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INFECTED BLOOD INQUIRY

WITN2658002

A SYNOPSIS OF HAEMOPHILIA

re: MR MALACHY DEVLIN

Mr Malachy Devlin, born on GRO-C 1934, suffers from severe classical haemophilia. He has had lifelong bleeding problems consequent upon the lack of factor VIII clotting activity in his blood. He has developed both common and rare complications of haemophilia. He has widespread arthropathy, hypertension and has had a proven peptic ulcer. He has a massive pseudotumour arising from his pelvis. The latter rare complication, associated with the more common haemophilic arthropathy, has led to severe physical disablement.

Hospitalisation was a frequent occurrence up until the late 1970s. Emergency admissions were necessary for the management of excruciatingly painful, spontaneous bleeds into muscles or joints. Planned admissions for unavoidable dental extractions were a feature of the mid 1950s to the mid 1960s. Mr Devlin commenced on home treatment programme in 1976, thereafter admissions to hospital became less common. They occurred for the management of lifethreatening bleeding associated with trauma, for example, following his road traffic accident in 1979; or for bleeding related to his pseudotumour which caused his admission in 1983. At other times he had planned dental extraction admissions.

Haemophilia treatment has undergone many changes during the last forty years. Up until the late 1960s there was no true haemostatic treatment available. Mr Devlin's age and longevity enables the treatment changes of haemophilia to be seen chronologically. His problems highlight the many difficulties encountered during the last four decades.

MEDICOLEGAL REPORT

1955: *Mr Malachy Devlin had his first documented admission to the Royal Victoria Hospital in 1955: from 18.5.55 to 4.6.55. At that time the history given raised the possibility that Mr Devlin might suffer from severe haemophilia. The history was characteristic, his bleeding episodes had commenced in early childhood and were spontaneous in nature, e.g. at the age of four years he bled for many days after losing one of his "milk" teeth. He was said to bruise easily and that the bruises were enormous after only minimal trauma. He was said to have had episodes of "passing blood in the urine" which were not due to infections. Furthermore, his joints were described as swollen and frequently painful, especially both his knee joints. The patient was aged 21 at the time of this admission.*

1956: *His diagnosis was established in 1956 by the then used Thromboplastin Generation Test. It confirmed that Mr Devlin had a severe deficiency of anti-haemophilic globulin (AHG). The terminology, Factor VIII, was not introduced until after 1965. At this time the treatment for haemophilia was conservative. Infusions of fresh frozen plasma were given to raise the patient's level of AHG but haemostatic levels could not be achieved. Many litres of plasma would have been needed to produce an adeqauate rise in AHG level. Inevitably ths would have caused heart failure due to overloading of the circulation. However, despite its inadequancy, fresh frozen plasma formed the basis of treatment for acute bleeding episodes and for control of the haemorrhage following dental extraction. Reactions to plasma infusions developed in many patients with variable severity.*

1956-66: *During the decade Mr Devlin had admissions for unavoidable dental extractions. The duration of his hospitalisation varied from 15-22 days depending upon the degree of difficulty in controlling his post extraction bleeding. Haemophilliac patients dreaded dental extractions on account of inevitable associated bleeding. Teeth being embedded in bone provide one of the strongest challenges to the body's haemostatic mechanism. Injuries occurring in other bodily areas can be compressed by pressure to help stop bleeding; this is not possible relative to dental extraction.*

1957: *During one such admission for the extraction of three teeth Mr Devlin suffered several reactions to the infusion of fresh frozen plasma. Thirtyfive minutes after the commencement of the plasma infusion, the patient developed a generalised urticarial (hives) rash associated with swollen eyelids. He was treated with antihistamines to counteract the allergic response, with good effect. However, five days later, despite using antihistamine prophylaxis, he developed a reaction during a further infusion. Suddenly he developed dyspnoea (breathlessness), pallor, drowsiness, cyanosis (skin turned blue), hypotension (low blood pressure) and tachycardia (pulse rate in excess of 100/minute). Eventually he responded to treatment with intravenous hydrocortisone, followed by further steroids in the form of oral Prednisolone. He had suffered a severe, lifethreatening hypersensitivity reaction. The patient recovered, but ALL subsequent plasma infusions required to be covered by intravenous hydrocortisone to prevent recurrence. The stressful nature of such reactions needs to be emphasised, particularly as they occurred in conjunction with the constant haemorrhage from the patient's tooth sockets and associated with a prolonged hospital stay. The duration of Mr Devlin's 1957 admission was 22 days for the extraction of three teeth.*

