a previously untreated patient, you get hepatitis after the first shot, which is understandable, because when you think of thousands and thousands of donors, it's quite understandable. So the first shot. With -- by giving cryoprecipitate you give less donations, so the risk is less. But the risk accumulates up, and then when they are exposed to multiple donations -- and usually haemophiliacs bleed, let us say, 24 times per year in average. And each time they are treated, supposing they need only one treatment - usually they need more than one - they are exposed to -- say they are treated with 20, 25 bags of cryoprecipitate, which means exposed to 25 donors, then

usually when treatment is not -- so go to 50, 75; each time multiply by 20, and you start to get a sizable number of donors. And, of course, it levels off. So the only difference of the hepatitis-free interval with a concentrate is practically zero, they get immediately the infusion; where this, it is progressive. And this has been -- this is shown, in a sense, by this study. Because, as I say, the difference is really not dramatic, and is also shown later on by a small but well-done study done by my colleague Dr. Morfini in Italy that compared prospectively -- or at least compared patients treated with concentrate with patients treated with cryoprecipitate.

Q. Yes. Of course, Professor, in that hypothesis that you have described for us, you are taking a patient who would have a relatively severe degree of haemophilia, who might require 25 treatments or something of that order in a year. Obviously if you have a person who is very mildly affected with haemophilia and might only require one or perhaps even no treatment, the advantage of using the cryo would be significantly greater, would that be fair?
A. Yes, it would be significantly great, and that's in a sense -- but not entirely satisfactory. Because if you are unlucky, even if you are treated for a dental extraction let us say two or three times only in your life, you may get the infection. That's why in the United Kingdom, my mentor Professor Ingram has always been obsessed by the -- 'obsessed' is the right word - in a good sense, of course - been obsessed by the possibility of finding a treatment for mild haemophiliacs that really are at high risk of developing hepatitis when the risk related to the disease is very small, is not a life-threatening situation.

Q. Yes.
A. So that's why he was always obsessed about developing a treatment, pharmacological treatment not derived from blood products capable of increasing Factor VIII level.

Q. Yes.
A. And, following his work with my colleagues we managed to find eventually, in 1977, a drug Desmopressin or DDAVP that does increase the level of Factor VIII without resorting to blood products.

Q. And I think we will come to that in a moment, Professor, in some more detail. If we could return to your statement for the moment, I think at page three.
A. Yes.

Q. You move on to deal with the question of the emergence of evidence of structural liver disease in patients with haemophilia and elevated transaminase. And I think you identified the first information in that regard as coming in 1977, is that correct?
A. It is correct. Nobody -- none of us in Italy or in Europe had the courage to do liver biopsy. We knew that it was safe in a sense because with concentrates you can do any sort of operation, so why not liver biopsy? But there was obvious reluctance to do a closed and blind procedure. So, it's good that our colleagues in Chapel Hill, a leading centre in the field of haemophilia, chose to do it in six patients. And that paper established something that was, I think, of similar importance: That established that Peter Levine and Dormandy findings of transaminitis were not called

transaminitis without any clinical significance; in that, the patients had some sign of liver disease, all the six patients if I remember.

Q. Yes.
A. But, at the same time, they established that the alterations were very mild and apparently, they didn't find any case of severe liver disease; and by "severe" I mean cirrhosis. There was three cases of chronic hepatitis. That was seminal work followed subsequently by other studies - the multinational study of Aledort that found that some patients had liver cirrhosis but in a small proportion of patients. So there was indeed a progressive increase of evidence that there was structural liver disease. But probably the study, the more focussed -- what was more alarming was the study published by Hay and Preston in The Lancet, where they found the highest incidence of liver disease, also because it was a very large study. So that really started to raise some concern, even though one had to consider, altogether, these were very small sera. And all these studies all together did show, as I said before, that the transaminitis was not entirely benign. But at the same time, they showed that not all the patients had cirrhosis and really very severe liver disease.

Q. Yes. I think just before we get to the Hay study, you have perhaps modestly overlooked a study of your own that you refer to at page four of your statement. And I think in the book of documents, it's at page 70.
A. Mm-mm, yes. That was a study carried out in -- the patients were followed prospectively, which was important, because all the other studies I don't think, as far as I remember, were prospective. But in that case, we did show that in some cases there was progression. And in one case that cirrhosis developed, one patient died of active cirrhosis during the follow-up period. It was prospective; it was a smaller series of patients. That is why I think in a sense that this study is not really the most important in this field of the -- of the biopsy studies.

Q. No. But the -- it hadn't yet come to the gloomy prognosis, because if we look at page 70 in the summary of your study, Professor, the final sentence of the summary "study of the serum and intrahepatic markers for Hepatitis B and delta viruses suggest that chronic liver disease is nonprogressive in haemophiliacs who have no intrahepatic viral markers."
A. Yes. Because, as I told you, we are still -- and after all, we are not so terribly wrong in the belief that the problem, the culprit was the Hepatitis B virus and not so much the non-A non-B virus.

Q. Yes.
A. Also, you have to consider that, I mean, to talk of a disease in negative terms was very unpleasant. So we were convinced, together with Professor Colombo and Professor- to say - both leading authorities in the field of hepatitis - that really the culprit, if anything, was the Hepatitis B virus. So the patient who died, died of Hepatitis B, if I remember. And also, he was infected by delta, and so we advanced hepatitis, this double infection with this new virus that -- the delta virus, which is a satellite of the Hepatitis B virus that was discovered by Rizzetto. So we tended to attribute progression to the Hepatitis B virus and satellites rather than non-A non-B Hepatitis.

Q. Yes. And I think in your conclusions in the article, Professor, page 73 --

A. Yes.

Q. -- where you say that: "This study suggests that in haemophiliacs with non-A non-B chronic hepatitis, progressive disease is not the rule. Our earlier choice to avoid restricting substitution therapy and to abstain from long-term and widespread use of corticosteroids is thus substantiated by clinical and histological evidence of low morbidity and nonprogressive disease."
A. Well, again, because we observed that -- small cases, 10 cases, but all the Hepatitis non-A non-B did not progress. In some cases even it showed a better clinical picture, which was only due to the fact that you sample a different section of the liver because we had two different biopsies. And so, our choice to avoid the restricting substitution therapy, we still think that at that time it was justified to do that. Also, because there was no other alternative and patients were dying or becoming handicapped. The story is ridiculous, because at the moment nobody would use corticosteroids - cortisone - I mean, in patients with hepatitis. But at that time when Interferon was not available, it was the only reasonable option that subsequently proved to be totally useless. That's why we mentioned corticosteroid. Now you make me laugh to mention that.

Q. I understand. But this is an article written at its time in 1975 -- or 1982. I beg your pardon.
A. This indicates one should not go back and read his own papers, because there are many things he wouldn't like to have written.

Q. You will understand, Professor, the Tribunal is anxious to understand what the state of knowledge and opinion was at the time and what information was being made available to your colleagues at the time.
A. Obviously I was joking. At that time, what I write here was state-of-the-art. And it was based on reasonable evidence coming from this paper.

Q. Yes. So, the two things really that you were saying in this was that your decision to continue using the concentrates, in effect - that's the first thing - the treating decision, that that seemed justified by this relatively benign outcome of the biopsies; and secondly, that the possibility of using steroids, that you were correct in avoiding doing that, that that form of treatment wasn't warranted by what you had found. Would that be a fair summary?
A. Yes. That was a fair summary.

Q. Yes.
A. You have to consider, also, one thing: That I don't think that really the emergence of the problem of hepatitis, I don't think, as far as I know, that in no place everybody thought of stopping replacement therapy because of the emergence of the problem of hepatitis; and quite sure in saying that, at most, there were people claiming that one should have used volunteer blood. But again, it has been shown that when it is from large pool, there is really very little difference in terms of risk of hepatitis, or, in some instances, cryoprecipitate. But again, as I mentioned before, it was only delaying the problem. So I don't think that really anybody -- the story of HIV is different. But the story of -- I don't think that anybody was really proposing to stop treatment because of this, because of this evidence.

Q. Yes. In your statement, Professor, you refer then at page 4 to a large retrospective study of liver biopsies, which is in fact in the book of documents, is the next page, at page 74. A study carried out by Louis Aledort and Peter Levine and others?
A. Yes.

Q. And --
A. Yes.

Q. That seems to have been, Professor, not a study carried out by them on any particular patients, but rather a review, a statistical review of the findings at biopsies by haemophilia treaters from all around the world?
A. That is -- they gathered the biopsies, specimens, from all those that they knew had done it, including ourselves, if I remember well.

Q. Yes.
A. And we supplied the material. And what they did was to have -- one of the problems, of course, in evaluating liver biopsy is the variation in interpretation of the finding by the different pathologists. So what they did, even with published material, they summoned a group of two or three pathology experts, particularly experts in the field of liver disease, and they reached a common consensus. So I think it was a good study that mentioned that -- that gives prevalence of cirrhosis, that start to be, in a sense, significant. At the same time, however, they also say I think quite clearly at least that -- no, they -- yes, they mention also there was no difference between cryoprecipitate and plasma, which is another confirmation. And so it was -- it was a good study, because of -- because of large number of samples put together.

Q. Yes. I think, Professor, if we look at page 78, they give -- they summarise some of their findings in their discussion. And in particular the first column, the second last paragraph: "The lack of severity of the histopathologic findings in the current materials may not be entirely reassuring. Some recent evidence suggests insidious progression of non-A non-B Hepatitis to cirrhosis, although other studies suggest the possibility of reversion toward normal hepatic architecture. Both progression and reversion as well as a static picture were observed in patients examined repeatedly in the present study. As in previous reports, hepatic biochemical and serologic tests did not predict the histologic lesions." So it seems that the picture is unclear. They refer to studies that would point towards a gloomy outcome and studies that would point towards a less gloomy outcome, and they give the references; would that be fair?
A. Exactly. The only thing I have to say, that this paper was -- again, the problem of the discrepancy between the evidence and the paper publication; this paper was published in '85, so relatively late. I must say that we knew the result, but the results were exactly as you mentioned. So, equivocal in a sense. We knew the results much earlier; because if I remember well, Dr. Aledort has been ill, and this postponed the publication of the paper for at least a couple of years. I think the evidence was available already in 1982 or -- if not earlier. But, basically, the statement that you picked up is very precise and very -- is very precise and reflects the situation in its uncertainty.

Q. Yes. Now, as I have already referred you to, Professor, and we can see it at page 80, there was an important publication by Hay, Triger and Preston and Underwood in The Lancet of the 29th of June of 1985?
A. Yes. This was a good study because it was one of the largest, at least the largest done in a single centre. And I don't remember whether they provided the cases also to Aledort. Anyway, and they did find progression more often than nonprogression. So there was -- they mention again that: "Symptoms and abnormal physical signs were uncommon in these patients". And they go on: "Chronic persistence hepatitis in haemophiliacs is not benign as had been --"So this paper is certainly towards the alarm, which was at that time in a sense already available.

Q. Yes. I think if we look at their discussion at page 81, they say that their observations showed that "progressive liver disease is a potentially serious problem in haemophilia. Of 79 haemophilic patients selected solely on the basis of previous exposure to blood products, 17 had evidence of progressive liver disease (9 cirrhosis, 8 chronic active hepatitis). Serial liver biopsies showed progression of chronic persistent hepatitis to chronic active hepatitis and cirrhosis within a period of two to six years." And so that was -- that was a much gloomier outcome than some of the previous studies, isn't that correct, Professor?
A. They spell it more clearly, I would say.

Q. Yes.
A. But if you look at the numbers -- and of course, now we know that they were right, on the basis of what we now know of the natural history of hepatitis.

Q. Yes.
A. If you look at the number; if you look particularly at what is really disease, these cirrhosis, is not really truly more prevalent than it was in the Aledort study and -- well, I mean, our series was too small to make any -- so I think -- I think that the significance of this paper stands on the large number, on the progressive evaluation, and the fact that they were, let us say, more pessimistic. There is, again, another place where there is a lot of expertise, apart from haemophilia, on liver disease. So I think it was an important paper because these patients -- these people have a lot of authority, because of their mixed knowledge and -- in haemophilia and coagulation and liver disease.

Q. Yes. They refer, Professor, at page 82, to the difference between their findings and your findings?
A. Yes.

Q. And make the point that one likely explanation for that is simply that their study is carried out later in time, and that therefore, the disease may have progressed to a greater extent than it would have done at the time of your earlier study?
A. That is a possibility. But another possibility - and in my opinion rightly - simply that we studied only 10 patients, where they studied nearly 80 patients. So a much larger number.

Q. I see. Yes. I think you also have referred us, Professor, at page 84 to a letter which was published in February of 1986 in The Lancet by Schimpf - Doctor or Professor?

A. Professor Schimpf.

Q. Professor Schimpf. And his retrospective study from West Germany also found a development of progressive liver disease occurring in about one-third of his patients, followed up during 13 years. Would that be correct?
A. Again, the only thing -- it's not a big detail, but I think it is a detail that -- I think that, really, chronic active hepatitis is -- the real evidence of severe liver disease is when you say cirrhosis. And if you look altogether, the three or four studies, except ours, more or less - they have the same incidence of prevalence, if you prefer, of cirrhosis - between, let us say, 10 and 15 percent; which is what is now known with more knowledge of the natural history of Hepatitis non-A non-B.

Q. Yes. But I suppose the cumulative result of what we have looked at, Professor, is that starting in 1980 and coming through to this 1985 and 1986, the picture has got progressively gloomier, would that be a fair --
A. You are right -- whether it got progressively gloomier because time has elapsed, as the investigator from Sheffield surmised, or whether it is because more patients have been studied, I don't know. But certainly, this is -- this is a fact.

Q. Yes.
A. And in fact, in 1985, there was concern, and action has already been taken to develop safer blood products.

Q. Yes. Now, I think at page five of your statement, Professor --
A. Yes.

Q. -- you summarise the situation at the -- at the top of that page. How would you summarise what we have just looked at?
A. "It was only in the mid-'80s that it was shown to be progressive, albeit in a relatively small proportion of these patients".

Q. Yes. And then what was done to try and deal with this problem, Professor, of the hepatitis, in general?
A. Several things. That really started, if you wish, at the end of the '70s. So, when -- I mean, none of us was happy. Even though it seemed to be nonprogressive to begin with and not a serious problem, obviously none of us was happy to see that our patients were harbouring this virus. So I think that action has been attempted. The only thing I tell you, that I think very few people really thought to stop replacement therapy with concentrate. But certainly, action was taken. There were various type of action. There were some people that were claiming to use the blood products derived from volunteer donors. I think at that time, it was reasonable; now we know that it wouldn't have solved the problem, particularly if you use large pool. Others thought to use - at least in the mild haemophiliacs, that is the patients more at risk; and in a sense in which the thing is more disturbing because of the low risk related to the main disease - to use DDAVP or cryoprecipitate. Cryoprecipitate has been, believe it or not, mainly abandoned. It was too practical, apart from the result that we know now and also we knew at that time. See the Levine study, it was too -- the advantages given by replacement therapy in the '70s, the home treatment, were so huge that the atients themselves, even they knew very well -- because they knew very well the problem of hepatitis, were not prepared to switch to cryoprecipitate and to have to go

to the centres for being treated; long journey; delayed treatment - no treatment sometimes. But certainly, the most important thing was that, at the end of the '70s, some pharmaceutical companies and also some independent investigators tried to develop the first virucidal method that seemed to be -- apart, of course, from the fact of screening, of improving the screening of the donors. But this we knew always, that would carry limited - not nonexistent, but limited advantages because of the sensitivity of the method. So the real breakthrough, in a sense, was the development of virucidal method, which started in the late '70s.

Q. Yes. Perhaps just before we come to that, Professor, you deal at page five with the question of Desmopressin and the development of Desmopressin in Italy. Can you just explain to us about that, Professor?
A. Well, as I said before, as a consequence of my friendship and collaboration with Professor Ingram, I became interested in this problem, of the problem of the possibility of raising Factor VIII; only Factor VIII is raiseable - can be raised as early as in the late '60s. Ingram and others did show that Factor VIII could be mobilising patients at a measurable level; so only the mild and moderate haemophilia. Unfortunately in those with unmeasurable levels there is nothing you can do to increase it. Let us forget those patients for which replacement therapy, exogenous replacement therapy is the only possibility. There are some hints that indigenous replacement therapy was a possibility, because -- well, quite apart from studies made by Canon, an American physiologist, in 1925, that did show that animals subjected to stress had a faster blood clotting. Ingram and others, and Rizza particularly, always, again, in the UK, did show that the infusion of adrenaline and of strenuous physical exercise could increase Factor VIII three or four times in patients with heavy measurable levels of the same factor. Obviously, it could not be conceived to give adrenaline, and to patients with haemophilia, even though it has been done experimentally. And he did show that also in haemophiliacs Factor VIII could be raised, but only on experimental basis because of the side effects of the -- obvious side effects of the treatment. And also, it could not be predicted that a haemophiliac could be taken to run in a stadium for about one mile at their fastest possible pace to increase the factor levels.

Q. Yes?
A. And so there was a search for drugs devoid of side effects, incapable of having the same effect. And over a long series of experiments and trials with different drugs that I developed with my associates in Milan, also something has been done, together with Ingram and Nilsson in Malmo; eventually we found this drug is derivative of the antidiuretic hormone, Desmopressin, that increases Factor VIII without significant side effects.

Q. Yes.
A. And once we did show that it did increase in volunteers -- in haemophiliacs not bleeding, so in experimental conditions we thought to -- there were -- we didn't know; the only thing we didn't know is whether this increase in Factor VIII of indigenous Factor VIII was haemostatically as effective as the exogenous Factor VIII. The only way to prove that was to give it to bleeding patients. So we first started with mild haemophiliacs undergoing dental extractions. We took this as a model because we thought if bleeding did occur, occurred -- was visible, and so there was really no risk of the patient; also because we could have given cryoprecipitate. So we found that it

was effective, that Factor VIII was raised but haemostasis was achieved. And then we went on and we gave the product to patients with -- more to prevent -- to treat more severe bleedings and to prevent major surgical procedures. So also when bleeding could not be seen. And the -- the thing worked out. This was done between 1975 and 1977.

Q. Yes.
A. And we published the paper in The Lancet in April 1977, and this was the demonstration, and that's how this drug became available.

Q. Yes. If we look I think at page 91, Professor, in the references. That's the paper that was published in The Lancet of the 23rd of April of 1977.
A. Yes.

Q. And I think that certainly initially the results that you note there in the summary were that there were four patients I think who were given Desmopressin before dental surgery. And "in two, there was no abnormal bleeding after dental extraction, whereas plasma concentrates were necessary to control oozing from the sockets of the remaining two patients." So in two of the four patients, the Desmopressin was entirely successful; and then in two others it was necessary to supplement the Desmopressin after the procedure with some cryoprecipitate, I think, is that correct?
A. Yes. The reasons for this failure now, they are very clear: It was -- we didn't know yet the right dose; and most importantly, we didn't know what was the lower limit of measurable Factor VIII that could respond to this drug.

Q. Yes.
A. I mean, for instance, there were patients with two or three percent Factor VIII in which we got an increase of Factor VIII. But let us say it went from 2, 3 percent to 6, 7, 8 percent. So still, insufficient to control bleeding. But of course, at that time there was little knowledge, and so it had to be acquired by trial and error in a sense, with the consent of the patients in a situation that was not risky, because we knew that we have a second net. And so we developed progressively the experience and we also used it in more challenging operations and in patients with higher baseline Factor VIII levels.

Q. Yes. And then I think you published a further paper, Professor, in 1981, at page 95.
A. Yes.

Q. Again, setting out your experience in the use of Desmopressin, is that correct?
A. Yes, that was -- that was more -- in a sense, that is a study that perhaps should have been published before the clinical study, because it's more a study finding exactly the right dosage; in a sense, probably most of these studies had been done before and published afterwards, just to give some evidence on the pharmacological response to the drug. Obviously, the most striking thing they wanted to communicate first was the fact that it did stop bleeding in patients.

Q. Yes.
A. So this is more a study done in healthy volunteers. It's a study done also in haemophiliacs in which we provide evidence how long the increase, indigenous

increase is lasting. I don't think -- it is probably an important paper but it is not the crucial paper.

Q. Yes. And what was found with experience with the drug, Professor, in terms of -- what level severity of haemophilia was capable -- was a person -- with what level of severity would this treatment be effective?
A. It depends not only on the severity of haemophilia, but also the severity of the bleed, of the bleeding episode. And that -- what we know, that in average, in patients with haemophilia, Desmopressin raises Factor VIII three times. That is put in that way. It depends on many circumstances. Supposing a patient with 5 percent Factor VIII has a minor bleeding episode, maybe a haemarthrosis; he would go to 15 percent, and Desmopressin might be enough to stop that bleeding episode. But certainly, I wouldn't dare now to do dental extractions or major surgery with -- in a patient like that, because 50 percent at the top level wouldn't be enough to secure haemostasis. But on the other hand, if you have a patient with 15, 20 percent Factor VIII, in which you may go to 50 to 60 percent; so to normal level, if not more. In this patient you can probably do, and it has been shown to be possible, to do any sort of major operation. So there are limits. The drugs is not a miracle; I mean, it works in certain conditions, providing you have the right indication in terms of the baseline level of the patients, and the bleeding episode to be treated or to be prevented.

Q. Yes. I think you also refer at page six of your statement to the Tribunal, is there another limitation on the use of the drug in that do patients become resistent to the use of the drug?
A. Yeah. That's called tachyphylaxis; probably the reason of progressive treatment of poor responses is related to the fact that the stores become deplete. Supposing this indigenous Factor VIII is released from the stores that these patients with mild haemophilia have, where those with severe haemophilia do not have, and this is why it cannot be used. The stores become depleted. It's called tachyphylaxis. There are other possibilities. There is the possibility that the receptors become occupied; anyway, this is a well-known fact which limits, again, the use of the -- of this drug. But again, it depends on the situation. Because with an example of 5 percent, it goes to 50 percent, and then you want to give another infusion the next day, you will find baseline levels more or less around 5 percent, and these lesser response, so it may go to 10 or 15 percent. So this patient will not benefit. But the others, those going up to 50 percent may get by on repeated infusion - still levels, so there are sufficient for haemostasis. Certainly one has to take into account, has to monitor and be aware of the problem, which limits the use of the drugs, but usually, see, the patient with mild haemophilia, once they are given a burst of Factor VIII at the time of the challenge, of the bleeding, of the surgery, and they reach at that time high levels - probably in the next few days - even if you can give DDAVP for only two or three days, this is enough to maintain the haemostasis that was secured by a single infusion.

Q. Yes. Now, I think did that publication in 1977, did that lead to a general use of Desmopressin in Italy, shortly after that, Professor?
A. Yeah. There is some Latin author - but in this instance, I think my colleagues in Italy did follow us and it was widely used, even though it was not immediately licensed. But the drug was available for the treatment of other disease, so it has been widely used in Italy.

Q. Yes. Do you know whether it was widely used in other countries or when, approximately, would it have come into more general use?
A. I don't know exactly. Certainly when this paper was published there was a lot of interest. But I think it was rather unfortunate; probably the first person that used it in the UK was Professor Gordon Lowe (?) from Glasgow, and he had a side effect, probably because of the indications in our paper were not solid enough. He gave it probably too frequently with frequent infusion and the patient developed a side effect of this drug, which is water intoxication; the drug is an antidiuretic, so particularly if you drink a lot of water and so on and you give a lot of it, it does present an antidiuretic effect. There was one patient that developed signs and symptoms of water intoxication and so -- and this was the first, let us say, publication after ours, a few weeks after it was published in The Lancet. I think this -- even though subsequently it was shown by being careful and not exaggerating with the dosage, which was a typical problem often experienced by them and also by us, it was shown a very rare event. And it was enough to be careful not to give a lot of fluids, to take the weight of the patient at regular intervals; very simple measure. But I think that paper was -- probably gave a very bad impression. Even subsequently there was demonstrations that the drug was efficacious. I think it did cause some reluctance to use it to the very beginning.

Q. Yes.
A. And so I think in -- there was a lot of interest for the paper and the study has been praised. There was an editorial accompanying it. But it's usually, you see, when you bring something really very new and revolutionary like this, people have to make up their minds.

Q. Yes.
A. So I don't think it was used -- I don't know exactly, really. I don't know exactly. You should ask the English treaters, but I don't think it was used on a large basis before the '80s.

