PROF. P.M. MANNUCCI

c:HIV rpt-mann

Third Draft/

HIV Haemophilia Litigation

Professor Pier Mannuccio Mannucci

I am currently Director of the Post-Graduate Haematology Specialisation School, University of Milan, and Chairman of the Institute of Internal Medicine, University of Milan. Since 1978 I have been Medical Vice-President of the World Federation of Haemophilia. I attach to this report a copy my Curriculum Vitae and List of Publications.

I have read a copy of the Re-Amended Master Statement of Claim and Master Defence of the Health Authorities. I offer this report based on my knowledge of events and with a view to objectively assessing the claims made.

HEPATITIS

Throughout the 1970's, the wide spread use of clotting factor concentrates for patients with haemophilia was associated with frequent emergence of abnormalities in liver function tests. With the implementation of programmed check-ups and the development of serological methods for diagnosing hepatitis, the important role that viral hepatitis plays in these patients became evident.

Anecdotal reports of the occurrence of antibody to hepatitis B surface antigen and of elevated aminotransferase activity in haemophiliacs first appeared in the literature in 1972

(reference 1 and 2). However, the first large study of liver function tests were published in 1975 by my group. (Reference 3). In that paper, we reported on a survey of 91 multi-transfused haemophiliacs and found that 45% of them had moderately elevated serum ALT levels. At the time of the publication, the medical profession expressed considerable surprise with the results, and indeed there was a debate as to whether our findings were indicative of liver disease or due to cases of intramuscular bleeding (reference 1).

Our findings were subsequently confirmed in other studies and in particular in a joint American/English study which demonstrated that ALT abnormalities persisted for years, lending support to the concept that they were a signal for chronic viral hepatitis. (Reference 4) Although non-A non-B hepatitis viruses were suspected to be responsible for a ALT abnormalities, a definite distinction between transfusion associated hepatitis and "transaminitis", i.e. an elevation of serum ALT due to non-viral factors (such as, for instance, drugs used to control pain or hypersensitivity reactions to allogeneic proteins present in clotting factor concentrates) could not be made.

Unequivocal evidence of the existence of structural liver disease in patients with haemophilia and elevated ALT came in 1977. Presenting the results of their liver biopsy investigations of six haemophilia A patients with elevated serum ALT, Lesesne et al (reference 5) diagnosed chronic active hepatitis in three patients and chronic persistent

hepatitis in the remaining three.

An important unresolved issue remained namely whether or not chronic liver disease in haemophiliacs showed histological signs of progression. A prospective study (reference 6) was undertaken by my group in ten haemophiliacs with non-A non-B hepatitis who were followed up for more than ten years. This demonstrated no progression of chronic hepatitis. In a large retrospective study collected from Haemophilia Centres worldwide, findings of histological evidence of progressive liver disease occurred in only 22% of cases, notwithstanding the predominance of non-A non-B hepatitis as the etiological agent. (Reference 7).

However the benign picture of the non-A non-B hepatitis emerging from these two studies was contradicted by two subsequent investigations. In one prospective study histological signs of progressive liver disease were found in 38% of 34 multitransfused haemophiliacs with chronic non-A non-B infection. (Reference 8). It appeared that in haemophiliacs, a histologically mild type of non-A non-B hepatitis can progress of severe liver disease. In a retrospective study from West Germany (reference 9) it was found that development of progressive liver disease occurred in about one third of multitransfused haemophiliacs during a follow-up of 13 years.

Hence it was only in the mid-1970's that it became clear that

hepatitis was frequent in haemophiliacs and it was only in the mid-1980's that it was shown to be progressive, albeit in a relatively small proportion of these patients.

The view at the time held by me and as far as I am aware, all my specialist colleagues was that the problem of hepatitis in haemophiliacs was a tolerable one where the benefits of concentrate far outweighed the risks involved. We sought to treat the patients who developed the condition but it must be emphasized that for the haemophiliac, we were not seeing severe liver disease recorded in postmortem records as a frequent cause of death. (References 10,11 and 12) The most significant cause of death remained bleeding, particularly intracranial haemorrhaging. For the severe haemophiliac, there was no option but to receive concentrate treatment despite the risks of hepatitis.

DDAVP

It was in treating mild haemophiliacs (who have little risk of dying from bleeding) that the risk of hepatitis was less acceptable and it was with a view to seeking to find alternative treatments for the mild haemophiliac that I undertook research into DDAVP. In 1977 we published our paper (reference 13) suggesting treatment by DDAVP for patients with moderate and mild haemophilia and von Willebrand disease. DDAVP caused a marked increase in Factor VIII related properties in these patients and was therefore seen as an effective form of treatment for dental or general surgery in these infrequently treated patients, as DDAVP is a drug which

does not carry the risk of transmission of hepatitis and other blood-borne infections.

In a further paper published in 1981 (reference 14) we provided additional information relevant to the use of DDAVP in the management of mild haemophilia and von Willebrand's disease. Its effect is to enable the patient to manufacturer their own Factor VIII. It was useless for the treatment of severe haemophilia because it does not raise the Factor VIII level to haemostatic levels. It can be used only for a limited period of time because the patient becomes resistant and there is no longer a rise in Factor VIII. Nevertheless, for the treatment of mild and in some cases moderate haemophilia where we perceived that the risk benefit of concentrates being infected by hepatitis was most acute, DDAVP was of considerable importance.

The first occasion when we DDAVP published our experience with in Milan was April 1977 and plainly colleagues needed some time to seek the confirmation of the value of the treatment. In my view, in England, the use of DDAVP was fairly rapid and I do not criticise it. Nevertheless, DDAVP was not used in large scale before the late 1970's early 1980's. There was then a report by Dr. Lowe of water retention in a patient of moderate haemophiliac treated with DDAVP. Whilst this was a very unusual complication, a letter was written in the Lancet (reference 15). As a result of this, there was a reduction in the use of DDAVP understandably, but we concluded in our

reply letter in the Lancet (reference 16) commenting on Dr. Lowe's report, that the risk of developing hepatitis for a mild haemophiliac was such as to justify consideration of the use of DDAVP and that water retention seems a very rare complication.

SMALL POOLS/CRYOPRECIPITATE

It is also necessary to point out that the question of small pools of donors and cryoprecipitate, as opposed to large pool concentrate is really only pertinent when considering mild haemophiliacs who are infrequently treated. With a severe haemophiliac, who is receiving frequent transfusions, perhaps three or more times a month, even small pools or cryoprecipitate will result in an exposure to the risk of contracting hepatitis, because of the contact with plasma from a huge number of donors. Small pools of cryoprecipitate can only delay the development of hepatitis, not certainly reduce or abolish it.

HEAT TREATMENT

I was aware that the German company Behring was claiming that they had manufactured a Factor VIII concentrate which was wet heat-treated and that it inactivated hepatitis virus. The first paper appeared in a house journal of the Behring company in 1980 (reference 17). Clinicians were unimpressed with the claims as there was little clinical evidence in patients and we felt that the Behring research was unsatisfactory. The invitro studies were interesting but the evidence was meagre and the design of the study poor.

In any event, the Behring concentrate was not available commercially in Italy, and indeed there was insufficient concentrate to meet even West German demand. If it had been available to me, at the same price as other concentrate, then I may well have used it, but even German authorities resisted it. It was two or three times more expensive than unheated product and the evidence that there was any advantage in it was sparse. Indeed it was not until a 1987 paper by Schimpf, Mannucci et al (reference 18) that it was satisfactorily scientifically established as a product safe from transmitting hepatitis.