Q. Yes. Now, I think then you also deal, Professor, at page 7 of your statement with the question of the possibility of the usage of cryoprecipitate for persons who are mildly affected with haemophilia.
A. Well, as I said before, this has been proposed by many, and also, adopted by us in patients with mild haemophilia. And certainly, it was a good choice; but barring the use of Desmopressin, it was the treatment of choice for patients with mild haemophilia.

Q. And therefore, would -- would you yourself in your own practice, Professor, have been using cryoprecipitate, say by 1980?
A. Probably not by 1980, except in the patients who were not spending to DDAVP, because of the availability of DDAVP. But certainly in some instances in particular patients with measurable levels of factor, I think we did use it.

Q. Yes. And have you any idea what proportion of your patients that would have been or what sort of level of usage of cryo you would have had in 1980 and after 1980?
A. Very little; we did use -- we did start our haemophilia programme in the late '60s on the basis of cryoprecipitate, but when the concentrates become a -- became

available, the use of cryoprecipitate had been nearly abandoned. And many centres stopped pro -- many blood banks stopped producing it, producing it at all.

Q. I see.
A. Still, something was produced for patients with von Willebrands Disease, but this is another story. And I can imagine that obviously you see, having sort of discovered DDAVP, we tended to use it, except in the cases where we knew that it wouldn't work, as I mentioned before.

Q. Yes.
A. And also in the cases of failure, but certainly very, very small proportion of patients, I would say. We used cryoprecipitate for von Willebrands Disease, but that is -- as I say, is another story.

Q. Yes. And for instance, for children who would have been treated say from 1980 onwards, would they have been receiving cryos, as a matter of course, from you, or what product would they have been treated with?
A. I -- in some instances probably, but the majority didn't want to use cryoprecipitate, because it was -- it carried some limits. You see, they had to come to the hospital. The temptation to use the little bottle, the little miraculous bottle of concentrates was very high, and the haemophiliacs wanted to use that.

Q. Yes.
A. They were not happy to have to come to the centre when they knew around then, maybe from their brothers if they had brothers, that they could be treated at home with concentrate.

Q. Yes. And then if we turn to Factor IX patients, Professor. I think at the end of page 7, the beginning of page 8, persons with Haemophilia B. Was -- I think you have already told us, Desmopressin wasn't a possibility for such patients?
A. No.

Q. And neither was cryoprecipitate?
A. No.

Q. The Tribunal would know that. So what treatment was available, say, in 1980, in Italy for such patients?
A. In theory, we could have used fresh frozen plasma, but again, there was very little use of that. Also -- because one thing that has to be said, that the blood transfusion service at that time in Italy was less developed than it was say, I'm sure, in this country and in the neighbouring British islands. So, it was -- there wasn't very many blood transfusion centres preparing plasma. And anyway, this was certainly not our case, we had plasma available. But again, with the prothrombin complex, concentrate was very simple, was very practical, and so we didn't use fresh frozen plasma.

Q. Yes. Would that prothrombin complex concentrate, would that have been manufactured by commercial fractionators?

A. Yeah, there was no -- in Italy there was no production by blood banks; I think it is an industrial production. Even in this country it was produced and in England it was produced by the National Health Service, as I know, but on an industrial basis.

Q. Yes. And similarly, the concentrates that we have been talking about, Professor, they would also at this stage have been all concentrates manufactured by commercial fractionators?
A. Yes, at least in our country.

Q. Yes, in Italy. I mean, that's what I was talking about.
A. Sure.

Q. Yes. Now, I think you go on then, Professor, to deal with the heat treatment, and other virucidal methods at page eight of your statement?
A. Yes.

Q. And what was the origin of that work; what were the first steps in the heat treatment process?
A. Well, as I say, commercial companies, commercial manufacturers started to think about virucidal methods in the late '70s. There is proof of that, of study done in animals in the United States by Baxter. Then certainly one of the pioneers in this field was Behring, with the pasteurised concentrate; and this German company Biotest with their beta-propiolactone heat-treated Factor IX concentrates. The problem was that -- I mean, the Baxter manufacturer provide data only in animals, and the data in animals were, let us say, they were quite misleading, as you knew retrospectively later on --

Q. Yes.
A. -- because they did show that there was transmission -- there was no transmission of the non-A non-B virus; and there was, on the other hand, transmission of Hepatitis B.

Q. Yes.
A. So they were quite misleading. But in any way, they looked promising but not entirely safe. Something was being transmitted. Anyway, it was not available for clinical trials before 1982. And I was the leader, the responsible investigator for this trial which started in 1982. And then there is the story that results were communicated.

Q. Yes.
A. The German concentrate looked promising, because pasteurisation is known to be an effective treatment for albumin, for decades. And -- but the studies that they did were not good; they couldn't provide the evidence. And the concentrate anyway was available in very limited amounts, only to Germany, and certainly not enough to satisfy the needs of German haemophiliacs. And we -- we had practically no access to it in Italy. And the same is true for beta-propiolactone; that this was an ingenious method developed by Biotest that did study it in humans, is something that is really monument to what now would be totally unacceptable on the basis of clinical study. But even at that time, totally unethical because they treated normal volunteers from their own company. They treated five healthy employees of Biotest, and they found

that there was no increase in transamination. So thanks God, the five poor people didn't develop any problem. Also, this didn't give good impression, because, I mean, the fact of treating normal volunteers with a product that was totally unknown was certainly not very satisfactory. Then they treated also a few patients, and again, they showed no transmission of hepatitis, but the concentrate was not available on a large scale, even in Germany.

Q. Yes. Was there a concern about the propiolactone itself?
A. Yeah.

Q. What was the concern about that?
A. Well, you see, in terms of concern, there were many concerns with the virucidal method. I will start from beta-propriolactone. There was some evidence it could be denaturing DNA, or being carcinogenic. It was a chemical, so not very happy about it, even though now we still use some chemical to produce concentrate. But it's also the heating, you see, didn't make many of us very happy because I'd been brought up and educated thinking that Factor VIII is very labile; you have to keep it in the fridge, the sample, because it gets easily inactivated, everything, in melting ice. So the idea of heating such a labile molecule came as a shock for many of us. And there was -- okay, I mean, obviously the fact that there was -- the factor was not destroyed was immediately evident. It was obvious that the company was not proposing a method destroying what they wanted to infuse. There were many other concerns: There were concerns that heating might induce denaturation of the protein, the formation of new epitopes, new confirmation of the protein, and so the risk of developing antibodies in haemophiliacs. There was the risk of aggregate, and this was a concern that was raised by many of us, including leading figures in the field like Professor Bloom and also Dr. Bird from the United Kingdom.

Q. Yes.
A. So there was not -- you have to understand that the -- to propose to a treater that was brought up with the idea that Factor VIII is very labile protein, to expose Factor VIII to heating was something we perceived as problematic, let us put it in that way.

Q. Yes. Now, Professor, I think we have already referred to your involvement in the International Committee on Thrombosis and Haemostasis. And I think what you have referred to, that that was the working party of what was an international society, a learned society, is that correct?
A. Yes, it is correct.

Q. And did that committee set a standard in I think November of 1984 for clinical trials in respect of attempting to define the risk of transmission of non-A non-B Hepatitis?
A. Yes. We did. Just because of the reason that I mentioned before, that the studies that presented in 1983 -- I think, yes, the Behring people presented some data that they were publishing. They also presented it to the Congress of the World Federation of Haemophilia in Brazil. I think it was in 1983, if I remember well. The day I remember I spoke with them and I tried to emphasise a few points that were not very convincing. In a sense they recognised the evidence was meager. Then I proposed to the International Committee to set up a Working Party to develop criteria. The Working Party was created under my chairmanship and we did present -- we worked

on the protocol. And it was in November 1984, at a meeting that took place in Miami, that we agreed upon a protocol that was recommended, and usually implemented without too much problems by my colleagues when -- and the companies, when they wanted to evaluate the safety of clotting factors concentrate exposed to virucidal methods.

Q. Yes. And can you just explain, I mean, without going into too much detail, the broad -- the basic terms of that protocol; first of all, I think did you require that there should be a number of patients involved in the --
A. Yes.

Q. -- study. I think approximately 20, would that be correct?
A. Yes.

Q. And what was to be the history of those patients; what sort of patients were required for these studies?
A. Based on the knowledge that really dated from the beginning of the '70s, but also, established more, in a more solid way by the English investigators later on; that with large pool concentrate, the patients more at risk were those previously untreated, so obviously not exposed to any potential immune defence or related treatment with the products. And also, the fact that these patients have 100 percent incidence of hepatitis with the first infusion, established solid by two studies conducted - one at Royal Free Hospital in London, and the other in Oxford - it was decided that there shouldn't be a control case -- control group treated with nonheated concentrate; also, because at that time obviously it was felt unethical. But that we assumed that the true prevalence with the unheated products was 100 percent, and so we -- but we aim at zero percent, because we are not happy with -- okay, we are happy with some improvement but obviously we wanted to get zero risk ideally. And we discussed later on whether this has been achieved or not. Anyway, it was established that to be a previously untreated, that transaminases at that time - there was no specific marker for non-A non-B - had to be measured at regular intervals and at least 20 patients had to be studied. And we also recognised that even with 20 patients, and with zero study, study with zero numerator, we couldn't be sure that there was no transmission of hepatitis. So we advised a very simple method to calculate the confidence interval, so that, for instance, with 20 cases, if I remember well, there was still a risk between zero, which was the observed risk; and 15 percent, if I remember. That was a table with all -- and of course, the risk of saying that the concentrate was safe, when in fact it was not, was smaller for larger study than for smaller study. The confidence limit -- was I -- am I clear?

Q. Yes. And I think there was also -- there was a required length of time for which patients would have to be followed?
A. Yes.

Q. And then a required level of frequency of examination, so that if they had fluctuating transaminase levels, they would be picked up; they would be examined sufficiently frequently so that that would be picked up?
A. Exactly. That's very important. Because in the study that was published in 1985, but it was indeed started much earlier, we had seen that in some instances some serious peak of transaminases, that was actually the marker at that time, could be

missed if patients were infrequently treated. Because it was known in the natural history of Hepatitis non-A non-B that one could get a huge peak of transaminases, maybe lasting for 15, 20 days. And then if treatment inter -- testing intervals were too scanty, too sparse of, say, one month or more, you could risk not to pick up the increase of -- the peak.

Q. Yes. Now, I think you referred, Professor, and we could just identify them because I think the Tribunal is familiar with these papers. You referred to the work of some English -- some English doctors in relation to the transmission of hepatitis, and I think the two papers are your references -- sorry, reference 18 and 19 at page 127 and 131. 127 is: "Non-A non-B Hepatitis After Transfusion of Factor VIII in Infrequently Treated Patients," Fletcher and others; and 131, "A High Risk of non-A non-B Hepatitis after First Exposure to Volunteers of Commercial Clotting Factor Concentrates," Kernoff and others?
A. Yes. One paper was published in December 1983 and the other one was published in 1985. But again, the second paper is the typical example of the situation of knowing before the published paper. Because I was in frequent contact with Professor -- Dr. Kernoff. In fact, I think I am among those that he thanks. And so, I was aware of the results, even -- no. I was not among those he was thanking. Anyway, I was in touch with him and I knew of these results at least one year before they were published.

Q. Yes.
A. So the two studies were more or less simultaneous from the point of view of our knowledge, and they were very basic studies. They established, in a sense, the rules for the evaluation of the virucidal method, and they also established the very important point that the first shot of concentrates gave hepatitis -- all the patients, if one did use large pool concentrates.

Q. Yes. Now, I think you have already mentioned to us, Professor, the study which yourself and your colleague Dr. Colombo carried out in relation to heat-treated product. And I think that was the Travenol dry heat-treated product --
A. Yeah.

Q. -- isn't that correct? And I think that the study started in 1983?
A. Yes.

Q. And you have told us that by a conference in Barcelona in September of 1983, you knew and were able to report to your colleagues that, in fact, hepatitis was breaking through; that there were people with raised transaminase levels in the study, is that correct?
A. Exactly. That is true.

Q. I think the actual formal publication of the results of the study doesn't come until July of 1985?
A. It didn't come before 1985, because we wanted to have all the results. There was also -- it was wrong, probably, but we wanted to see whether there was a decreased prevalence, at least some of us thought so, but at least maybe we will be able to demonstrate that the problem is less than with heated products. That was probably a mistake because really you want to have a 100 percent result; otherwise it's not

worthy. There was probably a reduction of -- if you look at those concentrates similar to these, they transmitted hepatitis, but probably not with 100 percent incidence, if you look at this paper and the papers subsequently published by others that are quoted here. Anyway, it was not published until 1985 for several reasons; some of them I don't remember exactly. But certainly, it was known to the scientific community that hepatitis was transmitted. And certainly, it was very well-known to me that the method was ineffective. And I remember many of my colleagues - there were also many American colleagues in Barcelona - were impressed and -- negatively -- by this result. And many said, okay, but then this heating is of no use. And automatically, one tended to transfer this result also to the store of HIV. And you must recognise - I don't know whether by intuition or by evidence; probably more by intuition than by evidence - Harold Roberts, I remember he said at that time, 'well, but it's better than nothing, it may work; it doesn't work with hepatitis but it may work with HIV'. So you have to recognise that he has been always, since the very beginning, a proponent of the heated concentrate.

Q. Yes. We will come back to that, to the question of HIV, in a few minutes, Professor. Just to follow out the hepatitis, I think that study is at page 142. It's your reference 20.
A. Okay.

Q. And I think, in summary, Professor, did it show that 11 out of 13 patients did develop non-A non-B Hepatitis, who had been treated with the Travenol product heated at 60 degrees Centigrade for 72 hours.
A. Yes. And as I said, this results -- I think the summary of this finding contrasts with the absence of non-A non-B Hepatitis in the chimpanzee modal, and again, this was again unpleasant because - you see, I mean, this discrepancy was very unpleasant because we thought that the chimp could be suitable modal to test the concentrate. This was one of the reasons why we did earlier, when the results were already available but before the publication, we did push towards the development -- towards the clinical validation of the virucidal method rather than the laboratory validation. We said we were not happy and content with the animal modal - even though, ideally, they are the best - because they proved to be ineffective or at least contradictory in this instance.

Q. I think, Professor, Dr. Prince, of whom you probably know, has given evidence to the Tribunal, and he would be a proponent of testing in chimpanzees. And his explanation for this particular problem with this particular product would be that -- not that there was anything wrong with testing in chimpanzees, but he felt the actual particular study wasn't correctly designed and properly carried out. Would that have been the perception of the time or would it have been the perception that you have given to us now, that chimpanzee tests were not a reliable guide?
A. I'm sure he is right, and of course, the evidence is there to demonstrate that. But at that time, the chimp, as it is called, was considered a good modal. Anyway, I mean, I don't remember Prince being very vocal at that time about it.

Q. Yes.
A. Certainly for us, there were clinical data indicating that it didn't work, and a clinician is always more convinced by clinical data than by data in animals. But

Prince is certainly an experimental hepatologist and he knows much more than us on the chimpanzee modal.

Q. Yes.
A. Anyway, believe it or not, the scientific community, since then, has accepted our concept, and all the concentrates have been tested in humans rather -- I don't think; except those, are the problem - the blood centre, they spent a lot of time with the animal. When they thought, on the basis of the in vitro studies, they could get rid of significant amount of virus, they went to the human studies.

Q. Yes. I think were there other studies carried out of dry heat-treated products in relation to the transmission of hepatitis, Professor?
A. Yes.

Q. And I think do you refer to some of those in an article published quite a long time after the event or -- sorry, it's a passage in Balliere's Clinical Haematology, which would have been published in June of 1996?
A. Yes.

Q. And you provided that to us as reference 21?
A. Yes.

Q. And I think that -- I think the Tribunal is probably aware of some of these studies, but I think -- I think, in summary, Professor, what do they show about the heat treatment; the dry heat treatment, if I might put it that way, in terms of its effectiveness against non-A non-B Hepatitis?
A. They did, in a sense, confirm, usually on a smaller scale also - because there was no reason to continue, after our experience, when they saw one or two cases of hepatitis, that it was difficult to imagine was due to some external factors, were obviously attributed to the concentrates - they found that other heating methods, more or less robust than the one that was used by Travenol, were equally ineffective in inactivating the virus. So Professor Preston studied the Armour concentrate treated at 60 degrees but for a shorter period of time --

Q. Yes.
A. -- and he found that it did transmit hepatitis. And Dr. Allen and others did study the concentrate heated at 68 degrees but for 72 hours, and so, in a sense, it was confirmed. But then there was subsequently the heptane, n-heptane and heat-treated products, and all did show that hepatitis was being transmitted. And these studies were published after our study in 1985, 1986, and so on, 1987, sometime. But the results were available before. So on the whole, they established quite clearly that the available heating method, mostly dry heating but also heptane is - okay, dry heating plus this chemical, were not fully effective. And again, they might be more effective in nothing, but we are not satisfied with that.

Q. Yes. I think were there further methods; did further methods become available of viral inactivation?
A. Mm-mm.

Q. And when was that, Professor, when would you identify the advent of more effective means of inactivating the hepatitis virus? I think you deal with this at page 10.
A. All that happened in that period, between 1985 and 1987. What is really -- the time is difficult to say, again, because some knowledge was available, even before the paper was published. Now, of course, the only source of reference is the published paper. But certainly in that period, people moved to, okay, pasteurised concentrates, and there there was a demonstration of effectiveness came out a few years later. But there were -- a proper study was carried out. In the United Kingdom, they developed the higher heating method - the super dry heating. And there was some evidence that it was effective. Then there is -- solvent/detergent method became available, and the vapour heating. The vapour heating, there were some problems to begin with, and we reported some cases of Hepatitis B that were quite annoying. But -- and one case that developed both Hepatitis B and Hepatitis C. But they improved the method, and subsequently, other studies have shown that it was reasonably safe. So let us say that, in those two years that these new products became available, still now represent the milestone of the use of products, plasma-derived products in haemophilia; even though subsequently there had been other modifications - I don't know whether of interest for these proceedings - the addition -- the development of double inactivation methods, but this was due to other reasons, particularly to the fact of the store of Hepatitis A. But I don't want to expand on that. You asked me specifically --

Q. Yes.
A. To conclude and to -- to conclude as to your question: It was in those two critical years, with some -- it's difficult to establish a precise time because of the difference in publication, the difference in the licensing in different countries, but it was in the two years that one became aware that dry heating was not enough for hepatitis, and new products were being developed that were much more satisfactory.

Q. Yes. I think if we look, Professor, at page 122?
A. Of what? Of my --

Q. Of the documents, of the references; the paper I think you have already referred us to, which was a paper by Professor Schimpf and yourself about the pasteurised product --
A. Yes.

Q. -- that was published in 1987 --
A. Yes.

Q. -- in The New England Journal of Medicine. And I think did that show the pasteurisation - the heating in solution at 60 degrees Centigrade for 10 hours before final lyophilisation - did that show that to be effective against the risk of transmission of non-A non-B Hepatitis?
A. Yes. That was a study carried out in a large number of patients, 26 or more, than the, let us say, magic number of 20 established by the international committee. Patients were infused with different batches of concentrate, which is another important thing, because I mean, if you use only one batch, even in a large number of patients, you only test one possibility; here there were the variations due to patients but also the variation due to batches. And altogether, I think it was a rather solid

paper; in fact, it was published in one that we considered one of the leading -- probably the leading journal, together with The Lancet, in general medicine, indicating that this problem raised the interest not only of the specialised person, the haematologist or the haemophilia treater, but also the general physician. In fact, also the study with Colombo was published in The Lancet.

Q. Yes. Now, I think at page 11, Professor, then you go on to deal with the situation
A. Eleven of the report?

Q. Yes, sorry, of your statement.
A. Yes.

Q. You deal with the situation since 1987, and the evidence of Hepatitis C infection since 1987, isn't that correct?
A. Yes.

Q. I mean, apart from the formal clinical studies that we have dealt with, I think you go on to consider, then, the more general evidence that there may be of Hepatitis C infection after 1987, isn't that correct?
A. Yes. I write here there was only a paucity of cases; certainly there was a dramatic fall from the late, say, 100 percent rate to the very few cases that were published here and there, somewhat anecdotal. And that's why I think we all tended -- product became much safer since 1987; let us say, 1987/1988, beginning of 1988.

Q. Yes.
A. I think would maintain that and I think everybody would agree with that.

Q. Yes. Well, if we just look at some of the studies that you provide for us there, Professor. I think the first one is a reference to a study by Morfini and others in 708 persons with haemophilia, which is at page 156.
A. Yes.

Q. And I think, in that study, two groups of patients were looked at. First of all, I think the paper identifies that in July of 1985, there was a switch in Italy from concentrates which hadn't been subjected to any form of heat treatment to concentrates which had been subjected to a dry heat treatment, isn't that correct?
A. That is correct, yes.

Q. And what the study did was it looked at 708 patients infused for the first time before 1985, and 80 patients infused for the first time between 1985 and 1991. And there was a very marked difference: The prevalence for antiHepatitis C virus was 83 percent in group A; and six percent - five out of the 80 patients - in group B. And then they identify, in relation to the five patients, what the -- what the source of their infection was. And I think if we look at page 157, it's summarised under "Results," and a reference is made to Table 2, which appears at the next page, at page 158. But the contents of that Table 2 are summarised in the following way under "Results: Table 2 shows that five patients were antiHCV-positive among those first infused between July 1985 and 1990. One of the three patients infected by HCV at the haemophilia centre in Florence had mild Haemophilia A and was first infused in 1985 with 3,000 international units of Koate HT (Cutter), dry-heated at 68 degrees C for 72

hours because he had to undergo surgery. The patient vaccinated against HBV developed symptomatic hepatitis one month after the treatment. Since 1985, he has been no longer infused with blood products. When first tested in 1990, he was anti-HCV-positive" --That was the first patient who seems to have been possibly infected by a Cutter product with Hepatitis C. "The remaining two antiHepatitis C virus positive Florence patients had Haemophilia B and had been infused exclusively with Preconativ T" -- a Kabi product -- "prepared with hydrophobic interaction chromatography plus dry heating at 65 degrees C for 48 hours. One patient with severe Haemophilia B has been treated very frequently between 1985 and 1991." He showed mild increase in ALT 10 months after the first infusion, but no increase in transaminase was detected afterwards.It goes on to deal with when he was tested. And then the -- there is a further, the next paragraph, a further patient: "The patient observed at the haemophilia centre of Parma was a Haemophilia A patient treated for the first time with vapour-heated Kryobulin on June 1986 (patient 4). A month later he developed severe clinical and biochemical signs of acute hepatitis; the patient has never been infused subsequently and when first tested in 1990 he was antiHCV-positive. "The patient observed at the haemophilia centre of Bari had severe Haemophilia (Patient 5). He was enrolled in the virus safety study on Haemate P from 1985 to 1986, and further, in the study of Beriate P from 1987 to 1989, remaining antiHCV-negative. Since 1990, the patient was infused very frequently with Haemate P, that had, meanwhile, been licensed in Italy. At the end of 1990 he developed acute hepatitis and seroconverted against HCV. Both the mother and the grandmother of this patient resulted at that time antiHCV-positive, whereas close family relatives and sexual partners of the remaining four seroconverters were antiHCV-negative." So, in fact, Professor, there seems to be quite a varied history of treatment in relation to those five patients, would that be fair comment?