Essentially, the earliest attempts by manufacturers (1985 - 1987) to inactivate or remove the hepatitis viruses in concentrates met with variable success. There were high attack rates of hepatitis in haemophiliacs infused with concentrates "treated" by the early virucidal procedures (heating in a lyophilized state at 60° or 68°, addition of chloroform) indicating that these methods of virus inactivation were not effective. The studies which evaluated these virucidal methods were imperfect in design. They included too few patients and/or patients not highly susceptible to develop hepatitis, as they had previously been transfused with blood or blood products, and therefore might be immunised against non-A non-B virus agents.

In an attempt to provide recommendations for the design of

more sensitive studies, the International Committee on Thrombosis and Haemostasis suggested in 1984 at the Miami Conference that only highly susceptible patients should be studied, i.e. previously uninfused patients (so called "virgin" haemophiliacs) on the basis of evidence indicating that these patients developed hepatitis with a rate close to 100% when they were exposed to large pool concentrates and non-commercial concentrates. The general finding of our study and others is that only 5% of patients studied so far developed post-transfusion hepatitis and it seems that the second generation of virucidal methods (pasteurization, heating at 80°C, vapour-heating, solvent-detergent and immunoaffinity chromatography) plus the use of ALT-screened plasma are better than the early virucidal methods for substantially reducing the incidence of hepatitis after administration of large pool concentrates.

Following the introduction of the guidelines to study the concentrate introduced by the International Committee, studies were conducted on the heat-treated products being produced by the manufacturers. In July 1985, Colombo et al published a paper in the Lancet (reference 19). It was the first study done under the rules of the International Committee and the results showed that using dry heat 11 out of the 13 patients did develop non-A non-B hepatitis.

AIDS

It was at around April/May 1984, that the HIV (LAV, HTLVIII) virus was identified separately by Gallo and Montagnier and

the first test for HIV was then developed. In conjunction with Montagnier we retrospectively tested some of the samples that we had previously taken in the hepatitis studies on heat treatment and reported in a February 1985 issue of the Lancet that there was an absence of antibodies to the AIDS virus. (Reference 20).

Although there were earlier proponents of the theory that heat-treating the concentrate would be effective against AIDS as its causative agent may be a virus, particularly Roberts at Chapel-Hill, the evidence was very unconvincing at the time. The research in relation to heat-treating because of hepatitis had led to unsatisfactory results with regard to dry heating. It also must be borne in mind that although by 1983 there was a general view of a possibility of the cause of AIDS being a virus, there were alternative theories. The idea of the immune system being effected by constant use of concentrates was well supported and there were two papers in January 1983 (references 21 and 22) published in the New England Journal of Medicine showing generalised lymphadenopathy in patients transfused with Factor VIII and that use of cryoprecipitate produced less change. However, it must be borne in mind that patients treated with cryoprecipitate were probably less heavily transfused in the first place.

Although some extreme views were held that haemophiliacs should not receive Factor VIII until the evidence was clearer, there was in my view, little alternative during this period

but to continue treating. In 1982, worldwide, there were only two cases of haemophiliacs developing AIDS. In 1983 there were no-more than 10 - 15 cases, and many of us had not seen a case until 1984 - 1985. The first case of a haemophiliace AIDS victim in Italy was in 1984. I certainly told haemophiliacs under my care of the risk of AIDS from the early stages but if one balances the risks that were known at the time, against the substantial benefits of Factor VIII treatment, it is not surprising that very few elected to discontinue the use of Factor VIII.

What I would have said to my patients at the time was that there was an association between lowered immune resistance of haemophiliacs which was similar to AIDS, but that there was no evidence that the relationship was causal one.

I am right at "the cutting edge" of specialised knowledge of developments in this area and would often hear of research before it was published. But one must realise that other than a few people such as myself, the profession relies on publications for its knowledge. It would not have been reasonable for the haemophilia carers to have responded in any different way and I believe that in England, the recommendations of the Haemophilia Centre Directors in December 1984 were timely.

Recommendations in Italy were made in January 1985 for the use of only heat-treated product and indeed because of our system of distribution where patients get Factor VIII through their

GP's, it is possible that the response time was much slower. Even though the problem of hepatitis has been known since the middle 1970's, there was no reason to believe that that relatively that that relatively benigh side-effect of haemophilia care was heralding the much more ominous AIDS.