A. Yes, I think it is fair comment. These are facts, they are not easily -- not always easily explained; particularly the pasteurisation, with the limits that are mentioned here. There were some cases in the family, but of course, cannot be sure at all that that was the cause. One has always to think of the most likely, and the most likely, if you wish it or not, is the concentrate. The Koate HT is known to transmit hepatitis. Why it was used, as far as I know, after July, I don't know. Probably wasn't -- the inventory, the information didn't reach -- I don't know, I have really no explanation; that, I don't remember. I have probably an explanation for Preconativ, because this concentrate has been tested by us and we published it, and is not included here, but we published in the Annals of Internal Medicine in 1985. And we published a study that was based on the careful follow-up of the six patients with Haemophilia B. And in those patients, even following using usual criteria, there was no case of hepatitis. But subsequently, and they are reported here, on the basis of that, the concentrate has been used for a while and then some cases of hepatitis were reported by Morfini in Florence, and these are actually the case; and also by Ingram in Sweden, because that was Sweden concentrate. So the message is that we probably published prematurely the study that no case of hepatitis did occur; the sample was probably too small - six cases; three divided by six gives a 50 percent possibility. Even with zero cases gives still a 50 percent possibility of having hepatitis due to the rule of three that I mentioned before. And so this is the typical example that when you study a limited number of patients - I don't remember whether the study was planned before or after the recommendation - the problem is that Haemophilia B is rare and so probably couldn't list in the study more than six patients; six patients previously untreated is not a huge number. The message there is that concentrate was infectious but it was not

known, on the basis of our previous publication, that it was infectious. So this explained the two cases. Now of course, since then, the concentrate has been abandoned. I think there is more or less an explanation for all these cases, but certainly we regarded these results with the individual explanation as rather satisfactory at that time. The study was done much later of course -- published much later. It was -- did confirm what was our impression: Since 1987, the product had become much safer, and basically, the epidemics, or whatever you want to call, of hepatitis in general - or let us say Hepatitis C, has been stopped or diminished substantially.

Q. Yes. And, Professor, can I ask you about your own treatment regime in, say, 1987; what products would you have been using?
A. I -- we certainly used only the products that we knew, on the basis of the evidence, were safer, although they were available. I don't remember exactly -- basically, four products in Italy: Koate HS, which is pasteurised, it is mentioned in the study -- Koate HS, which is pasteurised; Kryobulin 10-3 which is steam-heated, and was proven in a study, which is not mentioned here, to have no case of hepatitis; Beriate, Italian product; Haemoctot, that was solvent/detergent-inactivated. We used those concentrates.

Q. Yes. The Behring eight (sic) or Beriate --
A. Beriate is another pasteurised concentrate developed later. At that time was still -- similar to Haemate P or --

Q. Yes.
A. Similar to Haemate P, only more purified.

Q. Who would have manufactured the Beriate?
A. Behring.

Q. Behring. I see.
A. Like, Haemate P is the same manufacturer.

Q. Yes. And would -- and sorry, you said there was an Italian solvent/detergent product?
A. Yeah.

Q. What was the -- what was the origin of that, Professor; who was -- who was making that?
A. It was, and is still, manufactured by the main Italian industrial manufacturer of blood products, called originally Biagini; then they changed the name to Haima; and now Kedrion, on using, mainly now, Italian plasma, but also a substantial proportion - let us say 60 percent Italian plasma, 40 percent imported plasma. They produce Factor VIII and Factor IX concentrates which originally were inactivated only with solvent/detergent. Now they are inactivated with solvent/detergent plus heating because of the story of Hepatitis A.

Q. And from when were they producing solvent/detergent concentrate, Professor?
A. Again, it's difficult to say whether -- when the product was available experimentally, and obviously we put our previously untreated patients, those at risk

of this product -- I think they started to produce in a significant way in 1986, but mainly it was licensed in 1987.

Q. Yes. And was that -- was that firm, was that producing at a level of size and scale; I mean, was it an industrial concern, if I might put it that way?
A. Yes, it was an industrial production --

Q. Yes.
A. -- on a large scale. I don't know which is their share of the market, which was their share of the market at that time, but I think it was significant; probably 20 to 30 percent. So it was a significant product.

Q. Yes. Now, I think, Professor, could we go for a moment to the other book, the second book that you have there, and to page 20 of that book.
A. Page 20?

Q. Yes. This is, I think, described as "brief reports" in March of 1990, a study by Colombo and yourself, amongst others; is that correct?
A. Sorry, I have -- you are talking of the other one, the black one?

Q. Sorry, in the top right-hand corner, Professor?
A. Yes.

Q. That is a report in the Annals of Internal Medicine in March of 1990, and described as "brief reports," is that correct?
A. Yes, this study was done when the Hepatitis C virus was identified and the test was developed in 1988, if I remember. And Professor Colombo was involved in the original study by Houghton, so we had access to the preliminary test of Hepatitis C very early. And of course, we wanted to see -- we knew already that non-A non-B Hepatitis at that time had come on good grounds, Hepatitis C, and we wanted to see the prevalence of the antibody in our patients.

Q. Yes. And I'm just interested in particular, Professor, in one aspect of this: If we look at the second column, the column on the right-hand side --
A. Yes.

Q. -- under "Patients and methods", it mentions that "16 children first treated in 1985 or after were given exclusively concentrates dry-heated at 60 degrees Centigrade or 68 degrees Centigrade for 72 hours," being Hemofil and Koate heat-treated.
A. Yes.

Q. And I think if we look at the result then. Am I understanding this correctly, if we look at the next page, at page 21 --
A. Yes.

Q. -- under the -- second column down under "Type of concentrates: Dry-heated only. Total number of patients, 16. And then positive for antiHepatitis C virus, 9, or 56 percent."
A. Yes.

Q. Would I understand from that, Professor, that of those 16 children treated for the first time with -- in 1985, with these dry-heated products, that, in fact, there -- 9 out of those 16 children would have become positive --
A. Yeah.

Q. -- for hepatitis?
A. Yes. Is correct. We knew that these -- whether -- these 56 percent is like the story of cryoprecipitate versus concentrate and the Levine versus Dormandy paper. Whether this 56 percent is different from 89, I don't know. It looks different, but of course, it is significant actually; we did calculate a P value, but certainly it is -- so, it is a possibility that the dry-heated concentrate were giving less, were inactivating some HCV. But certainly, these data are not satisfactory and that is what led to the development and use of new products.

Q. Yes.
A. At the same time, we had to use these products in these patients because they were probably the only one available. Here we don't specify -- 1987 and after, until when it was after; I don't remember, we had to use this for the store of HIV. It was the --

Q. Yes. And then I think, just again, a further paper in this series of papers, at page 25, Professor. I think this is a report from the University of Pisa in Italy and, therefore, not your centre?
A. It is not my centre, no.

Q. Yes. But it reports in the summary; it reports, amongst other things: "Our patients were treated with dry-heated concentrates since 1985" -- presumably meaning pasteurised -- "and with wet heat or solvent-detergent-treated concentrates since 1988". They take, presumably, the beginning of 1988 as being the start of that regime in Pisa, and they report that "the absence of further seroconversions and of symptoms of acute post-transfusion non-A non-B Hepatitis since 1988 suggests that present virucidal treatments of concentrates are effective in preventing Hepatitis C transmission." So it appears that in that centre, by 1988, they had moved to either solvent/detergent-treated or pasteurised concentrate, and there were no further seroconversions for hepatitis --
A. Pasteurised -- pasteurised or perhaps vapour-heated, because vapour heating was -- the Kryobulin product was largely used, is my guess. They don't say that, but I think it's another possibility.

Q. I see.

THE CHAIRPERSON: We will adjourn for lunch and we will resume again at 2 p.m.. thank you.

THE TRIBUNAL THEN ADJOURNED FOR LUNCH.

THE TRIBUNAL RESUMED AFTER LUNCH AS FOLLOWS:

CONTINUATION OF EXAMINATION OF PROFESSOR PIER MANNUCCI AS FOLLOWS BY MR. FINLAY:

THE CHAIRPERSON: Good afternoon, Professor.

Q. MR. FINLAY: Professor, I think before lunch we were dealing with the question of infections with Hepatitis C. And I think you said that in Italy you would take the year 1987 as being an important year in that context, is that correct?
A. That's right.

Q. And in your view and in your knowledge, were there any significant number of infections after 1987, in Italy first?
A. Well, in Italy, as we say, there were very, very few cases, certainly cases that were sometimes not very -- not completely equivocal. Sometimes it was not very clear whether they got hepatitis from the community or from other sources. Subsequently, cases of hepatitis have been reported here and there.

Q. Yes.
A. Usually not a large number of patients. And the fact that a report of one or two cases was, in a sense, showing that the general belief was that there was no transmission, so the few cases in which it did occur were worthy to be reported scientifical -- had some scientific interest. That's what I wanted to say. So that was the general -- that was the general knowledge; that basically, except in very few cases, the epidemic had been stopped by the end of '87. And that subsequent cases were scanty and not numerous.

Q. Yes.
A. As you know, you provided me with the study which, I must confess, I was not aware, because I thought --

Q. Yes. Well, perhaps -- sorry, if we could refer to that so people know what we're talking about, Professor.I think in the second book at page 39 -- and indeed I think this is a document which was provided to the Tribunal by the Blood Transfusion Service Board as something they thought would be relevant to refer you to.
A. Page 39?

Q. Page 39?
A. In the -- okay.

Q. In the first divider.
A. Yes. Yes.

Q. And it's an article from transfusions, volume 41, March 2001. So it's quite a recent article?
A. Yes. And I must say, quite frankly and honestly, that it came to me as a surprise because I never heard --

Q. Well, perhaps -- sorry, Professor, so that it's clear, perhaps we better identify what the article says before you comment on it so people know what you are commenting on. I think one of the authors of the article is Bruce Evatt, isn't that correct --
A. Yes.

Q. -- Yes -- who would be very well-known in this field?
A. Oh, yes.

Q. And I think it's clear from the article that it was a general survey of a number of persons with haemophilia born in America between, I think, 19 -- most of them born between 1993 and 1996, isn't that correct? Sorry, a number of persons with haemophilia registered in the years between 1993 and 1996. But the particular -- the particular -- the particular part of the study that I want to draw your attention to, Professor, can be seen at page 41.
A. Yeah.

Q. The second and third paragraph down. In the second paragraph down they deal firstly with the prevalence of markers for Hepatitis B. And then towards the end of the paragraph they say: "A sharp decline in the prevalence of Hepatitis C virus infection is apparent in the 1987 birth cohort, but infections continue to occur in birth cohorts through 1991." Then they go on to say: "To extend studies of the prevalence of Hepatitis C virus infection past 1987, we examined independent data obtained from May 1998 through June 1999, as part of a newly-instituted blood-safety monitoring system. We conducted hepatitis testing on birth cohorts that comprised 275 haemophiliac children born between 1987 and 1989. Of these, 19 children were confirmed positive for Hepatitis C virus by RIBA testing, for prevalence rates that, similar to the HSS data, far exceed the rates in the general population of same-age males." Then they refer to table four: "Prevalence rates were higher among children with Haemophilia B than among those with Haemophilia A." And then if we go to table four, which appears on page 43, it shows Hepatitis C virus seroprevalence among 275 haemophiliac children born between 1987 and 1989 and tested by CDC-sponsored blood-safety monitoring system during 1998 and 1999. And in relation to persons with Haemophilia A, it shows that, in 1987, six out of 70 children born in that year tested positive for Hepatitis C, isn't that correct?
A. Yes.

Q. A prevalence of 8.6 percent. And for Haemophilia B in the same year, 5 out of 14 children born in that year; and therefore a prevalence rate of 35.7. And then for the next two years, for Haemophilia A, three out of 85 children born during that year were positive, and therefore a prevalence rate of 3.5 percent. And one out of 12 Haemophilia B patients, and therefore, with a prevalence rate of 8.3 percent. And then in 1989, none of 78 children born with Haemophilia A were positive. And four of 16 children born with Haemophilia B, or a prevalence rate of 25 percent, were positive. And I think that was already mentioned. But further on in page 43, towards the end of the third paragraph, where they say that they had taken into account the possibility that there might be false positives in these tests, and there they say in the last paragraph, last sentence of the paragraph: "Therefore, the results we report concerning haemophiliac males born since 1987 include only persons who were confirmed as positive through supplemental testing by RIBA." So in respect of these children, Professor Temperley --sorry, beg your pardon, Professor Mannucci; obviously, by definition, they were born in either 1987, 1988 and 1989, and clearly, by definition, could not have received any product prior to those dates, isn't that correct?
A. Yes, by definition.

Q. Yes. Obviously. And unfortunately what we're not told in this study is what product they did receive, or at least not that I can find?
A. No.

Q. But there does seem to be a surprisingly high prevalence of Hepatitis C virus infection among those children, those particular cohorts of children born in those three years?
A. I agree. Particularly for Haemophilia B. Let us say, this is -- seems to be a very well done study by a very well-known group. Dr. Evatt -- first of all, the place - the CDC, the Centre for Disease Control. So by definition, the best place where one does monitor infectious diseases. And Bruce Evatt is very -- he is the second author. He is a particularly reliable person because not only was he involved in the problem-solving factions from the very beginning - because they had the surveillance on HIV; the first two cases were reported to the CDC - but also he's a clinician, an expert of coagulation and epidemiology. So particularly suited, even though he doesn't see any patient himself, but he receives a lot of information, a lot of samples. So I think he's a particularly reliable person. And the study, from what it appears, is very well done. And I'm surprised that I didn't read it, but I think it's probably because it was published in 2001, at a time when there was very little concern about the problem of infection with Hepatitis B viruses in haemophiliacs. But having said that, it's a very well study. I would -- and is very well done; not only because in the first part of the study they took the data supplied by the six States of the United States, so data accumulated by others with the problem of reported -- reporting bias, but then to confirm the study they took this cohort of 213 haemophiliacs. They used -- they had their plasma, their serum, and they tested it, and they tested the virus themselves to be sure that they used the most suitable and state-of-the-art methods. So I think, as you say, that the crucial -- even though I think that one has to look at two figures, or two data. One is figure one, in which you can see -- I think figure one is really very interesting because you can see the decline of the proportion of cases from -- okay, HIV was really zero in 1985, as we say, due to the advent -- we haven't really talked a lot about HIV. It was zero by 1985. Hepatitis B did progressively improve but Hepatitis C did get to zero in 1987, because that's what it looks like, perhaps. I don't know. It's close to zero. But then there was this couple of bumps, which are certainly low proportion, but are quite evident that they still exist. So there is this trail, this dragon.

Q. Sorry, Professor, are you referring to a table on this -- page 42, the graph?
A. I'm referring to the figure on page 42, that one there.

Q. Thank you, Professor.
A. And I think it's self-explanatory.

Q. Yes.
A. As I say, HIV stopped by '85. It continued decrease of HCV, even in the early '80s, probably due to the fact that there was improvement in the screening, techniques for screening donors, but still very high level; 60 percent in 1985, when it was nearly zero for -- it was zero for HIV.Then it dropped in 1987, as we have foreseen, but there was this tail that is quite clear in that figure on the right. Then the other critical table,

as you did emphasise, is table four; I mean, the cohort of those that were tested directly by the people at the CDC.

Q. Yes.
A. And there, my interpretation is the following: '87, they had six cases out of 70 with Haemophilia A. This could be still due to the fact, you see, that many products has been licensed in 1987, but whether it was in January, February, March... So in some cases probably still existed. And even those, it's still possible that they use the products that were available at that time. But certainly this does not explain the Haemophilia B, which is really much higher prevalence. And this goes with the problem that perhaps you want to dwell later on, of the fact that the dates and safety of virucidal methods on Factor IX concentrate are less solid, for a number of reasons, than Haemophilia A.

Q. Yes. Professor, the 1987 refers to the year of birth of the patient; it doesn't necessarily mean that the patients who became positive who were born in 1987 received product in 1987, which caused their seroconversion. Is that not correct?
A. Probably you're right.

Q. So --
A. Probably you're right, because even though patients with haemophilia tend to be treated in the first year of life, it's not certainly sure. I mean, earliest starts to bleed severely when they are walking around. I did mention that because it is the hypothesis, the only hypothesis put forward by those who wrote this article. But I agree with you, that is not particularly convincing. Anyway, you can see that Haemophilia B cases developed as late as in 1989, whereas - I don't know if it's just by chance because the numbers are very small - but in 1989, you see a zero prevalence in Haemophilia A. But we are dealing with small numbers.

Q. Yes.
A. So I think this is an important -- this is an important article. How can it be explained? I don't know. They don't explain it themselves. They just provide these figures so there are very --

Q. Yes?
A. They seem to say that, in the four lines before the last, in the first column at page 43, they say what I say; it is agreeing. But you are probably right in agreeing. It says: "The residual transmissions after 1987 possibly represent the use of product already manufactured or product manufactured during the interval required to implement the new technology." That's probably right. So that's why -- but I agree with you that it is -- the criticisms can be applied to this statement. If I was a reviewer, I would say, 'what is the evidence of this?' because, as you say, they were born in 1987, not treated in 1987.

Q. Yes. I think if we return to your own statement, that's what you write at the bottom of page eleven?
A. Of my report?

Q. Of your report, yes, Professor.
A. Yes.

Q. You mention at the bottom of page eleven that, of course, there wasn't only progress in terms of viral inactivation; there was also progress after 1987 in relation to the selection of donors, and then -- and then from 1989 or 1991 onwards, the screening of plasma for HIV -- Hepatitis C antibodies, isn't that correct?
A. Yes.

Q. And obviously that -- both of those developments should have lessened the viral load in the pools which were used to make the concentrate?
A. Yes. This is the case, even though that is a strange story because, to begin with, the Americans didn't want to screen the plasma donations for antiHCV until, I think, 1981 or 1992, unlike Europe, because they thought that this would deplete the plasma pool of protective immunoglobulins. So there's been a period with a lot of discussion between the Americans and the Europeans. But still, I think, and I -- the big proportion of cases was halted before by the virucidal method. I think, I don't remember exactly, but I think in The States they were not implemented before 1991 or 1992. And so even all the plasma that came to the European fractionator from the United States was not screened. And the reason why they did that, because they were convinced that the antibodies were protective, which was not the case probably; but also because they thought - and the second instance they were right - that the use of virucidal method was -- had already solved the problem.

Q. Yes.
A. So whether these few cases that it is mentioned in the paper of Bruce Evatt could have been avoided by an earlier screening, I don't know. But certainly the test was not available on a large scale before 1990. And the first tests were available preliminary. So it's a little bit of a grey area.

Q. Yes, I understand. You go on there, Professor, at page 12 of your statement, to deal with the question of hepatitis in patients with Haemophilia B.
A. Yeah. Well, as I said, this is a complex situation, and certainly the evidence is -- the evidence that I tried to make available for Haemophilia A is not so solid for Haemophilia B, for several reasons: One is that the patients are less numerous. And so it was very difficult to implement a study according to the criteria of the international committee of at least 20 patients. It was very difficult. Has been done, but in very few instances. The other story, the other one was the fact that these concentrates are thrombogenic. They cause -- they did cause thrombosis in a number of patients. So the idea of applying heating or manipulations in general to a product that was considered as a potential bomb was felt even more -- we felt even more uneasy than we were with Factor VIII. And so it was only -- even though, from the beginning, some manufacturers applied the same method to Factor IX that applied to Factor VIII; mostly Immuno with the vapour-heated product. That was, in our country, inactivated from the beginning. The other products were not inactivated with the same method. For instance, only more recently Behring did apply pasteurisation to Factor IX concentrate. So the breakthrough really occurred with the advent of the solvent/detergent, because solvent/detergent is very mild treatment and the concerns that it could damage the protein and cause thrombogenicity was felt less cogent. But as I said, very few studies have been done with Factor IX. So it's still a grey area. Looking at the paper of Bruce Evatt I get more and more convinced that probably the virucidal methods were adopted later or they were not adopted in the proper way,

because it's quite important to see that the majority of the cases there are Haemophilia B; certainly out of the national proportion between the two diseases.

Q. Yes. I think the dry heat treatment methods were adopted for Factor IX, isn't that correct? For instance, the Cutter method would have been applied to Factor VIII and Factor IX?
A. Yes. Yes, they were, but they were never validated, you see. They were applied to the Cutter product and also to the Baxter product, but they were never truly validated. We did assume that they were effective, but the composition of the protein is completely different. So the assumption was probably unjustified. But again, this is with the knowledge of retrospective evidence. Also, they use even higher heating temperature, which was somewhat paradoxical; because on the one hand they were scared of inactivating the protein, causing more thrombogenicity, but some chose to use higher temperature. So it is a -- as I said, a grey area, that of Factor IX concentrates.

Q. Yes. And just in relation to your own practice, Professor, where you described to us the products that you would have been using by, say, the end of 1987, what products would you have been using for Haemophilia B patients or Factor IX patients by the end of '87?
A. I told you -- as I told you now, my country were more lucky in a sense because the steam-heated product at that time that had been improved, not caused any additional case of hepatitis, was available in our country. So we used that. Plus, the Italian manufacturer developed the solvent/detergent, if not in '87, probably in '88. So from that point of view in Italy, we had been more successful than others in using viral inactivated products.

Q. I see. Thank you.
A. And in fact, if you remember in the Morfini paper, there was no case of Hepatitis B.

Q. Yes. Yes. Now, if we could move on then, Professor. In your paper at page 13 you deal with the question of HIV infection and AIDS. Quite a large topic?
A. Yes. What is the question?

Q. Well, the question -- first of all, Professor, I think you identify, and this is something we would be aware of, that in 1982 there were two cases of persons with haemophilia who developed AIDS, and that was reported. I think you mention that in Italy, the first cases diagnosed of AIDS were in 1984, is that correct?
A. Yes.

Q. Yes. But from what stage would you have been concerned that there was a risk, first of all, that the concentrates might transmit the virus which caused HIV, or HTLV-III as it subsequently became known?
A. Yeah. This is a very critical issue, and it is an issue that makes uncomfortable, unhappy, all of us. Because now with the retrospective evidence, you cannot help thinking that we did overlook what was -- what now appears clearly as evidence.

Q. Yes.

A. And so that's something that really makes all of us very uneasy and very unhappy. Quite frankly, I have no much regret, just to be honest in front of you, as to the story of hepatitis. I think we have been always on the forefront on what the progress of knowledge was and stayed within the limits. Here, of course, one does wonder why we didn't understand earlier. Because after all, when this case of acquired immune deficiency occurred in two patients with haemophilia, in gay people, I mean these were -- in drug addicts, these were all categories at risk for blood-borne infections. And there is no doubt that many of us thought that it was due, immune deficiency, due to the treatment of the products, to the bombardment, as others have used, with proteins; one, of course, would wonder why not in the past, but it was thought that it might be because the treatment had become more aggressive with more treatments. But -- and so -- and then, of course, the putative virus was not known and it was difficult to imagine that a brand new virus could appear in the scene. Of course, this is all ridiculous now to think about, but --

Q. But what I do want to know, Professor, is what your state of thinking would have been about this, say in 1983; what you would have thought?
A. In 1983, the evidence that it was a virus was not yet there. If you really look, knowledge of people, as it came, it was at the end of 1983 /1984 that the evidence started to become solid. Anyway, even though at that time we started to think -- quite apart from the fact that I was personally influenced, right or wrong, because this is ridiculous about the fact that, in Italy, cases did not appear until 1984, and there were only two. And of course, scientists shouldn't be biased by his own perception because we knew of the literature and we were informed by our colleagues. In 1983, my main problem was that -- resisting to the use of heated concentrates was the fact that I told you, that the concentrate -- heated concentrate proved to be negative towards the Hepatitis C virus, non-A non-B. So the simple thing; if it is unaffected there, why should be it be affected with another putative virus that we don't know.

Q. Yes.
A. Then things changed, things changed because the virus becomes more overtly disclosed, because some tests were developed slowly, even though only in 1985 they became officially approved in some countries.

Q. Yes. Can I just stop you, because I want to come to that. But before we come to 1984 and 1985, in your own treatment of patients during 1983, did you make any changes or modifications arising out of the risk of the AIDS virus or HTLV-III virus?
A. No, we didn't. We didn't. We informed the patient of the possibility that this could be caused by a virus, but -- of the fact that this was happening in another country or in other countries.

Q. Yes.
A. I'm talking in '83 when there had been already no case in Italy and a handful of cases in the whole United States. So we informed them, but probably the information was biased by our beliefs. And I'm saying that, I mean, I don't know, but there is the pocket -- certainly the patient -- none of the patients -- really none in our country, and I think the majority of other countries did consider the possibility of stopping -- of stopping the concentrates because of this.

Q. Yes.

A. They took the risk, as much as now -- and of course, it's a different story that perhaps I shouldn't mention, but the story of the new virus CJD -- okay, I'm rambling so you'd better stop me.

Q. So therefore, to be clear, there wasn't any change in your treatment practice during 1983?
A. No, '83, not at all.

Q. Now, I think in 1984 then, I think there were developments in terms of I think there was the publication by Gallo in May of 1984?
A. Mm-mm.

Q. And of course, there had been the previous publication by Montaginier in May of 1983, isn't that so?
A. Yes. Montaginier himself in his paper recognises that there is no evidence that -- the virus that he has isolated was the cause of the immunodeficiency. But certainly it was published in 1983.

Q. Whereas Gallo I think did claim that to be his discovery in May of 1984?
A. Yes. So, he gave more evidence to where -- together with the more evidence gained by -- by Montaginier. And then would have been the story of the patient who had the antibody, that the antibody -- but again, that was a moment of confusion, because the antibody, for many of us, is something defensive. So okay, the first interpretation is that they came into contact with this virus but they developed the antibodies. So they are immune. And so a lot of -- a lot of confusion.

Q. And that, of course, would have been the case for Hepatitis B; that if you had an antibody to Hepatitis B, you were protected against further infections?
A. Yeah, that was certainly the case for Hepatitis B, and I think it was inevitable to make this translation to HIV. Then with HCV it sort of was different, because we had learned the lesson; and the antibody, you knew that it meant infection.

Q. Now, did you, in fact, have personal contact with Montaginier during 1984?
A. I had contacts because I heard, by rumours, that he was developing a -- he was developing a test to reveal the antibody, possible expression of the presence of the virus. So I arranged -- I called him on the phone from Milan. He was very nice and kind. He's a lovely person, Montaginier. And we met in Paris in October; I remember always that we met in a coffee of the Grand Boulevard in Paris. And I said to him, you have this test? He says to me, yes, I have it. It's very preliminary. It was called RIBA at that time, which I don't even remember what it means, but also, there was an antibody for ELISA test that he called anti-LAV. And I said, listen, I have a cohort of patients who were previously untreated, the patients included in the Hepatitis C study or Baxter that were treated exclusively with a heat-treated concentrate. I heard that there is some evidence that this putative virus, not yet fully established as a cause, is very labile to heat. And he confirmed that. And I said, would you like to do a case control study which would compare those patients that develop hepatitis but were previously untreated and treated only with the heated products, with a matched group of similar patients treated with the nonheated products? That was the end of -- that was at the end of '84. He said, yes. And I sent the sera -- I don't remember the numbers here. There was not a large number, but the

results were very clear-cut in that none of those treated only with the Baxter, 60 degrees treated product was -- had the antibody - anti-LAV or anti-RIBA, whatever you want to call - where all the others were invariably positive. We knew --

Q. Sorry, can I just clarify that Professor: You would have had samples which had been taken from persons with haemophilia for the purpose of the study -- of the hepatitis study that's reported by yourself and Colombo subsequently in 1985; the Travenol study?
A. Yes.

Q. And what was done: Those persons, unfortunately as we know, most of them developed hepatitis. But what happened was that you took the stored serum from those patients and tested it for -- or Montaginier tested it for any evidence of HIV antibodies. And it was found that none of those persons had become infected with HIV. Whereas I think there was another group then who had received untreated product, and their serum was also tested. And it was found that that had been infected with HIV. Is that the case?
A. You said it much more beautiful and clearly than I did. It's exactly as you say.

Q. Yes. Very well. And I think that was published then by yourself, Professor, in February of 1985, isn't that correct?
A. Exactly. We -- I was aware of the results at the end of December. We wrote the letter as quickly as we could. We chose to publish a letter - even though it is less prestigious than a full article - to be quick, which was quickly accepted by The Lancet; at the end of February, if I remember. And that was the first study, really, showing the facts and dates that heating was capable of inactivating the virus. The evidence was only indirect, but to prevent the development of antibodies, so the infection --

Q. Yes. And I think that, Professor, you've provided us with the reference for that at page 188 of the book of references that you provided to us.
A. '88.

Q. Just to identify it. This is the letter of the 2nd of February from yourself and, indeed, Dr. Montaginier?
A. Yes. Yes.

Q. Yes. And I don't think we need go through it; you've already explained it to us. But just to identify, that was the reference?
A. It is. It is the one, yes.

Q. Now, Professor, what was -- were there people who, prior to this, prior to the end of 1984 and beginning of 1985, had been advocating the use of heat-treated product as a means of defence against the risk of the transmission of what later became known as AIDS?
A. Yes, there were. The main advocate, the most prestigious and the most influential, was Harold Roberts, a director of the haemophilia centre in Chapel Hill, North Carolina. He even, in Barcelona, I remember he said that, okay, 'it does transmit hepatitis but it is heated, so it is better than nothing; it cannot be more harmful than the others so let us use it.' it seemed to me, and to many of us, that with

all the due respect that I had, and I'm -- even more so have for Harold Roberts, that the observation was really based on -- was not based -- was not evidence-based.

Q. Yes.
A. But he was adamant about that.

Q. Yes. And what was your view at the time of that point of view, Professor, that notion that one should use heat treatment on the basis it can do no harm to do so?
A. My view was that the product was not yet available in my country; so from the point of view of my country, I couldn't use it even if I wanted. The product was more expensive, which was outrageous, because heating in the dry state does not -- you just put the bottle -- you produce as normal, then eventually you put the bottle in an oven, so there is really no cost -- no loss or very little loss. So there was the problem of cost, the problem of -- and also the problem of the fear that he may alter, as I said this morning, the protein, and cause the formation of antibodies and neoantigens. And I was not alone in that. But we were proved to be wrong.

Q. Yes. But at the time, Professor, what would have been the view amongst the majority of your colleagues who were persons treating with haemophilia?
A. I don't think the majority of my colleagues really started to use heated products until our paper in The Lancet was published, because people need evidence to justify higher costs. And even though -- okay, to say it doesn't harm, you have to consider that it could have a harm and it was more expensive. So the majority of my colleagues started to move when The Lancet paper was -- Lancet letter was published. That was a point of no return.

Q. Yes. And I think there had also been a communication by the CDC at the end of 1984, in October or November of 1984. Do you have a recollection of that?
A. I have a recollection of that. I think, again, it was not based on evidence, even though at that time it was probably known that the virus could be -- could be labile. I think it was mainly due to the influence, good influence in this case, that Harold Roberts exerted in his country.

Q. Yes. Yes.
A. But -- yeah.

Q. Professor, can I ask you if we could go to page 163 of the references that you've given to us. And this is an article which was published in December of 1988. So quite a long time after the events that we're talking about. And you're one of the authors of the article?
A. Yeah.

Q. And it deals with a national survey of the HIV virus infection in Italian haemophiliacs in 1983 to 1987?
A. Mm-mm.

Q. And I think the -- the actual figures for persons with antiHIV-positive are given at page 166.
A. Yes.

Q. And in particular, at table five, where it divides up the number of persons who are positive in the various different categories of persons with haemophilia, isn't that correct?
A. Exactly.

Q. And first of all, if we just take two overall figures first: If we look, for persons with Haemophilia A, the total number of persons who were HIV-positive were 476; and that was, as a percentage, that was 29 percent of the persons who had been tested, isn't that correct?
A. Yes.

Q. And then if we look again, just coming down a few lines, for the total of persons with Haemophilia B, the total number found positive were 138, which was 44 percent of the figure of 313 people tested, isn't that correct?
A. It is correct.

Q. And then if we go back to the Haemophilia A patients, the division between severe, moderate and mild was that 37 percent of patients -- Haemophilia A patients who were -- persons with severe haemophilia were HIV-positive; 14 percent of moderate; and 4 percent of persons who had Haemophilia A of a mild variety were HIV-positive.
A. Yes.

Q. And then in relation to Haemophilia B, doing the same exercise, for severe patients it was 50 percent; for moderate patients, 41 percent; and for mild patients, 12 percent. First of all, Professor Mannucci, I think there's a very obvious difference between the figures for persons who had mild Haemophilia A where the rate of infection with HIV was 4 percent, and the persons who had mild Haemophilia B where the rate of infection was 12 percent. How would you account for that difference, Professor?
A. Well, this is -- I think for this I have an almost certain explanation; also, on the basis of a study that we did subsequently in which we studied more patients than these, probably the double. Anyway, it is quoted and we can look at it later. But basically I think this is due to the effect of the use of DDAVP, because there is no special reason to believe that this huge difference is due to anything other than the fact that we use DDAVP for patients with Haemophilia B -- A, and concentrates for patients with Haemophilia B. Why, then -- but this explains only the difference in mild and moderate. But it doesn't explain the difference in severe that is from 37 percent, A; to 50 percent, B. And there, this data, which is probably quite significant, has never been explained why, in Italy, we had, I would say, less cases compared with other countries with Haemophilia A affected by HIV than we had for Haemophilia B. It is really not clear. We tried to explain it into several ways, but we never managed to get convincing explanation. I could have offered some speculation but not founded.

Q. Yes. I think in this article, Professor, if we come down to the next table at the end of the page, there are comparisons set out for the figures of German persons with haemophilia, French persons with haemophilia and Italian persons with haemophilia. And I think if we look at it in terms of percentages: For German persons with

haemophilia, Haemophilia A, the rate of infection with HIV antibodies was 47.6 percent. And then if we --
A. Cumulative.

Q. As a cumulative. And if we look underneath that, for French persons with haemophilia, 36.9; and for Italian persons with haemophilia, 28.7. So, in that regard, the persons with Haemophilia A did better in Italy than in either France or Germany. But then if we look over at the right-hand side of the column: For German persons with Haemophilia B, the rate of infection was 45.6 percent; for French persons with Haemophilia B, 35 percent; and for Italian persons with Haemophilia B, 44 percent. Now, I think in France they had home-produced Factor IX. They weren't dependent on the commercial concentrates, the American-produced commercial concentrates for Factor IX. And maybe that could explain, to some extent, why their Haemophilia B figures might be a bit better. But in relation to the fact that I think in both Germany and France, for Haemophilia A, there was a significant usage of commercial concentrates, isn't that correct?
A. Yes. I have really no explanation for these differences, as I told you. I've only noted what we tried to find, but we have only speculation that I can offer. But they are not -- it is a fact and it is clear, fortunately, in the sense that altogether, because the more numerous patients were less frequently affected, we have less cases of HIV in Italy - nearly half than those of other European countries with the same population; about 60 million. But the reason for this is not clear.

Q. Because I think in most countries, it would be quite the reverse of what the situation is in Italy, because there would be, as a percentage, more persons certainly with severe Haemophilia A than there would be with severe Haemophilia B who would have been infected with HIV?
A. Not as far as I remember in the country, that it is more in our country also for us, because, also we used the same concentrates that's in the United States. I don't recollect the figures exactly, where perhaps you do, but I think that the prevalence in Haemophilia B was slightly less but not much less.

Q. I see. I see.
A. So that's the Italians' story, why so little in Haemophilia A remains unexplained.

Q. I think, Professor, I think, just in relation to something you've already mentioned to us at page 15 of your statement --
A. 15?

Q. 15, at the end of the page?
A. Mm-mm.

Q. Where you referred already to the fear that there was amongst treating doctors about the risk of the production of inhibitors, you refer to a reference -- your reference 31, which is a letter from Bird, Codd and Collins to The Lancet, which appears at page 190 of your book of documents and I think again the --
A. 190?

Q. 190.
A. For some reason I remember the letter. For some reason it seems not to be --

Q. I'm sorry, Professor. That just was a problem of copying?
A. Yeah, that -- I remember that article. It was rather ghastly against the editorial that -- in December, really the last issue of the Lancet, of 1984, has recommended the use of --

Q. Of heat-treated product?
A. -- of heated products; again, on no evidence. I don't know who wrote because it was anonymous. And here they bring about several reasons for being against that. And I remember -- and I'm sure there is also a similar letter of publication by Professor Arthur Bloom, that was, in a sense, the leading authority in the United Kingdom at that time. Which -- who was quite against the blatant declaration that one had to switch to heat-treated products.

Q. Yes. There was, of course, a strongly-put country point of view by a number of treaters in the United Kingdom at that time that one should move, and move swiftly, to heat-treated product, isn't that correct? I mean, that's what this letter is written in reaction to, as you point out; the editorial that had given that clear advice that that was the way it goes?
A. Yes, this is only showing that there was still some uncertainty; it was not universally-felt as a procedure to follow.

Q. Yes. Finally, Professor, I think in -- at the concluding paragraph of your statement to the Tribunal, you make some general comments on what the position was in the early 1980s.
A. Well, I think it is -- this reflects what I say. It is my interpretation of the events I think based on some evidence, is what I said to -- several times here, and I maintain that; even though whether respective evidence I was wrong.

Q. Yes. So I think what you said was that, "On the whole, everybody was in doubt in the early 1980s from 1982, when the cases of the first two persons with haemophilia and AIDS were reported, until February 1985, when Montaginier and myself did show for the first time that haemophiliacs treated with heated concentrates did not become infected with the retrovirus that on the same year was convincingly shown to be the cause of AIDS." And then you went on to say: "The failure of early virucidal methods based on dry heating to inactivate the hepatitis virus was a fundamental drawback, because it did convince many of us that the method had little virucidal activity, not only against the non-A non-B virus but also against any other blood-borne agents. With the evidence available at that time, the argument used by a minority of us" -- and then in quotes --"'use because at any event heating will not harm and will perhaps help'" -- end of quotes -- "was unwarranted."That was your concluding observations in your statement, Professor?
A. Yes, it is.

Q. Yes. Thank you very much.
A. You're welcome.

THE CHAIRPERSON: Thank you, Mr. Finlay.

Mr. Bradley, please.

MR. BRADLEY: Thank you, Madam Chairperson.

THE WITNESS WAS EXAMINED AS FOLLOWS BY MR. BRADLEY:

Q. MR. BRADLEY: Good afternoon, Professor Mannucci.
A. Good afternoon.

Q. I appear on behalf of the Irish Haemophilia Society. My name is Raymond Bradley. I want to go back right where you started this morning and look at the evolution of the knowledge in respect of hepatitis. And before I do that, I want to look at your article, and -- your article of 1982. That's to be found at page 70 attached to your statement.
A. Yes.

Q. You've got that article?
A. Yes, Nonprogressive course --

Q. -- of non-A non-B chronic hepatitis in multitransfused haemophiliacs.I'm going to look first at the final page, which is page 73. Final paragraph: "Whether unfavourable development and morbidity of CLD is more frequent in patients with HBV or delta infection remains to be determined. It is remarkable, however, that only two of the entire series of 91 haemophiliacs followed since 1974 have died from cirrhosis and that both were Hepatitis B surface antigen serum positive. One of these was a patient who was not biopsied because he died from encephalopathy and gastrointestinal bleeding in 1975 at the age of 23; the other was patient 10, who was also delta-antigen-positive. Since preliminary evidence suggests that the delta agent is a major cause of CLD in haemophiliacs, its role in progression of the disease should be evaluated more thoroughly."Now, this was an Italian group of patients; and in terms of the incidence and prevalence of Hepatitis B and the delta agent in Italy, would the prevalence be radically different to other areas in Europe?
A. I -- I cannot, at a glance, I cannot really answer this question because the delta agent was discovered by Rizzetto and it was thought to be a satellite virus to the Hepatitis B virus, and it was thought to be related to more severe cause of Hepatitis B, which, in turn, was thought to be more severe and serious than Hepatitis non-A non-B. But whether this has been confirmed subsequently, I'm not sure. So I don't think that we have really evidence that what is written here is valid in terms of the delta virus. It is certainly a fact that the two first patients that died in our series were Hepatitis B positive, and one was delta; the other one was not -- was not tested because he died without a liver biopsy. So don't take that as a strong statement except for the fact that -- of the Hepatitis B. But the delta has not really been solidly confirmed. Now, I wouldn't say that now. In the practice of a hepatologist, the delta virus is considered certainly an aggravation to the cause of Hepatitis B. But still, we consider Hepatitis B more severe than -- more rapidly progressive than Hepatitis non-A non-B.

Q. Which, as a concept in Italy, was - combination of Hepatitis B and the delta agent - more of a difficulty or problem in relation to the general population than it was throughout the rest of Europe.

A. I told you, since this was the hypothesis of ours that we put forward here, it was not really tested by others. So I cannot really make a comparison with other countries. This is more a hypothesis than a fact. So I don't think I can answer your question because I think the data is simply not available. The hepatitis/Delta story at that time was very fashionable, but subsequently did fade off as a significant cause of aggravation of Hepatitis B, for a number of reasons; because first there was Hepatitis B, then there was the vaccine, and so it has become less of a problem. So I'm afraid I cannot answer to your question the comparison with other countries. It is quite a speculation, this; it is a working hypothesis that subsequently has not been confirmed by us and has not been confirmed by others.

Q. Okay. If we look at the chart and the article at page 72, and we look at the histological findings on the heading of "tissue findings" for the various patients. And we see patient number one, age 21, spotty necrosis, then the final necrosis, inflammation. Patient number two is age 15, piecemeal necrosis, piecemeal; rare foci of necrosis. Patient number three, age 14, spotty necrosis, again. Patient number four, spotty necrosis. Patient number five, age ten, spotty necrosis. Patient number six, piecemeal periportal and spotty necrosis -- patient number six, spotty necrosis. Patient number seven, piecemeal periportal necrosis. Patient number eight, spotty necrosis. Patient number nine, piecemeal periportal necrosis. Patient number ten, spotty necrosis - and then patient number ten, active septa, and that patient died in 1978. And patient number eleven, spotty necrosis. I don't know whether you can assist in relation to the histological findings? We know that the terminology that we use in the British Isles would be fibrosis, necrosis, cirrhosis, decompensated cirrhosis, and the possibility of hepatocellular carcinoma. So in terms of histological findings, those findings were of significance, even at that time?
A. Were of -- sorry? Were of significance, you say?

Q. Of significance in terms of histological findings; the explanation of them remains to be ascertained. Would you accept that such findings and histology to a hepatitis in or around 1982 would be of significance?
A. This certainly indicates the existence of some liver disease in all patients, but -- except for -- you know, at that time the diagnosis of persistent, chronic, active and cirrhosis. The only case of cirrhosis - the one that you mentioned who died - persistent hepatitis is mild and minimal. Of course, we didn't know they could deteriorate. And we know that sometimes it can -- as much as we know now, that it can regress. Active hepatitis was considered more aggressive because there was some fibrosis. But altogether I would say, as they appear from the description on the diagnosis, these are all cases of mild hepatitis, except the case that died of cirrhosis. And --

Q. But it's --
A. And at that time we didn't really know. We still know now that chronic hepatitis can reverse or it can progress very slowly; not necessarily. Normally, say, 20 percent of the patients it does evolve towards cirrhosis, which is really the disease. Chronic active hepatitis doesn't cause any problem, doesn't cause portal hypertension. So on the whole, I think that these diagnoses are compatible with liver disease in all except one case.

Q. Okay. Would you accept that the study is limited to eleven people?

A. No doubt. I said this morning, this study, in my opinion, is not among the most significant because of the limited number of patients studied. Having said that, it was before the study from Sheffield; it was the only study that compared two different samples, so it had some significance.

Q. I accept that, Professor. Would you also accept that, in relation to the patients that were reviewed, that most of those patients were teenagers, children, or in their very early 20s, except for the last patient?
A. Mm-mm.

Q. So therefore, the time-span for development of liver damage would be limited?
A. I accept that. I accept that, even though you have to consider that these are all severe haemophiliacs, so there have been -- probably their first hepatitis was the first treatment. And the first treatment occurs in year one, at most in year two. So I don't think that -- of course, there's always -- longer is always better. But you see 21, 15, 14, 16, 10, 15, 18, except perhaps the last three or four, is sizable number of years of follow-up, because we tend to assume that the first hepatitis was the first treatment. So if you are 30-year-old, you have probably been dealing with the disease for 29, 28 years. And this is a logical assumption. So I do agree with the fact that the case material was limited and probably, to some extent, selected. The follow-up was not trivial, particularly with the knowledge that we had at that time, you see. Now we know that the patient can be well for many, many years and then develop liver disease. But at that time it was not known.

Q. But of that study, you'd accept one person died from cirrhosis, two people had chronic hepatitis and all the people who were studied had examples of histological findings that were suggestive of liver damage?
A. There is no doubt that there was liver damage, and we knew that from previous studies, but it is the extent of liver damage that matters. Chronic persistent hepatitis was considered at that time -- at that time, a nonprogressive disease, and the majority had persistent chronic hepatitis. And also chronic active hepatitis was not considered reversible -- or irreversible. We find in some cases, actually, here, a reversion from chronic active to chronic persistent. Of course, there are limits in all the statements. It could have been that the sample was obtained in a different area; there's no homogeneity of the findings, so this study has many limitations, no question. It has to be put in perspective what was the knowledge at that time; this, albeit small, was the first prospective study with evaluation of two different samples.

Q. And also there was the issue of the delta antigen agent in Italy as well that impacted upon your findings?
A. I told you, I accept that this was an emphasis that has not been confirmed, also because it has not been studied largely, probably derived mainly -- there's always bias, you see, when you write a paper. Rizzetto was the one who discovered the delta antigens. Since the only patient that died had the delta antigen, we thought that it could be the cause, because this was consistent with his findings. This problem - this issue, as I told you, has not really been further developed. Otherwise, Dr. Rizzetto would have got probably the Nobel Prize; and he didn't, because the dimension of the discovery has been put into a more correct perspective.

Q. Okay. If we move back in time to 1978 and the articles which were found in the medical journals at that time. Page 56 in your own booklet attached to your statement, you referred to an article in Blood, the journal entitled Journal of American Society of Haematology, published in July 1977. And "the liver abnormalities have been noted in intensively treated haemophiliacs, and have lead to less aggressive application of pooled plasma products by some physicians. In a prospective study liver function was abnormal in 68 of 98 haemophiliacs. The abnormalities of hepatic function tended to persist over one-year study period. There was no correlation between these abnormalities and the age of the patient, the presence of hepatitis-associated antigen or antibody, the presence or absence of splenomegaly (which was found in 26 of the 98 patients.) "These abnormalities did not suggest that a less aggressive infusion regimen was indicated for the haemophiliac but did suggest the need for careful long-term observation of such patients. "That was probably, would you accept, reflective of the state of knowledge in or around 1977; it was "wait and see, let's see what are the consequences in relation to this -- these particular abnormal liver function tests." Would you accept that to be a fair statement at that point in time?
A. He says more or less what we said before them, two years before them in the general clinical hepatology article. I don't think he was -- let me see, I don't think he was aware of our article, at least as far as I can judge from the fact that he doesn't quote it. So in a sense, it is nice to see that we both reached the same conclusions quite independently.

Q. That was the state of play in or around 1977. The following year there was quite a number of articles published in the various medical journals. I'm going to open each of them. First article at page 65. It's "Liver biopsy and Haemophilia A". It's by Henry Lesesne and also co-authored by Harold Roberts from Chapel Hill. And look at the headnote again: "Hepatitis is a significant complication of the treatment of Haemophilia A with Factor VIII concentrates. Chronic liver disease in these patients is infrequently documented in the literature. The results of percutaneous liver biopsy under the coverage of glycine precipitated Factor VIII in six patients with Haemophilia A who had persistence of abnormal liver function tests for at least six months are described. Three patients had chronic active hepatitis and three had chronic persistent hepatitis. No complications were encountered as a result of the biopsy procedure. These results suggest that the percutaneous liver biopsy should be considered in patients with Haemophilia A with continuously abnormal liver function tests to establish a histologic diagnosis and to guide for further therapy." So what was noted in relation to the six patients: Three of those patients had chronic active hepatitis; three had chronic persistent hepatitis. So therefore, would you accept that three had significant symptomology pertaining to the consequences of their hepatitis?
A. No, because as I told you before, chronic active hepatitis was considered more advanced than chronic persistent hepatitis, but it was as yet no evidence that chronic persistent hepatitis was inevitably leading to liver failure, and it was also no evidence that it was not reversible. So I don't think that these results, which were obtained before, are substantially different from the result that we published in the United States prospective study. If anything, we found a case of liver cirrhosis that they didn't find. So I don't think there's really any evidence here, except that, as I said this morning, transaminitis meant something abnormal in the liver. But not that -- this abnormality was something unfortunate considering that these patients were well,

were healthy. And it is mentioned here that the evidence -- that evidence was not available.

Q. Three of the six patients had chronic active hepatitis, not chronic persistent hepatitis. So the consequences were quite -- reasonably serious for those patients. Let's look at what those consequences were. If you turn over the page to page 66?
A. 66.