SIGNED.....

DATED.....

CURRICULUM VITAE

PIER MANNUCCIO MANNUCCI, M.D.

Date of birth: GRO-C 1939, GRO-C
Present address: GRO-C

Professional and academic carrier

1963	Doctor of Medicine, Univ. of Milano, Italy
1964-1965	Clinical Assistant, Dept.Hematology, St.Thomas Hospital, London, UK
1965-1966	Research Fellow, Blood Coagulation Research Unit and Dept. of Pathology and Hematology, University of Oxford, UK
5-1968	Assistant Professor of Medicine, Univ. of Cagliari, Italy
1968-1970	Associate Professor of Medicine, Univ. of Milano
1970-	Professor of Medicine, Univ. of Milano
1970-	Director, A.Bianchi Bonomi Haemophilia and Thrombosis Center, Univ. of Milano and Policlinico Hospital
1980-1986	Vice-Chairman, Institute of Internal Medicine, Univ. of Milano
1983-	Director, Postgraduate Hematology Specialization School, Univ. of Milano.
1986-	Chairman, Institute of Internal Medicine, Univ. of Milano

Honours and awards

1975-	Honorary Fellow, American College of Physicians
1981	International Prize, Association Française des Hemophiles
1984	Prize of Milano Medicina

Scientific Offices

1970-1978	Medical Secretary, World Federation of Haemophilia
1972-1984	Chairman, International Training Centers, World

	Federation of Haemophilia (WFH)
1973-1978	Member, Task Force on Disseminated Intravascular Coagulation, International Committee on Thrombosis and Hemostasis (ICTH)
1974-1977	Member of the Council, Italian Society for the Study of Hemostasis and Thrombosis
1975- 1978	Co-Chairman, ICTH-WFH Working Party on Partial Thromboplastin Time
1975-1980	Consultant, Task Force on Factor IX concentrates, ICTH
1975-	Chairman, Italian Committee for Standardization of Coagulation Methods (CISMEL)
1975-1977	Member of the Executive Committee, World Federation of Hemophilia
1978-	Medical vice-President, World Federation of Hemophilia
-1984	Member, International Committee for Thrombosis and Hemostasis
1980-1984	President, Italian Society for Hemostasis and Thrombosis
1980-1981	Co-Chairman, Sub-Committee on Factor IX, ICTH
1980-1984	Member, Sub-Committee on Factor VIII, ICTH
1980-1985	Member of the Council, International Society on Thrombosis and Hemostasis
1981-1984	Chairman, Sub-Committee on Factor IX, ICTH
1982-	Medical vice-President, Fondazione Emofilia
1984-	Vice-Chairman, Sub-Committee on Factor VIII-von Willebrand Factor, ICTH
1984-	Member of the Executive Council, ICTH
1985-1986	President, 17th Congress of the World Federation of Hemophilia
1985-1986	Chairman-elect, International Committee on Thrombosis and Hemostasis
-	Member, International Committee for Standardization in Hematology.
1986-	Vice-President and President-Elect, International Committee for Standardization in Hematology
1987-1988	Chairman, International Committee on Thrombosis and Hemostasis

Editorial offices

1973-1977	Editor, Thrombosis Research
1980-1985	Member of the Editorial Board, Clinical and

Laboratory Hematology

1980– Member of the Editorial Board, Hemostasis

1985– Editor, Thrombosis Research

1985– Member of the Editorial Board, Hematologic Pathology

REFERENCES

(1) Forbes CD, King J, Prentice CR, Mc Nicol GP. Serum enzymes changes after intramuscular bleeding in patients with haemophilia and Christmas disease. J Clin Pathol 1972, 25: 1034-1037

(2) Kasper CK, Kipnis SH. Hepatitis and clotting factor concentrates. JAMA 1972, 221:510