Q. 66. Patient number, case number one, "acute hepatitis - yes; fatigue; hepatomegaly; spider angiomata. Diagnosis - chronic active hepatitis. Patient number two: Acute hepatitis - no abdominal pain; hepatosplenomegaly. Chronic active hepatitis and cirrhosis. Patient number three: Acute hepatitis - yes; fatigue, abdominal pain, jaundice, fever, hepatomegaly. Diagnosis - chronic active hepatitis. Patient number four: Acute hepatitis - no; no symptoms or signs. Chronic persistent hepatitis. Less serious obviously. Patient number five: No symptoms or signs; acute hepatitis - yes; malaise. Chronic persistent hepatitis - diagnosis. Patient number six: Acute hepatitis - no; intermittent fatigue; no physical signs. Chronic persistent hepatitis. So for three of those six patients, the consequences of the hepatitis experience are suggestive of significant illness, would you accept that?
A. Well, it's -- it depends. Certainly these are symptoms that are mentioned, but you see, some of them are quite nonspecific: Fatigue, hepatomegaly. We recognise in our study there were some patients having slightly increased liver. So, I don't know to which extent these signs and symptoms of liver disease are not influenced by the knowledge of the diagnostic -- the diagnostic study. So I don't think it gives any bit of -- but then, there is also some contradiction because patient number two through three is defined as having cirrhosis, whereas, in the abstract, they don't mention any patient with cirrhosis. But certainly this, as I told you, this study was seen by me and by others as a sign that the transaminitis was not always -- let us say was sometimes accompanied by some changes in liver histology.

Q. The authors at page 67, column number one, last -- final paragraph, indicate: "Symptoms of liver disease were present in all three of our patients with chronic active hepatitis, but were also present in two of the three with chronic persistent hepatitis. Three physical and biochemical abnormalities were found only in patients with chronic active hepatitis."
A. Listen, I mean, it is written here, so I can say you are right. The only thing any hepatologist and any clinician will tell you, that until you get to the severe stage of liver insufficiency, the patient with chronic hepatitis, and also the patient with cirrhosis, is not affected by symptoms that are not subjective symptoms that any of us can feel because they're anxious about their disease. So I don't think this is scientific evidence. Scientific evidence is hepatosplenomegaly, cirrhosis, portal hypertension, and none of these symptoms, or most of these symptoms are quite subjective, if you think about it. So I don't think they are particularly worrisome, at least in my interpretation. Some people may have interpreted in a different way. The article is a key article because it does show, for the first time, as I've showed you, that transaminitis is accompanied by some alteration of the liver. But I don't think that many of us thought that this article was stating that patients had severe or significant liver disease because of the infection with the viruses.

Q. Okay. I have a number of further articles to open to you as well of the same year, and I'm tracing the progress of knowledge to the medical articles?
A. Which is page?

Q. The next article I'm going to look at is an article I think that's been handed in to you, it's a loose sheet. It's an article in The New England Journal of Medicine and it deals with asymptomatic structural liver disease in haemophilia. It's an article by Dr. Spero.
A. Yes.

Q. And you have that, and I'm just referring to the abstract: "Histologic studies showed chronic persistent hepatitis in eight patients, chronic active hepatitis in four and fatty infiltration with portal fibrosis in one." And this was a result of examination of 14 liver biopsies from 13 anti-Hepatitis B positive surface antigen patients. One article was published. And the next article I want to look at in some detail is an article of 1978 by Professor Preston, which is also a loose article that was handed in to you. And you referred to the that article, being the 1985 article, in your evidence this morning. I'm going to open the summary of the article to you, which states as follows: "Symptomatic screening of 47 haemophiliacs in Sheffield revealed abnormal liver function tests in 36 (77 percent) with a tendency for these abnormalities to persist. To assess the importance of these abnormalities, percutaneous liver biopsy was carried out on 8 symptom-free patients under Factor VIII cover. A wide spectrum of chronic liver disease was demonstrated, including chronic aggressive hepatitis and cirrhosis. The liver pathology bore no relation to clinical history or to biochemical findings. Hepatitis B virus markers were common but evidence suggests that this is not the only factor contributing to the development of liver disease. The high incidence of chronic liver disease seems to be a recent development and is probably related to factor concentrate replacement therapy." Now, on the following page we can look at the patients, the eight patients that were -- underwent liver biopsy, table number two. In patient number one, age 45 years, liver histology, micronodular cirrhosis. Patient number two, age 40, chronic persistent hepatitis and granulomas. Patient number three, chronic aggressive hepatitis, age 26. Patient number four, age 23, chronic persistent hepatitis. Patient number five, age 34, chronic lobular hepatitis and granulomas. Patient 6, age 31, chronic persistent hepatitis.And patient number 7, age 51, micronodular cirrhosis. Patient number 8, chronic aggressive hepatitis. And if we look at the discussion part of the article, "77 percent of our treated haemophiliacs had abnormal liver function tests and a history of hepatitis-like illness was elicited in 50 percent." And final paragraph "since each bag of cryoprecipitate is derived from a single blood donation, the risk of exposure to hepatitis viruses is quite small. The introduction of Factor VIII --"
A. Where are you reading now?

Q. Sorry, same --
A. Beginning of the discussion, and then you jumped.

Q. I jumped -- I jumped then to the last sentence of that paragraph. "Since each bag of cryoprecipitate is derived from single blood donation the risk of exposure to hepatitis viruses is quite small. The introduction of Factor VIII concentrates considerably increased this risk, since each vial may contain material from as many as 2,500 pooled donations. Like others, we found that these abnormalities tend to

persist." Next paragraph."We confirmed earlier observations that percutaneous liver biopsy can be carried out safely in haemophiliacs given adequate Factor VIII cover and appropriate laboratory control. As with any nonhaemophiliac patient there is a risk of haemorrhage with this procedure but our experience supports the statement of Lesesne, et al, that the 'potential risks of complications from liver biopsy in haemophiliacs are outweighed by the therapeutically important histologic information gained from the biopsy'."Next paragraph is important: "We also found a wide spectrum of chronic liver disease, including benign self-limiting chronic hepatitis, potentially untreatable (sic) chronic aggressive hepatitis and established cirrhosis." Go to the next column.Second paragraph down: "In addition, non-A non-B Hepatitis --"

MR. FINLAY: I think, Madam Chairperson, My Friend Mr. Bradley read out "potentially untreatable," whereas the article says "treatable".

MR. BRADLEY: That was cirrhosis. "In addition non-A non-B Hepatitis may well be an important factor and observations in four of our eight patients support this possibility. Patients five (chronic lobular hepatitis) and one (micronodular cirrhosis) have no serum markers of Hepatitis B. Patient 7 (micronodular cirrhosis) had a well documented bout of acute Hepatitis B surface antigen positive hepatitis and Hepatitis B surface antigen had cleared from his serum within three months. Liver biopsy only 13 months after the acute hepatitis showed a quiescent well-established cirrhosis. We feel that the time interval and clinical pattern makes it unlikely that the cirrhosis was caused by the Hepatitis B infection, preferring to implicate some earlier nonHepatitis B agent. Patient -- (chronic aggressive hepatitis) had an episode of acute hepatitis 18 months before his liver biopsy. At the onset of hepatitis his serum was negative for Hepatitis B surface antigen but positive for antiHepatitis B and antiHepatitis B core antibody. This suggests that he had probably acquired at least two separate hepatitis infections, although it was impossible to tell which was responsible for the liver lesion."Go down to the final paragraph: "We conclude that histological liver disease is common in haemophiliac patients. The nature and severity of these abnormalities can only be assessed by biopsy, which under suitable control can be carried out without undue risk. It is noteworthy that two patients with cirrhosis (one and seven) were mildly affected haemophiliacs requiring only occasional Factor VIII transfusion. Such patients may perhaps benefit from newly developed synthetic vasopressin analogue one - deamino-8-D -- vasopressin." Now, they're all articles from 1978. Most of those articles, would you accept, seem to suggest that patients with haemophilia who were in receipt of treatment for the haemophilia condition in the form of concentrates were exhibiting signs of liver damage.
A. Yes, I do.

Q. And if we look at the last article, consideration was also given to the format of treatment that should be afforded to people with mild haemophilia in the light of the risk associated with the treatment from -- of concentrates?
A. I agree with that. I said that this morning, that concentrates should not be given to patients with mild haemophilia. And I developed to that goal the agent I -- the people from Sheffield refer here to. One thing, however, that I have to object is the fact that liver biopsy has a purpose. Because a liver biopsy had a purpose before we knew what we have known from these studies, that there was liver disease, and it was not only transaminitis or biochemical alteration of no -- no significance. But what is

certainly wrong, what is written here and in another paper, probably the American paper, that the information gained for liver biopsy can help to treat the patients. Because at that time it was certainly not established that there was any treatment suitable. So that is certainly a statement that can be heavily criticised. That's why, whereas the -- consistent with their findings, the Sheffield people carried out hundreds, or tens, of liver biopsies, the majority of haemophilia centres until Interferon became available - probably even after Interferon became available - didn't carry any liver biopsy. Because it was simply useless except to establish the status of liver disease at that time. So I maintain that these studies - also the American study that gave results more similar to ours, more benign forms of hepatitis were important - were significant. And they are to be commended as good and useful for the progress of the science. But the indication for liver biopsy in haemophiliacs at that time was absolutely with -- of no use, because there was no treatment on which one could base, depending on the severity of liver disease.

Q. You're talking about treatment in relation to the consequences of Hepatitis C infection, or Hepatitis non-A non-B infection. What I'm focussing on at this point in time is the state of knowledge when it became apparent that concentrate treatment had risks attached to non-A non-B Hepatitis, and more particularly histological damage. And in or around 1978 would you accept that that was the situation?
A. Now I say that I accept that. But what I criticise is the -- the citation of Lesesne at page -- in the discussion of page 122 -- I mean, I say that only for fun; not that it is particularly relevant. But if you look, the Sheffield people quote: "The potential of risks --" have you got it? Page 122, "discussion," the second paragraph in the middle. Is it available?

Q. It is, yes.
A. They say, between inverted commas, "the potential risks of complication for liver biopsy in haemophiliacs are outweighed by the therapeutical important histological information gained from the biopsy." I would have written "by the pathogenetic important information" obtained for liver biopsy; not therapeutical. It was as no use therapeutical. But that is something in between that I wanted to mention. But I accept that -- particularly the Sheffield cases that were larger, that were followed prospectively, were those -- as I say this morning, that those that gave the most important contribution to show that, at least in some cases, hepatitis was progressive to cirrhosis. By the way, another thing that I would object is the use of the term "chronic aggressive hepatitis." This term is no -- is not used and was not universal accepted outside the United Kingdom at that time. The more correct term was "chronic active hepatitis," but just for the records.

Q. But in terms of the state of knowledge in 1978, it was appreciated that patients with haemophilia who received concentrates could develop chronic active hepatitis, and also that certain patients would develop cirrhosis, as is evidenced from the medical literature that we've gone through.
A. I would certainly agree with the second. I would also agree with the first, except that I don't think there was any evidence at that time that chronic active hepatitis was inevitably progressive towards liver cirrhosis. In our study is an example of that. And if I remember, even in the progressive study -- in the control study done subsequently by the people of Sheffield there were some cases where there was some

regression. Whether it was regression or simply different sampling is another story. This is the limit of the situation.

Q. Would you accept that as at that date in terms of safety of concentrates, that there were issues of concern that were relevant to both treaters and patients?
A. Yes, I do accept that. And that's why I told you. In fact, even though the first papers did not receive much attention from the Journal of Clinical Pathology, also the Levine paper, there was -- there have been several attempts to improve the situation. Certainly nobody was considering to stop treatment. I'm sure this applies -- I don't want to interpret them, but this applies also to the Sheffield people. And the story of cryoprecipitate has already been destroyed by the paper of Levine, if anything, showing that the incidence of abnormalities of transaminases were similar because they received cryoprecipitate. So it is -- we were worried then that, I reckon, and I confirm that I don't think -- I hope I didn't give you the impression to say we were not worried. It was a minority of patients, the natural history stance now; because, fortunately or unfortunately, depending on the point of view, only one fifth of patients with Hepatitis C developed cirrhosis, which is really the end point. Chronic active hepatitis is not the end point. So I do agree with you.

Q. If we look at the second booklet, Professor --
A. Second?

Q. Second booklet not attached to your statement, at page 84. An article by, among others, Arie Zuckerman. And it's also an article from 1978 and it indicates the issues that would have been discussed at that time?
A. Can I have a look at it? It is the Spero paper?

Q. Not the Spero paper, it's in the second booklet at page 84. It's an article by RJ Wyke, Anthea Thornton, B. Portman and Arie Zuckerman.
A. Thank you. Page?

Q. Page 84.
A. Yeah.

Q. And it's an unusual study in that it transcends both the chimpanzee study and study of patients as well: "Of 17 patients who received a concentrate on account of chronic liver disease, four developed hepatitis, and in three of these the illness proved fatal. The incubation periods ranged from 42 to 103 days (mean 65 days) and then three chimpanzees were inoculated with the concentrate from the same batch used on the above patients, a further commercial batch upon which no adverse reactions had been reported and plasma from a known non-A non-B carrier. All developed hepatitis after ten weeks' incubation. Liver biopsy when serum-aminotransferase was at its highest level showed features consistent with acute hepatitis. As in the patients, viral markers for Hepatitis A and B, cytomegalovirus and Epstein-Barr virus were unchanged." Now, if we look at the conclusion of the authors, final paragraph, to be --
A. "Discussion"?

Q. Page 88 in "Discussion: Until blood donors can be screened for the non-A non-B Hepatitis agent, it would seem wise to restrict the use of both commercial and noncommercial concentrates to life-threatening situations. In particular, their use in

patients with chronic liver disease should be avoided as the risk of a serious illness resulting appears to be increased".So, would it be fair to say that, as we leave 1978, the consequences of concentrates were appreciated and, therefore, treaters and physicians were looking at how the management of those consequences could be limited or ameliorated?
A. This is a very special situation, I would think. It's an important paper that -- but it is a very special situation, particularly because they find three fatalities in the animal and no in the patients. And this is extremely unusual with Hepatitis C. Everything can be said about Hepatitis C, but it does give -- usually the acute portion of the disease is benign, and cases of acute liver insufficiency are much more frequent with Hepatitis B and Hepatitis A than for Hepatitis C. So it is a very unusual situation. I don't know how much of it was the interplay between the virus and the concentrate, which is a Factor IX concentrate, that may have caused some liver damage because of thrombotic complications, but again, I don't want to speculate. The other thing that certainly -- so this is certainly a case -- but the thing that certainly I don't agree is that when they say that "until blood donors" -- in the last sentence -- "can be screened for the non-A non-B Hepatitis agent, it would seem wise to restrict the use of both commercial and noncommercial concentrates to life-threatening situations." This is certainly something that no haemophilia treater would have endorsed at that time. All the haemophilia treaters felt that the treatment of haemophilia did outweigh the risk because of the change in the pattern of life and the change -- and I think also haemophiliacs felt in that way. So this statement is really very personal and somewhat arbitrary, in my opinion, and I would be very hesitant to write something like that.

Q. I'm not asking you to endorse the sentiments. But what I'm basically asking is the question, as we left 1978 and entered 1979 -- the issues as to how the consequences of the treatment could be alleviated or ameliorated were issues that were uppermost and foremost in the treating physicians' minds at that time: Whether people with mild haemophilia should receive DDAVP; whether people with mild or moderate haemophilia should be prescribed cryoprecipitate as opposed to concentrate, et cetera. But those were issues, because of the state of medical knowledge in 1978, that were uppermost in the medical community's mind?
A. Quite frankly, the medical community, as I told you, was aware of the problem, and became progressively cognisant of the fact, as I told you, that the original concept of transaminitis that was the -- I wouldn't say the blame, but it was the criticism applied to our first paper in the Journal Clinical Pathology 1975 was wrong. It was not no accident by a chemical abnormality. There was some damage to the liver which was -- could be predicted. As I told you, I was surprised in 1975 to find that they put in doubt that it could be an expression of liver disease and they thought of other organs. So the evidence was mounting, particularly apart from the story of Hepatitis B, the evidence was mounting that Hepatitis non-A non-B was causing some liver damage. There was concern. Measures were being taken. DDAVP, on one hand; the development of virucidal method, on the other hand, of the industry. So one from the medical community, the other from industry. But I think, quite frankly, that it is probably my personal opinion -- but very few of us, even those like me that were pioneers in this field and had been brought up - must recognise Preston and his colleague - with an ambiance of a lot of knowledge of liver disease felt that one had to change the treatment of a patient, of a haemophiliac, simply because there was no alternative, except DDAVP and the virucidal method that came about. The collection

of national blood was not the answer. And it was proven that cryoprecipitate was not the answer except in minimal treated patients or patients with mild haemophilia that did not respond to the DDAVP. So I agree with you but the -- I think it's consistent with what I did say this morning: We became increasingly conscious of the problem and we tackled the problem in an aggressive way. But none of us, or very few of us I would say, was prepared to change pattern of treatment. Not to say -- not to say of the haemophiliacs.

Q. I'm moving on to another topic, Madam Chairperson. It's past quarter past four, if that's a convenient time.

THE CHAIRPERSON: It's only ten to four.

MR. BRADLEY: Sorry.

Q. Moving right along in relation to the options that were available and what was occurring at that time, many of -- I will ask you about Italy first: Were treatment protocols put in place to minimise risks of exposure to hepatitis, both Hepatitis B and Hepatitis non-A non-B, in terms of treatment options for people with mild haemophilia, people with moderate haemophilia and people with severe haemophilia, from 1980 onwards, arising from the articles that appeared in the journals during the course of 1978/'79?
A. I think I did explain that to you. The -- for mild and moderate haemophiliacs, persons that are at risk and in which even a minimal risk of liver disease was judged unacceptable, the -- either the use of DDAVP has been recommended or aided one year after our publication by the people from Sheffield. And those who did not use -- could not use that probably used cryoprecipitate because the risk was definitely less, even though not totally unexistent (sic). And we looked with interest at the development of virucidal method, after all started in the late '70s. But as I said before -- and I think the evidence that they were efficacious and safe was too meager to make them a universal applicable. And then there is the story that I mentioned, of the failure of the first method to be effective. So there was a concern. There was concern, no doubt, among the -- the physician community and among the haemophilia community. But there was little more that could be done. As I said, I don't think that what the article before says - that one should treat only for a life-threatening situation - was in the late '70s an acceptable concept. Haemophilia moved from that situation in the '50s to the success story of the decade; the '70s had been the time of liberal treatment, of home treatment, of prophylaxis, and the benefit seemed to widely outweigh the risk. And believe me -- I mean, believe me, you can only believe me, but the haemophiliacs were happy with that. They were concerned, like us, and they fought with us and they were informed about the problems of hepatitis.

Q. When you mentioned the options of cryoprecipitate versus factor concentrates, were you referring to wet cryoprecipitate versus the factor concentrate?
A. Yes.

Q. And are you familiar with freeze-dried cryoprecipitate as a product?
A. The only -- it carries -- it was not widely produced. I don't know of many centres that produce it on a large scale. This has been used in some -- and is still being used in some developing countries. Because in a sense, you lost the advantages of the

preparation of wet cryoprecipitate, which can be easily made in a blood bank. I suppose you want to emphasise that lyophilised preparation could be used at home. But, again, believe me, the time that it took to dissolve it, the side effects -- not related to viruses, really made -- I don't know. I know a programme with a lyophilised cryoprecipitate in Thailand, but I don't know, quite frankly, at the time, of any programme like that in western -- in the western world. Because nobody really could conceive -- I'm sure there are some papers published on home programmes with cryoprecipitate in South Africa, probably also in the Netherlands there's been, but there's really very limited studies and I don't think patients were happy with that, because really diminishes their freedom. And also, the size and the bulk was such that, yes, they could be stored at minus -- at four degrees instead of minus 20, which is not a trivial advantage, but believe me, it didn't change substantially, the situation.

Q. But in terms of minimising the risk in relation to hepatitis, and minimising the donor exposure, freeze-dried cryo, as an option, would be preferable for people with less than severe haemophilia?
A. I recognise that, but the patient with the less than severe haemophilia could easily come to hospital. There is no problem. Their home treatment -- because they bleed rarely and usually spontaneous, probably never; and when they are to be treated they are to be treated because they have an invasive procedure. So I don't think it was -- wet cryoprecipitate was equally feasible because the only advantage of lyophilised is that it can be stored at four degrees. But for a blood bank it doesn't really make any difference. And so I hope you understand what I mean. There was no reason to use lyophilised cryoprecipitate because wet cryoprecipitate was very convenient for hospital use before dental extraction or before major surgery.

Q. So are you saying that, in terms of minimising risks of hepatitis transmission for people with severe haemophilia, that would have been the option that would be preferable?
A. I didn't say that. I spoke -- I said that about -- mild haemophilia. In terms of severe haemophilia, I don't think that cryoprecipitate would have slowed the product; it would have only delayed it, because they are several papers including, I told you, the Levine paper, that shows that, on a long-term -- for patients that are intensively treated and they become exposed to hundreds of donors, even if from single donor the risk is more or less the same.

Q. But in terms of treating children with severe haemophilia and minimising their exposure to Hepatitis non-A non-B, would freeze-dried cryo have been the preferable option in the light of the knowledge that was available in 1978 that we referred to?
A. You would have deferred the development of hepatitis, and I don't think there is any evidence that deferring it when you're older is better than having it when you are a child. With this I don't want to say that you should prime the patient immediately, but really, it is -- I don't think that the whole activity's worth the bother and the problems, and the fact that the reactions of the numerous following proteins -- you see, cryoprecipitate was considered obsolete in the '70s, by the majority of the members of the scientific community and, again, I take the liberty to say, of the patients. Nobody wanted to go back to cryoprecipitate.

Q. But you're talking about wet cryoprecipitate?

A. I'm talking also of dry or lyophilised cryoprecipitate, because the only advantages, as I said, is that it is more convenient for storage. That's all. It's the only advantage. And also, believe me, to my knowledge - you can perhaps feel my gap of knowledge - I don't remember any big problem based -- big problem based on lyophilised cryoprecipitate. Do you know of countries; maybe this country? I don't know, I'm not aware of problems.

Q. Finland, Netherlands, Scotland; we use it here as well?
A. Lyophilised cryoprecipitate?

Q. Lyophilised cryoprecipitate.
A. In those countries they tried to develop, quite early, some fractions, but anyway, you may be right.

Q. Talking about minimising the risks for children and delaying the possibility of infection. But would that not be sensible in circumstances where virucidal agents were about to be introduced or development of viral inactivation was in the process or in the pipeline?
A. In principle, yes. In principle, yes. I think that -- in principle I think that, as I explained, knowledge was not yet available that concentrates were -- virucidally-treated concentrates were making so much progress. But in principle, I think, with the evidence that is available now, it would have been a good move. But again, with retrospective evidence --

Q. But would the evidence that was available at the time in respect of the effort that was being put into the development of heat treatment as a method of eliminating hepatitis, would it not have been sensible to place patients, more particularly children with severe haemophilia, on products that minimise the exposure risk to hepatitis?
A. In principle, yes, but, as I told you, you mentioned some countries that are certainly not the most numerous in terms of patients. I'm sure it's true that this country had a programme. To my knowledge, I didn't know that country -- I'm not sure. Finland; I know the situation of Finland quite well. I don't know of many publications, you see. Did you know of publication or only by word of mouth? Because the countries that had -- like those that he mentioned, the Netherlands, Finland and -- Netherlands, Finland, and what also did you mention?

Q. Scotland?
A. Scotland. They had quite a developed Blood Transfusion Service. They started -- they were strong believers in voluntary blood donations. So rather than moving to cryoprecipitate, they used their technology to start to prepare large pool concentrates, rough concentrates but better than cryoprecipitate, on the basis of voluntary donations. That was their means, that was their goal. Typically, also France, you see, that was very dedicated to voluntary blood donation. The problem that I didn't understand; that, even among voluntary blood donors, there is a lot that carry this virus. But anyway, it seems to me -- really I'm glad to have the evidence that serious programmes based on lyophilised cryoprecipitate were implemented, published and that information has been given to the scientific community. I tend to believe that this is done only recently, by the way, in developing countries.

THE CHAIRPERSON: With that, Mr. Bradley, I think we'll leave it until tomorrow morning. We'll resume again tomorrow morning at 10:30. Thank you.

THE TRIBUNAL THEN ADJOURNED TO TUESDAY, JULY 17, 2001, AT 10:30 A.M.