(3) Mannucci PM, Capitanio A, Del Ninno E, Colombo M, Pareti F, Ruggeri ZM. Asymptomatic liver disease in haemophiliacs. J.Clin Pathol 1975; 28: 620-624

(4) Levine PH, McVerry BA, Attock B, Dormandy KM. Health of the intensively treated haemophiliacs with special reference to abnormal liver chemistries and splenomegaly. Blood 1977; 50: 1-9

(5) Lesesne HR, Morgan JE, Blatt PM, Webster WP, Roberts HR. Liver biopsy in haemophilia A. Ann Intern Med 1977; 86: 703-707

(6) Mannucci PM, Colombo M, Rizzetto M. None progressive course of non-A non-B chronic hepatitis in multitransfused haemophiliacs. Blood 1982; 60: 655-658

(7) Aledort LM, Levine PH, Hilgartner MW, et al. A study of liver biopsies and liver disease among haemophiliacs. Blood 1985; 66: 367-372

(8) Hay CRM, Triger DR, Preston FE, Underwood JCE. Progressive liver disease in haemophilia: an understated problem? Lancet 1985; 1495-1498

(9) Schimpf KL. Liver disease in haemophilia. Lancet 1986; 1:323

(10) Aledort LM. The cause of death in haemophiliacs. In: Frantantoni JC, Aronson DL, eds. Unsolved therapeutic problems in haemophilia. Bethesda: US Department of Health, Education and Welfare. DHEW publ. No. (NIH) 77-1089, 1976: 9-14.

(11) Lewis J, Spero JA, Hasiba U. Death in haemophiliacs. JAMA 1976; 236: 1238-1239.

(12) Biggs R. Haemophilia treatment in the United Kingdom from 1969 to 1974. Br. J. Haematol 1977; 35: 487-504

(13) Mannucci PM, Pareti FI, Ruggeri ZM, Capitanio A. DDVAP: A new pharmacological approach to the management of haemophilia and von Willebrand's disease. Lancet 1977; 869-872

(14) Mannucci PM, Canciani MT, Rota L, Donovan BS. Response of Factor VIII/von Willebrand Factor to DDAVP in healthy subjects and patients with haemophilia A and von Willebrand's disease. British Journal of Haematology 1981; 283-293

(15) Dr Lowe. Letter published in Lancet Sept. 17. 1977 p. 614

(16) Mannucci PM, Ruggeri ZM, Pareti FI, Capitanio A. Letter published in Lancet DDAVP in Haemophilia. Lancet Dec. 3 1977; 1171-1172

(17) Heimburger Dei Gelben Hefte. Vol. XX 1980

(18) Schimpf K, Mannucci PM, Kruetz W, et al. Absence of hepatitis after treatment with a pasteurized factor VIII concentrate in patients with haemophila and no previous transfusion. N. Engl. J. Med 1987; 316: 918-922.

(19) Colombo M, Mannucci PM, Carnelli V, Savidge GF, Gazengel C, Schimpf K. Non-A non-B hepatitis transmitted by heat-treated factor VIII concentrates. Lancet 1985; 2: 1-6

(20) Rozioux C, Chamaret S, Montagnier L, Carnelli V, Rolland G, Mannucci PM. Absence of antibodies to AIDS virus in haemophiliacs treated with heat-treated factor VIII concentrate. Lancet 1, 272: 1985 (letter).

(21) Ledertman MM, Ratnoff OD, Scillian JJ, Jones PG, Schacter B, Impaired cell mediated immunity in patients with chronic haemophilia N. Engl. Med. 303: 79, 1983

(22) Menilove J.E, Aster RH, Casper JT, Lanex SJ, Gottschall JL, Williams JE, Gill JC, Wheeler DV, Piaskowski V, Kizchuer P, Montgomery RR. T-Lymphocyre sub-populations in patients with classic haemophilia treated with cryoprecipitate and lyophilized concentrates N. Eng. Med 308: 83, 1983