THE TRIBUNAL RESUMED ON TUESDAY, JULY 17, 2001, AT 10:30 AS FOLLOWS:

CONTINUATION OF EXAMINATION OF PROFESSOR PIER MANNUCCI AS FOLLOWS BY MR. BRADLEY:

MR. BRADLEY: Good morning, Madam Chairperson.

Q. Good morning, Professor Mannucci. Now --
A. Good morning.

Q. We'll start up where we left off yesterday evening. I'm going to track through the history of Hepatitis non-A non-B and then I'm going to ask you some questions in relation to HIV. It's quite similar focus to the focus that Mr. Finlay went through yesterday with you. First article I wish to look at is an article attached to your statement at page 74.
A. To my statement. Aledort?

Q. Aledort, that's correct. It's a study of liver biopsies and liver disease among haemophiliacs by Louis Aledort and Peter Levine and Margaret Hilgartner. Now -- and if you look at the summary of the particular article: "Hepatic histologic materials (biopsy or autopsy) and associated clinical data from 155 haemophiliacs were collected by an ad hoc haemophilia study group and analysed by retrospectively in an effort to determine the spectrum of liver disease in this population, and to examine the relationship between the severity of liver disease and treatment history. Clinical information on the frequency of complications from 126 biopsies and 115 haemophilic patients provided a unique opportunity to assess the safety of liver biopsy in such patients. The incidence of cirrhosis (15 percent) and chronic active hepatitis (7 percent) was lower than previously reported. The frequency of severe liver disease (chronic active hepatitis or cirrhosis) in patients receiving large pooled concentrates was no greater than patients treated principally with cryoprecipitate or plasma." And we referred to this particular article yesterday and you indicated it was authority with a proposition that the risk attached to cryoprecipitate was no greater -- was similar to the risk attached to concentrates for people with severe haemophilia because of the cumulative effect of exposure. The population that was looked at at that particular -- in that particular study were a United States population. And therefore, would the incidence and prevalence of hepatitis non-A non-B in that population have been greater than would have been in other populations throughout the world?
A. Which population, sorry, this population?

Q. This population. The study is predominantly based in centres of high population such as New York, Pittsburgh, reference to London as well, Massachusetts. There are high
centres of population.

THE CHAIRPERSON: Where do you see that, Mr. Bradley?

MR. FINLAY: Mr. Bradley is mistaken in this because the very commencement of the article "Material and Methods" says that centres were contacted throughout the United States and western Europe. So --

MR. BRADLEY: And if you look at the second column, bottom right-hand corner, you'll see from the department -- the different departments that were involved. And the point I'm seeking to establish is to whether the incidence of Hepatitis non-A non-B in one country can be different to the incidence of Hepatitis non-A non-B in another.

THE CHAIRPERSON: That's a perfectly valid question, Mr. Bradley, but I don't think you are correct. Because if you look at the -- that side, it says the Royal Free Hospital and School of Medicine, London as well. So --

MR. FINLAY: There seems to be Belgium.
A. So if you look at the acknowledgments, if I am allowed to interrupt, you'll see that there is my name; Dr. Larrieu, who is French; Klaus Schimpf, who was German, and I think we did contribute with the substantial number of cases. I don't know whether they split the case material by centre, but it is not true that there was only American centres. The authorship is due to the fact that there were the organisers of the study, and there are also some pathologists. Aledort is American; Levine is -- Levine is also American; Hilgartner. They were the three leaders in the field in the United States at that time. Dr. Blatt is from Chapel Hill, so another famous centre. Joel Spero, you'll remember he did do a study himself on liver biopsy. So probably because he gave the biopsy, was included among the authors. All the others are pathologists from different countries, including Switzerland, Belgium. So they are -- that does not indicate the source of the patients, of the biopsies. But if you look at the acknowledgment, you will see that although I recognise they are -- the majority of the names are American, so there is a substantial number of Europeans. And probably we were among those that provided the largest number of patients, because I know that we provided at least 20 patients. And Schimpf - which is wrongly written here - Shrmipf provided 40, 50 patients. So I think probably one third were Americans, the samples -- sorry, one third were Europeans and two-thirds were Americans.

Q. Okay. But the vast majority of the people, locations, are centres of high population, if you look at the cities that are referred to.
A. You mean you look at the authors or if you look at the acknowledgments?

Q. The acknowledgments where the authors and where the studies were undertaken, they were cities of high population?
A. Yes, I agree with that.

Q. So therefore, the incidence of Hepatitis non-A non-B in cities of high population could be greater than in certain other areas, certain other countries?
A. You see, we don't know -- we didn't know particularly at that time the epidemiology of non-A non-B Hepatitis also, because, by definition, it was a negative

definition. So the epidemiology was not so well-known. Now, we know more that the antiHCV testing is available. And certainly the disease is frequent in Italy, is frequent in -- but is not particularly frequent in the United States. It's probably more frequent in large cities, but I don't think this has been truly convincingly shown. So it may be true what you surmise, but I don't think we have any evidence from this study.

Q. Would you consider that the category of donor would have an impact upon the likelihood that that donor was infectious for any particular condition, including Hepatitis non-A non-B?
A. There is no question that certain population and certain donors are a higher risk. I mean, particularly the paid donors from plasmapheresis centres that were used at that time, in the previous era in the United States. But the point I wanted to make is when you deal with a large pool of thousands of donors, the facts show, quite clearly, that there is not much difference between countries using paid donors and countries using voluntary donors. When you come to the large pool, the difference is lost. That's a little bit like the story of the accumulation of donation with cryoprecipitate. You see, when you go beyond a certain number that nobody knows, but certainly with precision, but certainly is something like, I don't know, more than 100, the advantage of having selected donors and nonpaid donors is particularly valid when you deal with single transfusions. But when you have a pool, the advantage is lost because one contaminated unit is enough to contaminate a whole lot. So --

Q. But there are two factors also that need to be taken into account: The number of times treatment is required in respect of the cryoprecipitate, and that's dependent upon the severity of the haemophilia condition; and two, the category -- the risk category of donors?
A. Yeah, but I -- we discussed already at length, I think, the problem of the frequently treated patients, in all haemophiliacs. And there I agree with you, that pooled concentrates should not be given. And the evidence was already available at that time that cryoprecipitate or DDAVP should be preferred in terms of the quality of donors. Again, it depends -- it depends on many situations. As I told you, there is no doubt that the risk associated with paid donors and probably with donors coming from large communities in the West Coast, in the East Coast, more drug addicts and so on, there is no doubt in terms of single or small amount of transfusion. But when you come to the pool, to the pooled concentrates, this advantage is lost. And the paper of Kernoff in a sense, Kernoff and Oxford, the Oxford paper, is showing that quite clearly. Because even using -- even once volunteer donors were used, the difference was -- well, the impact of hepatitis with the first infusion, the fact that the first infusion caused hepatitis is quite obvious. So I recognise that there is a difference in the quality of donors. But when you get -- you come to the plasma pool, this advantage is lost.

Q. Okay. If we turn to page 76, you can see that among the 15 autopsied patients known to have received concentrate, the incidence of severe chronic hepatitis or cirrhosis was 20 percent. If we turn to page 78, we can see some recent evidence suggests that insidious progression of non-A non-B Hepatitis to cirrhosis?
A. Where are you reading?

Q. Page 78, second paragraph down. Second sentence.
A. The lack of severity?

Q. Yes. "Lack of severity of histopathologic findings in the current materials may not be entirely reassuring. Some recent evidence suggests in insidious progression of non-A non-B hepatitis to cirrhosis." So in conjunction with the Preston study that we looked at yesterday, Mr. Finlay looked at yesterday on page 80, it appears that chronic active hepatitis now -- or chronic persistent hepatitis was no longer considered to be benign, and it could therefore develop to cirrhosis by 1985. Would that be a fair state of knowledge at that point in time?

MR. BUTLER: Madam Chairperson, before the witness answers, could I ask that Mr. Bradley would complete the sentence where he stopped at the reference to insidious progression.

THE CHAIRPERSON: All right. Would you finish the sentence. Perhaps if you just read it in its totality again, Mr. Bradley, please.

Q. MR. BRADLEY: All right. "The lack of severity of the histopathologic findings in the current materials may not be entirely reassuring. Some recent evidence suggests insidious progression of non-A non-B hepatitis to cirrhosis, although other studies suggest the possibility of reversion towards normal hepatic architecture," and there are two references to that; reference 19 and reference number 20. One reference is a reference by Koretz, RL, and the other is a reference by Professor Mannucci. And if we turn to page 80 -- and I'll also open the article by Professor Preston so that all articles are opened. The summary, this is an article also from 1985: "In an eight-year study of 79 unselected patients with haemophilia who had received clotting factor concentrates, there was evidence of chronic progressive liver disease in at least 17 (21 percent). Eight patients had chronic active hepatitis and nine had cirrhosis, (five with oesophageal varices.) Histological evidence suggested that non-A non-B Hepatitis was mainly responsible, although the influence of other viruses could not be excluded. Serial liver biopsies showed progression from chronic persistent hepatitis to chronic active hepatitis and cirrhosis within six years, suggesting that chronic persistent hepatitis in haemophiliacs is not as benign as hitherto supposed. Symptoms and abnormal physical signs were uncommon in these patients. There was no relation between the degree of abnormality of serum aminotransferase levels and severity of the underlying liver disease. It is anticipated that liver disease in haemophiliacs will become an increasing clinical problem in the future." So in terms, we've referred to four articles: The article that I opened and expanded upon by Louis Aledort and Peter Levine, the two references to that -- in that article; one by yourself; and one by Dr. Koretz; and then the subsequent article by Professor Preston, and the Sheffield group. Now, would it be fair to state that, by 1985, that the indications were, if you look at the four of those articles, that people who had chronic persistent hepatitis could go on, as a possibility, to develop cirrhosis?

A. That evidence came from the -- not from our study. Our study actually did show the opposite, but again, in science there is always a variability comes from the study of -- of the people from Sheffield, that undoubtedly, as I mentioned yesterday, was the one that gave the most gloomy picture. And certainly we took into account -- you see, in 1985 we were already struggling to find this problem with the virucidal method. The only thing we knew already, that they were not working. But certainly, I agree with you that there was a progressive -- since 1975, when our Journal of Clinical Pathology paper was published -- and I emphasise, unlike Peter Levine, we also did a

study test of liver function. You see, those tests, they're altered in cirrhosis and in serious hepatitis and they were practically all negative. Through the biopsy studies and other biochemical studies, there was certainly some evidence that the disease was not so benign and nonprogressive as we had hoped, but with caution in that article. So over those ten years, the concept that in a proportion - which corresponds to what is now the knowledge of the natural history of Hepatitis C - that some patients could progress was known. One should not concentrate too much, in my opinion, to what I conceived as bias, on the Sheffield article, and considered also other -- there are more cautions. Like, for instance, Aledort; that it was, after all, a big series. But this -- certainly this concept came about and we were worried. But in a sense, believe me, we started to be worried in 1975, even though we saw that there was no evidence of severe liver disease. So it has been a continuum; science, and knowledge in science, is that. And the only thing that is clear, that apart from haemophiliacs, also nonhaemophiliacs, the natural history of this elusive disease defined in a negative way, that is non-A non-B Hepatitis, became progressively known, but it was quite unknown in the '70s.

Q. Would it be fair to characterise the three stages: There was the stage in or around 1975 when you wrote your article, where there was concern in relation to abnormal liver function tests and what that might lead to in the future, but that was -- there was a concern at that stage. There was a question to be answered. Would that be a fair evaluation of that point of -- in time?
A. Yes.

Q. When you get to 1987, it is clear from the articles that I opened yesterday that there were incidences of chronic active hepatitis being found on liver biopsy; there were incidences of cirrhosis being found on liver biopsy; therefore, the -- and there were also indications of chronic persistent hepatitis, but it was unknown as to whether that would develop to cirrhosis. So that was the state of play. It was known that people could become -- could sustain liver damage to that extent at that time. Would that be a fair synopsis of the situation in '87?
A. It is a fair synopsis. And in fact, the problem has been tackled; for instance, with the use of DDAVP and with the development of virucidal methods.

Q. Then when we come into 1985, there is an additional issue of concern, and that additional issue of concern is that patients who had chronic persistent hepatitis now appeared to be capable of developing the cirrhosis. Would that be -- and --
A. That's, quite frankly, I don't think it is so solid as you say. You have to consider that this is -- in haemophiliacs, this is more a number of cases -- as large as it can be; the Sheffield series and also the Aledort -- well, the Aledort series was not prospective. So it's still not an accepted concept that chronic persistent hepatitis can develop to cirrhosis. After all, only one-fifth of patients with Hepatitis C do develop cirrhosis so - not all the forms - even without any treatment, that's natural history.

Q. I'm not saying all patients will develop from chronic persistent hepatitis to cirrhosis, I'm saying that certain patients will develop?
A. Okay.

Q. Was that the stage of development at that time, or state of knowledge at that time?

A. I don't think that was really solid evidence of that, but -- because, you see, you cannot really make a conclusion from one, two, three, four, five cases in a special environment, special cases. So I think the possibility -- we heard, we read the paper and, of course, we are concerned, as we are even before reading the paper, but I don't think it is an -- it was, at that time, an established fact.

Q. But there was a conflict in the medical literature. And if we look at the four articles: We look at the article by Louis Aledort, we look at the references he refers to; and we look at one of those references, being your own article; and then we look at the Sheffield study. Three of those articles seem to indicate the possibility that chronic persistent hepatitis can develop to cirrhosis, and would you --
A. I don't want to -- I don't want to defend that point. The Schimpf article, for instance, is an abstract, and also, by definition, can give relatively little information. But anyway, I don't want to give the impression of defending that point. We were concerned, you are right. We are concerned about this possibility, even though I think it was not firmly established. There was concern.

Q. You'd accept that treating physicians would be concerned about that possibility and that would be a matter that they would be taking into account in respect of treatment options?
A. That's -- that's -- I don't agree. I think we are concerned, but we had no treater -- other treatment option, as I told you; except, perhaps, for patients with mild haemophilia. The story of lyophilised cryoprecipitate, as I told you, was really adopted by very few people; and I told you, again, that also cryoprecipitate, if given intensively, leads to the problem. And so I don't think there were other options. Also, because the haemophiliacs were refusing to use cryoprecipitate --

Q. But, Professor Mannucci, we're now in 1985, we're now at a time when pasteurised products were available, when the advent of solvent/detergent products was on the horizon. So there were options. So at that particular point in time was that a matter that treating physicians would have been taking into account, the possibility that patients who received both heat-treated and nonheat-treated product could go on to develop cirrhosis?
A. But we considered that, we did the study; and the study was that not in 1985, we're studying in 1983. So this is showing that we are concerned and we hoped that the virucidal method would solve the problem. Unfortunately, the evidence of internal hepatitis was not there because I told you the story of Barcelona in 1983. I told you that the pasteurised concentrate was not available on a large scale; that the result presented in abstract form in Rio, Brazil, were not convincing. So we tackled the problem in 1984 in the international community, the ISDA should tackle the problem. I was responsible for the study of the -- with the Baxter problem. So we were concerned and we used it. But you have to consider that until we got -- I agree that the solvent/detergent was on the horizon, but even there there is something I can tell you, because I didn't present it here, but I met -- I met Dr. - what's the name - Horrowitz, the guy from the New York Blood Centre. And to begin with, as solvent, they're trying to use ether, chloroform, sodium cholate, and I remembered we discussed with him the fact that we tested an experimental product treated with ether and it caused two cases of hepatitis. I didn't include this reference, but it is in the series of articles probably published after our case, our study in The Lancet. So it was

on the horizon but still not firmly established as the safe and good method that it is now.

Q. I think we're looking at two separate time-spans, Professor. You're looking back at what the situation was in 1984 and you're talking about ether in relation to the solvent/detergent method. That was superceded by tri (n-butyl) phosphate. So that particular issue did not become apparent at that time, subsequently -- I'm looking at from 1985 onwards, towards '86, '87, '88 -- when virucidal methods became available. And I'm saying that the state of knowledge in relation to the risk of hepatitis and the damage that hepatitis could cause were matters that treating physicians should take into account, and in many instances did take into account in the prescription of treatment for previously untreated patients. So I'm not looking back at the period '83, '84, '85, I'm going to come back and deal with that in relation to HIV. I'm purely looking forward from this point in time where we know that the -- both the heat-treated and the nonheat-treated concentrates can have consequences pertaining to -- pertaining to patients who received them in relation to hepatitis. So would you accept from that period on, treating physicians were looking at methods to minimise exposure to previously untreated patients?
A. Yes, not only to previous -- I didn't recognise that. Those were the crucial years in which a better method did eventually develop, so we're all concerning -- we are all waiting, we are all doing clinical trials. Some openings were on the horizon, including the demonstration that the pasteurised product was really good, but that the steam-heated product was useful, and the first evidence about solvent/detergent. So I do agree with you there.

Q. Those were the treatments of choice for previously untreated patients as soon as they became available arising from this particular state of knowledge at that time?
A. Well, yes. Not only for previously untreated patients; since in 1987 -- '85, in the majority of European countries and The States, nonheated products were no longer used by law. This was enforced by law. It was enforced in the United Kingdom in Spring; in our country in July; in France -- it was in October, I remember that distantly when there was that trial for Dr. Alane (?). So the evidence that we are concerned with, it took the right measure; using this product, even if not ideal, stems from the laws that were enforced in many different European countries to stop the use of nonheated products.

Q. And in your country, the products that were used were pasteurised products and solvent/detergent-treated products for previously untreated patients --

THE CHAIRPERSON: What time are we talking about?

MR. BRADLEY: From '87 onwards, 1987 onwards.
A. Not only that we used steam-heated products because it was proven to be effective after some initial problems, we used pasteurised product; not in a large amount, but we used a pasteurised product. We used solvent/detergent, and we also used -- yes, we used these three in our country, yeah, since 1985 -- since 1987. 1985 to 1987 is the grey area in which we use this concept in many patients under control, condition of clinical trials.

Q. So in the period 1985 to '87 you used -- was it pasteurised and steam-treated factor concentrates under trial conditions for your patients; most especially those patients, I presume, that were previously untreated patients?
A. Yes, because they were on the trial. So following the recommendation -- so those patients had been exposed to the better concentrates, because they had the luck to be involved in clinical trials.

Q. And would you have expected, at that time, that the risks and incidence of Hepatitis non-A non-B would be reduced by those products?
A. We think it was reduced dramatically.

Q. You mentioned yesterday to Mr. Finlay that there was a national producer of factor concentrates in Italy. When did that producer start producing product?
A. He was actually in producing products even before 1985. But it was, I think, an intermediate product that was originally unheated, and then, if I remember, heated in the dry stage. But it was not used anywhere except in the Pisa Haemophilia Centre, which is the one, by the way, that reports -- is one of the studies reported here. We didn't use it because they had a very limited production and, for some reasons, they were -- they had enough only for this centres in Pisa, and probably a few others, but really a tiny fraction of the market. But then in 1985 they started - 1986, I don't remember exactly when they started the production of a new product, which was more purified and was treated with solvent/detergent. And then it was largely used; not only -- it was not the only one used, even though it was a national product in Italy. Probably had its share of one-fourth, one-third of the market, no more than that.

Q. In terms of the other products that were in the market up to 1985, were any other products derived from European plasma at that time?
A. I don't think so. By the way, even the Biagini, the Italian plasma, was not of Italian origin at that time; it was imported from The States. That's what I want to emphasise. I think the other applies to the other concentrates because even though the German product was German, the Austrian product was Austrian, I think that the plasma came from the United States, was plasmapheresis plasma coming from the United States. Because there was not enough in Europe except part; but only in part in the United Kingdom, a small part -- among the big countries, I'm talking of the big countries. The story is different, to some extent, in small countries that, very early, developed an advanced fractionation system, like Finland was mentioned yesterday; like the Netherlands. There, to which extent I don't know, they use also local plasma. But there was also a sizable proportion of commercial plasma and commercial products made from commercial plasma. But of the big countries, nobody was really self-sufficient. If anything, in the United Kingdom there were -- they were said to be self-sufficient in terms of Haemophilia B but not in terms of Haemophilia B -- A. And the story, the same applies to France. Germany and Italy were -- had practically no -- at that time, no local production. That's why, in the paper in which I give the history of the development of AIDS in Italy together with my colleague Gringeri, I said that really the country for which the comparison is more valid is Germany, because at that time Germany has 60 million people, like Italy, and we practically use the same products. And believe me, none of them was of European origin. There were some plasmapheresis centres in Europe; I don't want to be nasty, but the companies took some of us around to show these centres, but then they had to

recognise that the majority -- they were only for showing off. The majority of the plasma was imported from the United States in a totally legal way.

Q. If we look at page 18 of the second booklet, it's an article in relation to HIV infection in Italian haemophiliacs?
A. Yours or my --

Q. It's an article by yourself and Alessandro Gringeri. Page 14 of the second booklet.
A. Page 14 of --

THE CHAIRPERSON: Mr. Bradley, was it submitted by you --

MR. BRADLEY: Blood Transfusion Service Board.

MR. FINLAY: Yes. In the Professor's book it's at page 164.

THE CHAIRPERSON: Thanks.

MR. FINLAY: 163 in the Professor's book.
A. Yes. Thank you.

Q. MR. BRADLEY: And if you look at page 17?
A. 160 --

Q. Sorry, it's 278 of the actual text?
A. Of mine?

Q. Of yours?
A. No, I don't get to two --

MR. FINLAY: In the Professor's book, it's page 163, is the article.
A. 163.

THE CHAIRPERSON: And Mr. Bradley's referring to 165.
A. Okay, yes I got it.

Q. MR. BRADLEY: We see that the incidence - you're comparing the German haemophiliac situation to the Italian haemophiliac situation - the incidence of HIV positivity is 47.4 percent; and the incidence in Italy is 22.8 percent. You've indicated that both countries used commercial Factor VIII concentrates derived from US plasma to a similar extent I think already in your evidence. Would that be fair to say?
A. So you are comparing, in table six of the last column --

Q. Last column?
A. German, 45.6; and Italian, 44.1.

Q. Yes.
A. No, but that's Haemophilia B.

Q. Sorry, I'm comparing Haemophilia A. 47 -- the first column, 47. --
A. 47 -- yeah, I told you, I don't know. It is still a mystery, of course, it's a pleasant mystery for once; why, in Italy, we had so fewer patients with Haemophilia A affected by HIV. And I really have no explanation. And I don't want to speculate on the possibilities, because really, as we write in this paper, we have really no explanation. We are happy with that, of course.

Q. In the article at page 18, you indicate, "There are several possible explanations for these differences: In West Germany Haemophilia A patients were treated annually with larger average doses than Italian haemophiliacs in the early '80s, when most infections occurred."

THE CHAIRPERSON: Sorry, where are you reading from, Mr. Bradley?

MR. BRADLEY: Following page, page 279.

THE CHAIRPERSON: 167.
A. Yes, page 167.

Q. MR. BRADLEY: What can you tell as being one of the possible explanations for the fact that the dosage of factor concentrates administered in Germany were larger than the dosages administered in Italy, and therefore, the exposure would be greater?
A. It is a speculation. It is a possibility, but it is not proven. It is a reasonable possibility because unlike -- that, again, is really not very solid evidence, but whereas for Hepatitis C, as we said, with the large pooled concentrate, the contact of one shot of concentrate with the body gave rise to Hepatitis C in almost 100 percent. We don't get that impression with haemophilia -- with HIV. But again, these are not solid data because there, in that instance, we have the transaminases that developed -- I don't think -- I don't think -- it is a speculation. It may be true but it is not so 100 percent certain.

Q. It is not scientifically proven?
A. No. Yeah.

Q. But it is a possible explanation?
A. It is a possibility. We wrote -- sorry, I don't want to negate what we wrote, but it is a possibility. No evidence-based medicine, the reviewer would say.

Q. So therefore, the frequency of treatment had the determination upon the likelihood of infection?
A. Again, I wouldn't say that. That's what we speculate, but I don't think that collectively, from other people, from other experiences, that really that evidence -- there is the suspicion, yes. And in fact, in Italy we have never been big users of Factor VIII concentrates like in Germany. We didn't put, at that time, many patients on prophylaxis. You see, you have to consider that in the '70s not only -- the patients were treated at home so they could use whatever they wanted, because they had the concentrate there in the inventory and they could use whatever they wanted. Which was, I'm sure, many of them would recognise it was something that they considered advantageous. Now, of course, maybe they would judge in a different way, but you

have, again, to consider the perspective and retrospective evidence. There was also a push to give prophylaxis; I mean infusion every other day independently of the bleeding episodes. And this has been certainly adopted much more intensively in Germany than, I would say, in other European countries, big European countries; I mean UK, Italy and -- UK, Italy and France that have -- you see, I always compare them because, at that time, they all had more or less the same population, 60 million people, so they are quite comparable.

Q. In terms of France, we see that the prevalence of HIV infectivity in the general population was the highest in Europe, and that might be an explanation as to why the French haemophilia figures are quite high, although they were using a domestic product. Would that be a fair assessment?
A. Oh, yeah, that's a fair assessment. Because particularly for the HIV story, the story of local versus foreign plasma was very misleading. Because there were some countries that had such a high incidence -- I mean, America was certainly not preserved from infection. But I wouldn't say that, considering the incidence per capita, clean countries like Switzerland, for sake of example, or -- were immune. They had a very high prevalence. So this reflected, of course, into the donor population. And that's why the famous local blood, pure and clean, was certainly not pure and clean. And there is evidence of that.

Q. But it depended upon the risk attached to the particular population, and certain populations were higher risk than other populations throughout your -- would you accept that?
A. I accept that.

Q. Okay.
A. And I accept that the example that I make here of France, for sake of an example, applies also to Switzerland, applies to Spain. They were countries with a very high incidence of HIV infections from the very beginning.

Q. Mr. Finlay asked you yesterday about your state of knowledge in relation to HIV and when HIV became apparent to you as a treating physician. When did it cause you concern?
A. Can you say it over again?

Q. Sorry, Mr. Finlay was asking you yesterday in respect of your state of knowledge pertaining to HIV infection, and when the risk attached to HIV infection became apparent to you as a treating physician?
A. Well, if I had to answer precisely to your question, I would say when there was the true unequivocal demonstration that AIDS was due to infection with a retrovirus that was later called HIV - and this was not really before 1985, because the association between the disease and the virus is measured with the antibody. But I recognise that the concern occurred from the very beginning, occurred after the publication of the -- of the two cases in the Mortality and Morbidity Weekly Reports. That, of course, is a personal experience. And I cannot mention the person, but I remember in 1982 to have seen a couple of very well-known patients with haemophilia that told me about the presence of fever, lymphadenopathy, wasting. So I -- we were all aware of the problem and there was, I am afraid, a lot of confusion, because you have to consider that, at that time, HIV was not known; the test was not

known. So the only thing on which you could base our preoccupation were the cases of AIDS, the terminal disease. And originally there were only two; it was thought to be in America -- all this is very ridiculous, of course, if I think now. And believe me, I mean here I give a sort of personal reflection; whereas, to be quite frank, I don't feel -- I don't think I have any -- I don't feel any guilt in the story of hepatitis. I think I did act personally and together with my colleagues in the most timely way, and I really have no feeling -- now -- but of course, with the retrospective evidence, I realise that when you see something happen in haemophiliacs, I mean the cases of pneumonia, Pneumocystis Carinii, and then you find a few other cases, haemophilia -- patients with haemophilia by definition, they must multitransfuse; they are the multitransfused patient. So to think that it is something related to transfusion is only too logical. And of course, we thought about it, but there were pros and cons, I told you; seemed to be an American disease. In Italy we thought it is not an Italian disease. This is all -- it was thought to be related to the gay people in the West Coast. So there were a lot of confusing factors also because the agent was not known and was not identified. But certainly -- whereas as I said even with the retrospective evidence, I don't think -- I have nothing to blame myself for for the HCV story. The HIV story, if you think about it now, but with the evidence that we have now; we did probably overlook many things. But it was, to my relief, it was quite universal. Sometimes you get a relief of your -- of what you did by looking at what the other did the same. So this is, in a sense, a confession that I'm prepared to do in front of this -- in front of this Tribunal. The story is different. But the knowledge was -- there was very little knowledge. There was a lot of confusion. There were haemophiliacs themselves that were not worried, that prefer to be treated. They have been informed, but most of them preferred to continue to be treated because of the advantages that they got from treatment rather than the disadvantages. Since I am in this personal recollection, I can tell you -- well, no, I don't think I will tell you that. Sorry. That's probably too personal.

Q. I don't know what question I should ask now. Let's look back at what factual evidence was available at the time, rather than looking back with the retrospective scope. From December 1982 -- well, July '82, it was apparent that people with haemophilia had become infected with AIDS. CDC had reported those incidences. You were vice-president medical of the World Federation of Haemophilia at the time?
A. Yes.

Q. Would you have been aware of those particular reports?
A. Oh, yes, I was aware. There were only two cases, but I was aware, and certainly there was information in the medical community. And in 1983 -- in 1982, there was not much fuss about it because there were only two cases. But in 1983, when we met in Stockholm, there were a few more cases.

Q. Can I slow you down. The very important intervening event: The December '82 transfusee recipient, being a child and infant who became infected with the AIDS agent, as it was then known, and who was infected in circumstances where the donor was also identified. So would you accept, from that point in time, that it was known that the unidentified agent, whether it was a virus or whatever it was, was then believed to be capable of being transmissible through blood or blood products?
A. Yes, with the evidence available now, this is -- this looks really very absent but -- that we didn't consider that a proven fact. But again, you have to consider that it was

thought to be an American problem, an American disease and -- but certainly, you are right. Because as much as I said that when something happens to haemophiliacs, they are the epitome of the multitransfused patients. Now you have to think that it is related to the transfusion. I mean, that certainly added the evidence of the 1980 -- of the June or May, or whatever it was, the two cases. I agree with you.

Q. In early 1983, the fractionators started withdrawing lots of products that were contaminated by AIDS donors. Did that heighten concern at that time?
A. Well, we thought it was -- it was in a positive way. We knew there was concern, but it was considered a very wise thing, done out of precaution as much as we considered it -- if one does look at the story of new variant CJD, I think that it is good to reclaim all the products that had been reclaimed since the decision of the United Kingdom not to use the local plasma. Again, we think that there is no evidence, but this time we have learned the lesson. So I think that everybody is much more cautious. So I agree with you, that the December case of transfusion -- of course, there could be always alternative explanations. You say that blood transfusion causes immunodeficiency, particularly repeated blood; that boy, if I remember, he had a very serious illness to start with, for which he was transfused. So there were always alternative explanations. But I agree with you.

Q. But the major issue with that particular child was that the particular donor, the AIDS donor was identified?
A. Mm-mm.

Q. So from that point in time, you'd accept that it was likely that AIDS was blood-borne. Now, as we move into 1983, you mentioned Montaginier, in 1984. In May '83, Montaginier identified the LAV virus as a retrovirus.
A. Yes.

Q. What was the appreciation among haemophilia treaters of the consequence of a retrovirus getting into the blood supply system, and more particularly, the products that were used to treat patients with haemophilia?
A. At that time the retrovirus has been isolated from a patient with AIDS, but there was no evidence that it was the causative agent. I think it is recognised in the paper by Montaginier himself. It was an additional cause of concern. But the demonstration that was -- that giving retrovirus was the cause of AIDS, it could be transmitted, was always and indirect stemming mainly from the case that you mentioned in December 1982.

Q. Was it appreciated at that time that the causative agent mimicked or was similar to Hepatitis B, that it was found in the same high-risk populations; did it seem to be transmissible by blood? Was that an appreciation among haemophilia treaters or among virologists or among the medical community?
A. Not -- I don't think that was particularly important because, as I told you, the haemophiliac, the multitransfused haemophiliac is, by definition, the one exposed to all possible viruses. So this doesn't mean, just because they are multitransfused doesn't mean that the virus -- the virus is pathogenic. It could be the cause of AIDS. The haemophiliacs harbor, unfortunately, so many different viruses, because of the blood transfusion; that didn't seem to be anything special. There was concern about

the other HTLV-I, HTLV-II; that it, you know, causes some disease, but it was -- but certainly the observation was an important one.

Q. In terms of the first six months of 1983, there were certain actions that were taken to minimise risks of transmission, and one was the NHF MASAC recommendations of January the 4th. Would they have been something that you would have been aware of at that time?
A. Oh, yes, we were aware -- let us say that the general awareness really took place in June, I think, when the World Federation of Haemophilia met in --

Q. Stockholm?
A. -- in Stockholm. But certainly, even on that occasion, you see, there was really no recommendation to stop the use of concentrate. That was a mixed patient-and-doctor gathering.

Q. But in terms of the scientific programme, the scientific programme would have included people who would have been foremost in the investigation of the issue at the time, such as probably Dr. Bruce Evatt; I think he was in attendance?
A. He was -- now, I don't remember. What I remember distinctly of that meeting was a big meeting that was summoned rather -- I don't think it was official, but in practice, everybody attended, it was very lively. But so -- Bruce was officially in the programme. Have you seen the programme? I don't remember that.

Q. I haven't seen the programme. I've seen the discovery from CDC and I've seen references to -- about the aftermath?
A. I realise that. But I thought you meant that he was there, he gave an official talk at the conference -- he gave a talk.

Q. I think you got a copy of his slides as well --
A. Mm-mm.

Q. -- after the conference. But after the conference --

THE CHAIRPERSON: What are you saying that he said?

MR. BRADLEY: What I'm saying, basically, is that, from that point in time, the haemophilia treaters were made aware of the investigations of CDC on a worldwide basis; there was a greater knowledge-base arising from that particular conference.
A. Yes, with -- we knew before probably, but certainly that's -- with that conference, the information reached everybody, as far as you can say. Because I don't think that he could have said more than he did in the Mortality and Morbidity Weekly Report, the two cases, loss of a few more that probably occurred in between, but still a handful and the story of the transfusion.

Q. In terms of the manufacturers of the concentrates, did you -- were you conscious at that time of the high-risk category of the donors into those products arising from the information that was unfolding?
A. Yes and no; in the sense that the manufacturers, when interrogated, always told you that the plasma was collected usually in colleges, middle -- the very healthy and clean middle west. But that, of course, was more or less shaky; not very many people

believed that. There were certainly plasmapheresis stations in such places, but I'm not sure it was really the majority. But the thing that, in a sense, reassured those like us that were obliged to use American plasma because of the insufficiency in our country, like in Italy - but not only in Italy - the reassurance came from the fact that the - and this is true - the plasmapheresis stations were licensed and approved by the FDA. We thought that agency that had a good reputation for defending the consumer in terms of food and drugs, was, let us say -- was justified enough that the donors were not exploited, that there were no high-risk donors. But certainly the problem that there were high-risk donors loomed large, and not only for the story of HIV. Because, after all, the risk groups are more or less always the same, as you know already, for the story of hepatitis.

Q. But in terms of when products started to be withdrawn and high-risk donors had got through the investigative process, did that cause additional concern?
A. It did cause additional concern, yes. The more -- the cases became more numerous, and so I think the main concern was of the fact that the cases became more numerous. That was really the main concern.

Q. Linking into that time, did you examine your patients for signs of lymphadenopathy, physical -- did you undertake physical examinations around that time for signs of AIDS-related consequences?
A. Yes, we did. And as I told you, that was, as far as we are concerned, one of the most misleading aspects. Because in Italy, there was nothing in 1983. And the first two cases appeared in the second part of 1984. And so one tended to endorse the concept of the American, quote/unquote disease, even though we knew there were some cases in Europe, but not very many, I must say.

Q. But you're talking cases of actual AIDS. What I'm --
A. That is the only thing that was available at that time, so...

Q. Were there any -- were you undertaking examinations for physical signs or symptoms of adverse consequences associated with the treatment, such as lymphadenopathy, night sweats, malaise; was that something --
A. We took that into account. We took that into account. And I think we have some -- we have reported that here. We took that into account because we knew it was, in a sense, a prodrome of the syndrome; or, let us say, softer and less severe form of the problem. So we took that into account. So there was nothing, nothing significant. You see, these symptoms are quite nonspecific, but certainly it is something we would have noticed because there was no reason why haemophiliacs should have lymphadenopathy, nor sweats and decrease of blood-borne -- body weight, and so on.

Q. Are you saying that the incidence of those conditions, more particularly lymphadenopathy, were not apparent during that period, the first six months of '83?

MR. FINLAY: Madam Chairperson, I wasn't at all clear. We've suddenly now honed in on the first six months of 1983. Up to this the discussion has ranged over the whole of 1983 and 1984. I wasn't at all clear that --

MR. BRADLEY: It hasn't ranged over 1984, and I've gone very clearly to June 1983 and I'm going back dealing with different issues for that period of time.

THE CHAIRPERSON: Yes, well the Professor has answered in relation to 1983 and also 1984. So what you're -- this particular question you put --

MR. FINLAY: I think the questioned should be asked directly, when he started looking for lymphadenopathy in his patients.

THE CHAIRPERSON: I think he's already answered.

MR. FINLAY: I don't think that's clear, Madam Chairperson, to date.

THE CHAIRPERSON: He did, as an example of a patient for lymphadenopathy in 1983, nothing; 1984, yes. Whatever. I can check the transcript. In any event, Professor, if -- just to redirect you; when was the first time that you examined your patients in Italy for lymphadenopathy.
A. Well, we actually, since 1985 -- 1975, I mean, when we discovered the story -- before the patient came to the centre only to be treated, which was our main burden, in the, say,'60s. In the '70s, with the advent of a home treatment, they treated themselves at home. So, considering also our findings that we published in '75 - but were already there in 1972 /'73 - of the transaminitis, we decided to, in a sense, to walk by ourselves, by asking the patient to come at regular intervals to do what we call a checkup, even though they had no problem. So we took a blood sample and, of course, we did a complete physical -- physical examination. And as far as our centre is concerned, I know for sure that lymphadenopathy wouldn't have been missed, because we did a thorough physical examination. But -- so that's -- what I'm saying is that the first cases appeared in 1984, is true.

Q. Okay.
A. But certainly, looking at table two, I must recognise that in other Italian centres, being in 1983 or '84, 14 cases of so-called AIDS-related complex, which I imagine included lymphadenopathy. So there were some cases of lymphadenopathy even in 1983 in Italy; not in our centre, but in Italy. That's a list of what looks -- AIDS-related complex. Now, AIDS-related complex, I define here persistent generalised lymphadenopathy as PGL; and AIDS-related complex as ARC, without more precise information. And then in table two of the paper, 186 -- 164 of my compilation, AIDS-related complex seems to have occurred in 14 patients, 0.5 percent in 1983, to become 1.1 percent in 1984. And this includes also our cases and then two increase.

Q. But you'll also probably remember that in Italy you had lower incidence of AIDS than other countries; therefore, the signs would have been less and would have been apparent in other countries where there was a higher incidence?
A. That's probably true, yeah. I think it is actually true. It is a good explanation.

Q. You mentioned that you were involved in the Baxter-Travenol trial pertaining to hepatitis. And I have to ask -- I want to ask when did that trial commence, and was it prelicensed in The States, which would be pre-March 1983?
A. Was it -- it was licensed in The States in March 1983?

Q. March 1983?
A. Are you sure?

Q. I am. The application was in June '82. The application was lodged in June '82. Or was it prelicensed or -- in Italy or in Europe?
A. No. No. In Italy it was not licensed until 1985, not licensed. But we were certainly offered to participate in the clinical trial probably -- I don't remember exactly, but probably the end of 1982. And I remember that in Stockholm there was a meeting of the investigators and the -- since the beginning, had not really appointed persons responsible for the study; I was appointed the Chairman of the study in June 1983. And it was during the summer that some cases of hepatitis were -- in patients treated in our own centre were known to us. So that in September in stock -- in Barcelona, I reported this to the scientific community. But I don't remember exactly when we got the product. Certainly the product was not licensed in Italy before -- I think before 1985. But it was -- I didn't realise, it was -- but it was not -- it was licensed as early, as you say, as in 1983.

Q. As early as March 1983. In terms of -- we discussed that Montaginier isolated AIDS as being a retrovirus, and you were involved in a study pertaining to the heat treatment of a factor concentrate. Were there any investigations undertaken in or around that period to ascertain as to whether the heat treatment process would be effective in terms of eliminating that retrovirus that had been isolated?
A. There were two papers: One, if I remember, published at the end of 1984 by Gallo; and one published by the -- not by Gallo, it was by the people of Cutter, actually, Levy and Mozen investigation; and one published in 1985, probably after our paper, at the same time by the French, by the French group. That -- to the general surprise, at least to the surprise of people that are not really extremely familiar with retroviral diseases, it was shown to be very labile and very easily inactivated by very common measure. And that was the knowledge which probably came to me before the publications of either, was the fact that triggered my contacts with Montaginier and the idea of testing the samples that had -- that developed, including the hepatitis safety study for LAV, or whatever you want to call it.

Q. Your contact with Montaginier was in October '84?
A. Yeah.

Q. The cohort that you had established had been established in late '82 for hepatitis?
A. No. '80 -- was started -- this study, I don't remember exactly when the first patient is enrolled. You have to consider that they were enrolled over a large period -- long period of time. Certainly they were still enrolled in 1983, because, as I told you, probably the first case occurred in 19 -- of hepatitis occurred in 1983, even though the studies started before. There were meetings and so on. So that that is the story in terms of the dates.

Q. What I'm seeking to ascertain is as to whether, prior to your mention of the study in October '84, the company that you were involved with were undertaking investigations to ascertain whether that particular retrovirus, LAV, was potentially eliminated by heat treatment?
A. Not as far as I know. Not as far as I know. Cutter did those studies. Because if you -- you seem to concur with me that the first paper by Levy, that was also an

officer of Cutter, among others, Mozen, if I remember -- it was a scientist of Cutter, but not Baxter, as far as I know.

Q. Would you have received leaflets from the various pharmaceutical companies indicating that their heat-treated products could be potentially effective in respect of the elimination of LAV or HTLV-III?
A. No, not really. As I told you, as I told you yesterday, there were some people but not from -- not particularly from the industry, as far as I remember. There was -- there were doctors, a few doctors that voiced that opinion.

Q. There were doctors who voiced that opinion based upon whatever criteria they used?
A. Based on, in my opinion, on no evidence, just as I wrote in my report on the concept that you can do no harm and is likely to be better. I mean, I wrote to the centres at the end of my report. They said, 'we have no other weapon, let us try that, even if there is no evidence that it works'. And the fact that there was no evidence was indirect from the fact that there was evidence that it was not working against it. But, again, here, a lot of criticism can be done; but believe it or not, at that time that was -- that was quite an impressive finding, and I mean, it led many of us, including myself, to believe why should it work with a virus which we didn't know yet the particularly labile properties, when it didn't work with hepatitis for which the method has been developed and tested in animals? Of course, these proved to be all wrong in that and we did show that in February 1985.

Q. But it was known that retroviruses, even before the discovery of LAV, were heat sensitive?
A. Quite frankly, I must confess that before we found this beast in our -- in our path, I knew very little about retroviruses. I don't know whether the others, HTLV-I or HTLV-II, are labile or not.

Q. That would be a matter normally within the knowledge of a virologist, a virologist's area of expertise?
A. I'm sure they have, but not me.

MR. BRADLEY: Thank you very much, Professor.

THE CHAIRPERSON: Thank you, Mr. Bradley. I think before I take up the next person, I'll take a short break for five minutes. And we'll then resume with you, Mr. Butler.

AFTER A BRIEF ADJOURNMENT, THE TRIBUNAL RESUMED AS FOLLOWS:

THE CHAIRPERSON: Mr. Butler, please.

MR. BUTLER: Thank you, Madam Chairperson.

THE WITNESS WAS EXAMINED AS FOLLOWS BY MR. BUTLER:

Q. MR. BUTLER: Professor Mannucci, my name is Nicholas

Butler. I represent three haematologists: Professor Temperley, Dr. Daly and Dr. Jackson. And I just have a few short questions to ask you, and they're about the use of cryoprecipitate in the early 1980s. And the evidence the Tribunal has heard, from you as well as from other people, was to the effect that there was a general view that, for mild haemophiliacs, generally speaking cryoprecipitate was a desirable product to choose because of the smaller donor pool, and you've qualified that view by saying that the number of treatments could increase the actual exposure significantly. And I just wanted to ask you, in terms of decisions about specific patients, were there instances where, even for a mild haemophiliac, cryoprecipitate would be inadequate, for whatever reason, to raise the factor level?
A. The only reason that I can envisage is the need of a lot of transfusions for, say, very, very major surgery lasting -- in which a replacement therapy lasts for ten or more days, then it is a little bit like plasma, because cryo contains a lot of proteins. So there may be a risk of volume overload. But I don't think -- we have carried out major surgery in the '60s with cryoprecipitate without any special problem. It is true that we didn't treat patients even for surgery for as much as 20 days, as one does do now. So that is the only limit that I can envisage. A very prolonged need for whatever reason, for whatever clinical reason, of a very prolonged treatment whereby the protein and the fluid given with the cryo could cause circulatory overload.

Q. And in those situations you would choose a factor product -- a concentrate rather than cryo, is that the position?
A. If it is -- the surgery was -- yes, I would think so. If the surgery was needed. To be quite frank, it happened -- in my experience, it happened very, very rarely, if any.

Q. And could there be instances also in a mild haemophiliac where he would experience a serious bleed for which cryo would not be adequate treatment and you would require factor concentrate instead, is that a possible situation?
A. Again, the only limit -- cryo is effective if it contains what it should contain, that is Factor VIII, which can always be monitored by testing of the patient plasma. So that gives you evidence that the treatment is going to be effective. So again, for acute bleeding, I think cryoprecipitate is always adequate, unless, again, the bleeding is such and the condition is such that you have to treat him for 20 days or more, and then we are going to have the same situation that I depicted before.

MR. BUTLER: Thank you very much.

THE CHAIRPERSON: Thanks, Mr. Butler. Mr. O'Brolchain, please?

MR. O'BROLCHAIN: I have no further questions, Madam Chairperson.

THE CHAIRPERSON: Mr. Aston, would you wish --

MR. ASTON: One or two very short questions.

THE WITNESS WAS EXAMINED AS FOLLOWS BY MR. ASTON:

Q. MR. ASTON: Professor Mannucci, I represent the National Drugs Advisory Board. I have one or two questions of general interest to ask you. Can I first of all refer to your -- the article you did with Colombo which is at page 142 of your book.

You have indicated already that those in the scientific community were probably aware of a lot of the contents of this study before it was published. But others who perhaps relied on reading it obviously wouldn't know of its contents until it was published. I think you say in the summary that, of the eleven patients who developed non-A non-B Hepatitis, only one had symptoms. So am I right in saying that somebody reading that would not get the impression that the non-A non-B Hepatitis was apparently serious; in other words, it didn't appear to be chronic hepatitis?
A. Didn't appear to be severe?

Q. Severe chronic hepatitis.
A. Well, as I said yesterday, I think in response to other questions, the problem with Hepatitis C, or non-A non-B if you prefer, is not the acute phase. In spite of the effect -- the cases of death that are reported in that case of Hollinger that was mentioned yesterday, this is really very, very, very rare. The acute hepatitis is very often asymptomatic and it doesn't cause any symptoms; probably many patients don't even realise that they have hepatitis -- don't even have fatigue or gastrointestinal symptoms - the problems, as we know now - and the chronicity; the fact that it gets almost invariably chronic, that it doesn't resolve. So what we found here is very consistent with the clinical presentation of Hepatitis C. And in a sense it was already known at that time that Hepatitis non-A non-B presented with these features.

Q. Now, I think initially you studied 21 patients, but you weren't able to follow up with seven of them, is that --
A. If I remember --

Q. The following page, page 143, the paragraph headed "Results," I think it says: "21 patients were included in the study: 13 were followed up regularly as planned; seven missed some visits critical for the evaluation of post-transfusion hepatitis." I just wanted to ask you, incidentally, was it ever possible to follow up those seven patients, if you like, to complete the figures?
A. Well, I think -- I forgot that, because I didn't read the article recently. I ought to know it. But if you look at page 144 in the first column at the bottom: "Among the eight patients with incomplete follow-up, two have non-A non-B Hepatitis; three had sporadic ALT, which means transaminase, rises; and three showed no evidence of ALT elevation. All concentrate lots transmitted hepatitis. The frequency of hepatitis was not related to the number of infusions." So in a sense, even though there were no bona fide cases, these confirmed the data in these patients are incomplete - the great majority of them did develop hepatitis. So the number -- so the evidence is really --

Q. Is really all there?
A. Is really stronger. But on the other hand, even one or two cases would have been already significant to state that the concentrate was not safe because the likelihood to get hepatitis from the community in patients that are being transfused is very -- is very unlikely, is the story that -- as I said before, when there is a viral infection in multitransfused patients like haemophiliacs, you have to think that it was the transfusion.

Q. Thank you very much, Professor. I just want to refer to one more article in relation to hepatitis, and that's an earlier article by Fletcher, which is at page 127. And I think you said yesterday that the significance of that was that it showed that all

the patients who were transfused for the first time with concentrates developed non-A non-B Hepatitis. Is that correct?
A. Is correct, yes.

Q. And was that the first study, do you know, that was done on previously untreated patients; in other words, it was a study that these patients were examined before they were given their first treatment with concentrates?
A. It is the first published. As I said yesterday, the paper of Kernoff, which follows in a couple of years, was around -- almost at the same time of this. And I had information on it. But for some reason, Dr. Kernoff was not as fast as the Oxford people to publish the data. But there was confirmatory evidence coming from the -- from Kernoff people.

Q. Kernoff and Lee, I think?
A. Peter Kernoff and Lee. And also, if you look at the first paper which I quote here, the one from Kasper and Kipnis, the letter in Journal of the American Medical Association, I think the first one that I mention and it is at page -- page 46, they mention already that those who have little exposure to blood products have a high risk of developing hepatitis. And if I remember, they also mention that they got it usually after the first infusion. So there was already -- even though at that time everything was mainly based on the occurrence of jaundice, because it was the only way to diagnose hepatitis, and we know that jaundice is only the tip of the iceberg of -- the majority do occur without jaundice. There was already there some evidence that unfrequently-treated patients treated with large pooled concentrates are at risk of developing hepatitis.

Q. For those who hadn't maybe read that earlier article or letter in 1972, would Fletcher and Kernoff really be the first very solid indication that these were --
A. It was the first solid indication, because they gave evidence with transaminases that, barring the evidence coming from serological tests of Hepatitis C, was at that time the only criterium used to make a diagnosis. So I agree that that is really the milestone.

Q. There was a lot of suspicion before that, but here was sort of scientific evidence?
A. Exactly.

Q. Thank you. Now, there's just one very short thing I want to just ask you about as well. Mr. Bradley asked you about the conference that took place in Stockholm in June of 1983. I think that was the meeting of the World Federation of Haemophilia, is that correct?
A. (Nods head.)

Q. And I think there was some discussion with you as to whether Mr. Bruce Evatt was on the programme or wasn't on the programme. Professor Lee, who will be giving evidence next week, I think her evidence will be that there was nothing on the programme relating to immunodeficiency?
A. It is also my recollection, but I'm not sure. I would like to see, but I'm sure -- I would like to see the programme. I think that, anyway, something, a report -- so that meant -- what was -- what -- that was not as surprising after all because June 1983, well, the problem was one year before, I don't know; maybe the programme was

made, I'm not sure, earlier. So in a sense, it is not surprising, but certainly it is bad that there was no -- nothing official in the programme. But does it mean -- I, quite frankly, don't remember. But certainly there was a document produced in that instance by -- as a sort of report, a sort of minute of that meeting; that even though I don't think I can find it out, I'm sure that Mr. O'Mahony, who is, as you know the current president of the World Federation of Haemophilia who is here, if he looks in the records of the organisation in Montreal they should find that document. And I would like to have a copy myself, if you can find it out, if you think it is useful and you can find it out.

Q. Thanks very much. My recollection is that he didn't have documents himself but maybe --
A. Excuse me.

Q. My recollection is he didn't have documents himself but maybe --

THE CHAIRPERSON: You think there's a depository of records in Montreal? Yes. Well, we can -- we can see.

Q. MR. ASTON: But I think Professor Lee's recollection is that there was one crowded lunchtime seminar where -- I think chaired by Dr. Hilgartner from New York?
A. Yes, it's true; it was Hilgartner not Aledort, but the two are sort of twins so I tend to confuse them. They are very good friends so I tend to -- it was Hilgartner, you're right.

Q. And in fact, there was some discussion, but her recollection is that -- I mean, she herself presented some information about the ratio between various T-cells - T4 and T8 cells. And at that stage it was known that there were immunological disturbances in haemophiliacs but it wasn't yet appreciated that that was caused by an infective agent. Would that be -- would that correctly summarise it?
A. Yeah, that's right. As you know, in January 1983 - and they are quoted here - two American centres -- one in Cleveland in the grand (sic) lakes -- one in Cleveland and the other in Milwaukie, did a report on the presence of these immunological abnormalities; and then being, again, haemophiliacs, the T-cells abnormalities being more frequent in those who use concentrates compared with cryoprecipitate. And that was an important paper. At that time the HIV was not yet discovered and so that paper -- so Christine Lee certainly did pursue those studies and she did the same study also because she had -- she has a strong immunological background and she was one of the leaders in the United Kingdom in the early studies for, let us say, AIDS, and subsequent HIV disease. And her recollection -- I mean, I have the same recollection. I would like to see -- to see the document that was produced; because I think at least some minutes -- and probably they were published in the bulletin, so I'm sure that they kept the records in Montreal.

Q. I'm sorry, I can't help you there, Professor. And I think you said earlier today that it was 1985 before it was clearly understood that -- despite Montaginier's publication in 1984, it was in 1985 it was clearly understood that AIDS was the retrovirus?
A. In the second part of 1984, the evidence started to be quite compelling, but it was always indirect. It was only really in 1985, in a paper published in the -- because after

all, you see, to demonstrate that this was the cause, you have to establish a relationship between the agent, the virus and the disease. And it was only in 1985, relatively later during the year, that that demonstration came in a paper, if I remember, that was published in the Annals of Internal Medicine when it was understood; when the antibody testing became more easily available. And it was inferred that the antibody meant the presence of the virus, not protection. Because when -- in 1984 the first test - and also the beginning 1985 - became available. That's something we haven't discussed at length. Nobody was sure what an antibody meant because, in general terms, the antibody's meant to be countered with the virus; but protection, in as much as we know, that many patients did come in contact with Hepatitis B virus. But when they have the antibody, they are protected. There was some people that were thinking on a legitimate basis that the antibody meant only previous contact with the virus, not disease.

Q. Same is true with Hepatitis A, of course; if you have the antibody then you're immune from the disease?
A. Yes, Hepatitis A, yes.

MR. ASTON: Thank you, Professor, very much indeed.

THE CHAIRPERSON: Thank you, Mr. Aston. Mr. McGrath?

THE WITNESS WAS EXAMINED AS FOLLOWS BY MR. McGRATH:

Q. MR. McGRATH: Just one or two issues. Professor Mannucci, Michael McGrath is my name and I represent the Blood Transfusion Service Board. And I just have a few questions, really by way of clarification of a number of issues.Now, as I understand the situation, just dealing with Factor IX, my understanding is that the usage of Factor IX in Italy was effectively imported product, is that correct?
A. Yes, it is.

Q. Yes. So through the '70s and into the '80s, it was imported product, and of course, was, as I understand the situation, it wasn't treated up to 1985, is that correct?
A. Is that correct -- it is correct.

Q. And then heat-treated Factor IX was imported in 1985, as I understand, and used from 1985 on? That's my understanding of the situation.
A. That's correct.

Q. Now, just in relation to that, an article that Mr. Finlay opened to you yesterday, it's one of your own papers. It's on page three of the documents which we introduced. It's the first section of three and it's the Annals of Internal Medicine, I think an article from July of 1987.
A. Yes. I think that -- yes, it is here, yes.

Q. You recall this one. And now, that study, as I understand the situation, was effectively on three patients. The
first patient --
A. Six.

Q. Sorry, six, but certainly of the three -- of the ones recorded here, if we look at the first one; it's a 25-year-old patient with severe Haemophilia A; then the second one was a 17-year-old patient with severe haemophilia; and the third one, a 16-year-old boy with severe Haemophilia B. Do you see where I'm referring to, Professor?
A. Yes.

Q. Yes. Now, just in relation, I'm interested in the Factor-IX-deficient patients, the Haemophilia B patients on the right-hand side. It would seem that, just to deal with those, "a 17-year-old patient with severe Haemophilia B treated between June 1985 and July 1986 with 23,000 units of a Factor IX concentrate steam-heated at 60 degrees for 10 hours plus 1,500 units of concentrate freeze-dried at 68 degrees for 72 hours became seropositive in July of 1968; the last seropositive result was obtained in March of 1986." Then we go on to deal with the third patient, who was "a 16-year-old boy with severe Haemophilia B (treated between May 1985 and September 1986 with 73,000 units of steam-heated Factor IX concentrate plus 4,000 units of a concentrate at 68 degrees for 72 hours) became seropositive in September 1986." Now, as I understand it from the particular study, you weren't able to identify which particular product was actually responsible for the seroconversions on that study, is that so?
A. Yes, because they were treated with more than one product. As I told you, it was not unusual - right or wrong - in our country. But certainly a limited number of concentrates were implicated. All the concentrates implicated were those that I would call of the second generation that should be -- should have been safer in terms of -- no, were of the first generation in terms of HIV. The first generation, yes.

Q. Again, my understanding from the actual criteria that you used in assessing the infection and the likely source of infection was that you looked at the previous results which were seronegative, and had been seronegative for a particular period; and then you looked at the seropositive results thereafter?
A. Yes.

Q. So effectively, insofar as the study is concerned, again my understanding is that you were operating from a base whereby it was -- on the basis of the criteria being applied, it was taken or assumed that the patient was seronegative before they received the heat-treated or steam-treated concentrate.
A. But don't -- don't we give, at least in some of the evidence, that he was seronegative before?

Q. You do, that is correct. That's the basis upon which I understand this study was put forward. So that would seem to -- in fact, it does suggest that with the administration of heat-treated Factor IX concentrate, between -- it would appear between -- the earliest seems to have been May of 1985, and the latest September 1986, if you take the two dates as between the two patients, that there were seroconversions in Factor IX patients who had received heat-treated Factor IX concentrate?
A. Yes. This paper is one of the few examples of residual seroconversions to HIV which occurred after the introduction of heat treatment. Also looking at the Bruce Evatt paper yesterday, really 1985, in that cohort, there was no further case of HIV seroconversion. But a few cases have been reported by us and by the CDC. The CDC collected a larger series, about 20. And in some instances, this was clearly due to the use of ineffective dry heat treatment, particularly the 60 degrees for 30 hours.

In other cases it was due to the use of the n-heptane. In these cases, these concentrates should be, as far as you know, safe, in that they are quite efficacious because of -- the temperature is high, the period of exposure -- so that's why we reported. And there have been some cases here and there for all the heated concentrates. But then, subsequently, none has been shown. Whether this was due to the fact that, I don't know, the blood donors were not yet screened? So in some lots there were very, very high titers that could not be inactivated. Whether it was other reasons: Maybe the first test looked negative but it was a false negative; we don't know. Certainly the concentrate for which there was unequivocal evidence of several cases of development of HIV was the one treated at 60 degrees for 30 minutes. The others are scattered cases that have not been confirmed. There was one also with a Baxter procedure; here there's one, at least in principle, with the Immuno and with the Cutter procedure, but --

Q. Yes. I see.
A. -- the most solid cases that are in the other article, this -- this article, quite frankly is not particularly significant. If you want to get the information about the efficacy of the early virucidal method and the few documented failures, the best article to look is the one of the Morbidity and Mortality Weekly Reports --

Q. I see. I see.
A. -- which was based on international collaboration to which we did participate and I think is quoted among our papers.

Q. Now, just in terms of the number of treatment centres in Italy. As I understand it there are -- well, I've seen numbers of 29 or thereabouts. Are there more than 29 treatment centres in Italy?
A. Yes. There are about 40, as I think in the United Kingdom there are even more. Some of them are very small, but there are about 40.

Q. I see. And I just notice from your evidence yesterday that in terms of the introduction of solvent/detergent products, that in your centre, that was introduced in 1987, as I understand your evidence?
A. Yeah.

Q. We have a study from Pisa which seems to suggest that they didn't introduce it until 1998. You've seen that study there?
A. I noticed that. I cannot -- I cannot explain why they mention 1988, quite frankly. I noticed that and it is -- it was a surprise for me. But you are right, I read that.

Q. And it seems that it's 1988 -- I just reread the article and it seems that that's a year that comes up several times throughout the course of the article. It's not just --
A. I know. I know. Listen, I mean, I have no explanation, particularly so because in Pisa they were in strong and close collaboration with the Italian manufacturer, only for the reason that the Italian manufacturer is established close to Pisa. And I told you that that centre were the centre that used the Italian commercial industrial concentrate before heated -- the only one producing on a limited scale by Biagini with heat -- before the advent of heat treatment. So I am surprised they mention 1988.

Q. Just again, just to finish with that point: In terms of the Italian-produced Factor IX concentrate, do you know when that was first produced in Italy?
A. The Immuno vapour-heated -- from that point of view -- but again, this is very contradictory because we have so many cases with Haemophilia B. But that probably occurred because -- before 1985, because we used the -- in some countries there's been a problem in the sense that even when the Factor VIII concentrates, first generation, were available, the Factor IX was not available because of the problem that I mentioned; fear to heat them, different protein composition and so on. But I don't think this happened in Italy because of the vapour-heated concentrates was available immediately in the early -- in the early -- in the late -- in the end of 1984, beginning of '85.

Q. Yes, I see.
A. But certainly the large number is probably due to the previous exposure, except that this case, which was the vapour-heated concentrate, is implicated; but with other concentrates, we haven't seen any case of seroconversion.

Q. What I was really just wondering is in terms of the home-produced, as it were, Factor VIII, the Factor IX product produced in Italy, did that come on the market before -- in 1987, or was it later than 1987?
A. Which Factor IX, the solvent/detergent?

Q. The Italian -- yes, solvent/detergent.
A. No, it came -- it came on the market on the large scale at the end of 1986, beginning of 1987. Probably even later because it -- to produce first -- they did license first the Factor VIII Emoclot solvent/detergent, and the AimiFIX, they called it - because AimiFIX is Factor IX you see - came later, came probably at the end of 1987, if not the beginning of '88. But we had other products, so we are not -- we had the Immuno products, so we are not particularly worried about that.

Q. We had understood, and maybe you can help us on this, that in terms of the Factor IX product, the Italian Factor IX product, that that was produced by way of the solvent/detergent method in 1991; that's what we had understood.
A. You may be right. I don't remember. I think I don't remember, because for us the important thing is that we had the immune concentrate. So we were feeling on the safe side. It's true there is only one, so we are happy when another become available. It was certainly licensed afterwards. So if you say that, you may be right. I don't remember exactly. Seems to me a little bit late.

Q. That's -- I was just wondering if you had any comment to make on that, because certainly we had charts produced at an earlier state of the Tribunal which showed the introduction of the Factor IX.
A. In Italy only in 1991. So it may be true. If you have that information, I'm sure it's true. The only thing I want to say, that unlike other countries, in Italy we had a heated concentrate -- Factor IX concentrates, practically together with the Factor VIII concentrates. It was only one, so that's why also I don't -- I don't remember, because there was another product, okay, we are happy. But we were happy with the previous product. There was also some Konyne, some of the 78, because it was mentioned here, you see.

Q. Just finally, Professor Mannucci, in terms of the introduction of the solvent/detergent and the superheat-treated factor concentrates, I think you, together with Colombo, carried out a survey and wrote a paper for The Lancet in October of 1988?
A. Yes.

Q. It's on page 8, again, of the same booklet I was referring to earlier?
A. Eight?

Q. Yes.
A. Yeah. That was a review that we were asked to write for The Lancet as we are considered, right or wrong, leaders in the field. And it is an accurate -- I think an accurate, reasonably accurate description of the events.

Q. Yes. And again, I don't wish to go through all the various tests which were carried out, but in terms of your conclusion, which is on page eleven, now, this would suggest that at that time clinical studies were still taking place, at least up to the time of the submission of the article for publication. Clinical studies on the various --
A. Where are you reading?

Q. Sorry, page -- I haven't started reading just yet. Conclusions. It says: "To date published clinical studies indicate that viral inactivation by pasteurisation and to a lesser extent by vapour heating definitely improve the safety from hepatitis of Factor VIII concentrates over that of unheated concentrates and concentrates heated in the lyophilised state at temperatures lower than 80 degrees Celcius. Other methods (such as solvent/detergent, superheating at 80 degrees and monoclonal antibody techniques) might prove to be of equivalent safety but the small numbers studied and the lack of details allow us at the moment only to say 'presumed innocent.'".I think those were the words you were describing at the time?
A. Yes, I must have write the book that I'm sure you know.

Q. That was the feeling that both yourself and Colombo had at the time in 19 -- in October --
A. Yes. It was the feeling -- because in that period, even though the concentrates were available, the study was still being done -- or as I mentioned before, that the studies had been done but were insufficient the number, below the magic number of 20. So there is a word of caution, even though of course now with the evidence that we have now, many of these products revealed themselves very safe. As usual, it is another example of how knowledge changes. Now, I wouldn't write that only the pasteurised and vapour -- to lesser extent vapour heating, because we had those cases of hepatitis in the early studies; but we were doing the international study which showed no case. So that's why there is some reservation on the vapour heating. And the others mainly because of the relatively small number of patients mentioned in page -- in page nine, your numbering, in table three. Prospective safety study of less than 20 patients. So since it was below the magic number of 20, we considered them very less solid.

MR. McGRATH: Thank you, Professor.

THE CHAIRPERSON: Thank you, Mr. McGrath. Mr. Murphy, have you any questions?

MR. MURPHY: No.

THE CHAIRPERSON: Mr. Finlay?

MR. FINLAY: Just a couple of very brief things, Madam Chairperson.

THE WITNESS WAS FURTHER EXAMINED AS FOLLOWS BY MR. FINLAY:

Q. First of all, Professor Mannucci, the commercial company in Italy that produced factor concentrate, I think Mr. Bradley referred -- asked you about it as the national producer. Did it -- in the mid-1980s, was it a government sponsored organisation or was it a private commercial firm?
A. No, it wasn't -- it was a private company in the -- it is still a private company. What happened subsequently, that they established a contract with the government whereby the plasma which is collected by regular transfusions is now sent to them. The blood transfusion centre, the blood banks are obliged to do that, to send it to them. And they return the products. But still, they fractionate quite a lot of American plasma. But certainly now there is about 500,000, 600,000 litres of recovered plasma; not plasmapheresis, plasma that is collected in the country.

Q. And just the other thing, I think Mr. McGrath referred to their product as being the Italian Factor IX. At the time that was first produced, what would the source of the plasma have been; what was the source of plasma for this commercial company?
A. Well, he mentioned, and he may be right, that the AimiFIX was licensed only '90/91. So at that time probably, but I'm not sure. The concept of the use of the Italian plasma had been already implemented. But basically, I think it was commercial plasma. It's still now -- you see, they are two different productions; at least that's what they say. And they have a contract with the government. They give you what has been collected -- say my region, in Lombardy. They give you back these products from Lombardy plasma. But there's also other -- and this is distributed by the region, through them, but it is not commercial in a sense. But that then continued to produce a truly commercial product, and that's -- is certainly with plasma produced from the United States. What is the proportion, quite frankly, I don't know, but I expect it is probably around half and half. But don't take me seriously.

Q. Yes. Just also, Professor, just in relation to your use of products between say 1980 and 1985, and to try and understand clearly what your usage would have been as between concentrates, Desmopressin and cryoprecipitate; first of all, would you in fact have been using cryoprecipitate in those years, between 1980 and 1985?
A. Not except for those patients - quite rare, but existing - that had been poorly and frequently infused; which we would have used DDAVP as a first choice but we thought that the baseline levels and the type of operation or bleeding were such that DDAVP would not be sufficient. So, I mean, some instances perhaps we have used cryoprecipitate, but mainly the only reason to keep certainly production of cryoprecipitate at that time was for the use in patients with von Willebrands Disease, in which there are some special reasons why cryoprecipitate at that time had to be used. Now, it is no longer used even in those because it is thought that they -- even

though now the safety is much more, even with cryoprecipitate, because of course of the selection of donors, the general recommendation is to use commercial heated products now.

Q. Yes. So just to be clear, if you had a person who was mildly affected with haemophilia, your first choice would have been to use Desmopressin?
A. Yeah.

Q. And if that for some reason wasn't possible, in that instance then you might consider using cryoprecipitate as the next choice?
A. Yes, particularly if the person that you mention was untreated and negative in terms of transaminases. I mean, he had -- if he had been treated many times before, as often happened, or even once before with the large pooled concentrates, and they did acquire hepatitis - it happened - then probably we did both or less to give cryoprecipitate.

Q. Yes. And for children, Professor, if a child was not a person with mild haemophilia, if a child was a person with moderate or severe haemophilia who was going to require regular treatment, what would have been the treatment prescribed between 1980 and 1985 by your centre?
A. I'm afraid to say that at that time we would have used concentrates, unheated. Certainly we tried to enroll as many as we could, just because that was the protocol in clinical studies - evaluating the heated products - but still a number had been treated with unheated large pool products. But since there are not very many, because practically those were the newborn haemophiliacs, I think probably a consistent number had been treated with the heated product because there was a large number of centres in Italy that were involved in those studies being carried out. You see, there was first the -- we were involved in the Baxter study; but then there was the Immuno study with vapour heating, the Schimpf study. There are some Italian centres, if you look at those publications.

Q. And just in relation to that, Professor, the article that you referred us to at page 156, the Morfini article of which you were a coauthor?
A. Yes.

Q. That identifies --
A. 156?

Q. 156 of your book of references. In the abstract certainly there it identifies July of 1985. It says: "In July 1985 all coagulation factor concentrates were withdrawn from the market in Italy and replaced with virally inactivated concentrates."
A. Yes.

Q. Can you explain to us, Professor, what happened; I mean, was there an actual point in July of 1985 --
A. Oh, yes.

Q. -- when products were -- unheated products were withdrawn and replaced with heated products?

A. There was a -- I remember there. For once I can be very accurate: It was the 15th of July when the Ministry of Health issued a circular which instructed us to use only heated products. And the circular reached all the haemophilia centres, and so we didn't -- we didn't use any longer the unheated concentrates.

Q. Yes. Now, would there have been, Professor, between --
A. I also think that I must say that even though there was knowledge -- because we had several meetings in which we summoned haemophiliacs. One thing that the government unfortunately didn't do - probably because it was difficult to do it and we couldn't do it either - was to send the police or whatever in all the houses of the haemophiliacs to look into their fridges and to see whether there were still inventories of unheated concentrates. This was not done probably because it was very difficult. But I can tell you that after our paper in The Lancet, the -- we, the Haemophilia Centre Directors, together with the Haemophilia Society, did summon a number of meetings and issued a number of recommendations. So hopefully the information must have reached all the patients. There is no claim of cases that developed afterwards, but even though sometimes you hear some rumours.

Q. Yes. I was wondering, Professor, what happened between January of 1985 when you would have had the information, presumably that you subsequently published in the February letter in The Lancet, about the effectiveness of heat-treated product; what happened between then and July of 1985, in Italy, in relation to efforts to move to a heat-treated product?
A. Well, certainly from that point on, unfrequently treated, previously untreated patients were treated with heated products. Because of the lack of products, because some of them had not yet been licensed, there was perhaps some cases that continued to use it; probably I would say not in our centre, but I cannot rule out also, because of the nonavailability of the products, that some cases, some people still used the unheated products. There is really no evidence that cases of HIV seroconversion took place, but it is something that I cannot rule out.

Q. So just to be clear, in your own centre the practice would have changed --
A. Oh, yeah.

Q. -- at the beginning of the year to heated products?
A. Yes.

Q. And then there was a nationwide, definite point where the government imposed the use of treated products -- heat-treated products in July of 1985, is that correct?
A. Yes. In some countries it had been issued a couple of months, if not before, certainly the United States, Italy, in the UK; in others like France, it was issued only in October.

Q. Yes, I understand.

MR. FINLAY: Thank you very much, Professor.

THE CHAIRPERSON: Thank you, Mr. Finlay. Thank you very much indeed, Professor. Thank you for coming.

THE WITNESS THEN WITHDREW.

THE CHAIRPERSON: We'll adjourn then to tomorrow morning at 10:30. Thank you.

THE TRIBUNAL THEN ADJOURNED TO WEDNESDAY, JULY 18, 2001, AT 10:30 A.M.