1965: *In April Mr Devlin was admitted on account of vomiting blood. He also gave a history of onset of severe pain in his right hip joint with the loss of sensation affecting his right thigh. He was treated with plasma infusion under steroid cover without complication. Subsequently he was placed on an ulcer regime with antacids and diet. The findings related to his right hip were compatible with a haemorrhage occurring around the lumbar plexus. A comment from the discharge summary states that: "The prognosis for full recovery is poor but no special treatment is indicated." This reflects the degree of difficulty existing in the management of haemophilia at the time. However, during 1965, Poole and Shannon published a method for the preparation of concentrated AHG from a single plasma donation. It was termed* ***CRYOPRECIPITATE.*** *It was the first haemostatic material available for the treatment of haemophilia.*

1966: *On 26 October Mr Devlin was admitted for treatment of a traumatic haemorrhage into his right thigh. It dated from being kicked by a cow! He had a large haematoma (a blood-filled swelling) over the injured area. He was treated with intravenous Cryoprecipitate. His AHG level was maintained above 15% for 36 hours, his baseline level being less than 1% activity of normal. Clinically the patient improved and had no adverse reaction to the new treatment. During this admission the presence of a right-sided pseudotumour was first noted (see X-ray report 26.10.66).*

1967: *A further admission occurred which required Cryoprecipitate treatment. No reactions occurred. It is unclear from the hospital notes if steroid cover was given routinely on each and every occasion when Cryoprecipitate was administered.*

1968: *No further admissions are documented until October when Mr Devlin was admitted for elective dental surgery. It was cancelled following discussion with Mr Devlin. He had been under the impression that Cryoprecipitate could never result in a severe hypersensitivity reaction as such occurred in 1957. However, as Cryoprecipitate is derived from plasma, no guarantee could be given to Mr Devlin and the extractions were cancelled.*

1970: *During an admission in March Mr Devlin's blood pressure was found to be elevated at 200/110 mmHg. High blood pressure, namely hypertension, is a well recognised complication of haemophilia. The aetiology is unproven but thought to be related to bleeding episodes within the renal tract. Mr Devlin gave a history of passing blood in the urine during both childhood and adolescence. His pressure normalised during the admission and no treatment was given.*

1971: *In February of the following year Mr Devlin was admitted complaining of ulcer-type symptoms, namely epigastric pain, nausea and constant heartburn. A barium meal showed no radiological evidence of a definitive peptic ulcer. However, the patient was replaced on appropriate adtacids and given further advice regarding diet, etc. In March and April Mr Devlin developed reactions to Cryoprecipitate despite being given antihistamines and steroid cover prior to injection. In August Mr Devlin developed jaundice. At the time he did not attend hospital but described his condition at a later date. Laboratory investigations were undertaken to test for infection with hepatitis B (possibly derived from his Cryoprecipitate). They were negative.*

1972: Mr Devlin had an admission for treatment of a swollen right hip joint and a bleed into his left wrist. On this occasion clinically the swelling arising from the right side of his pelvis had increased markedly. Radiological assessment indicated continuing expansion in the size of the pseudotumour plus extensive arthritic changes affecting the left hip joint. In addition there was a little left ventricular enlargement seen on his chest X-ray. In view of the latter and the then modestly elevated blood pressure, 140/100, the patient was placed on regular diuretic treatment with Thiazide (Navidrex K).

The pseudotumour had been first noted on X-ray in 1966, reviewed in 1971 and was now clinically significant. The development of a pseudotumour is an uncommon but well recognised complication of haemophilia. The incidence is 0.5 to 2%. By 1969 only 47 published cases had been documented (Steel, Duthie and O'Brien). Prior to factor VIII haemostatic treatment being available, treatment was hazardous with a high mortality. Conservative, non-surgical treatment was advocated. However, in this instance, in view of the clinical enlargement, it was decided that Mr Devlin should receive weekly prophylactic injections of Cryoprecipitate to try and minimise further episodes of haemorrhage into the tumour. This was arranged to be carried out nearer to home, namely at the Mid-Ulster Hospital, Magherafelt. It was continued for a brief period. The duration is not documented.

1974: *On 29 September Mr Devlin was admitted for the planned dental extraction of nine teeth. In view of his previous reactions to plasma products, he was given a test dose of a new freeze dried factor VIII concentrate called* ***KRYOBULIN****, manufactured by Immuno Limited, Vienna. The amount given produced a satisfactory rise in Mr Devlin's factor VIII clotting activity and producedno adverse reaction. The extractions were duly carried out under cover of daily Kryobulin, oral antifibrinolytic tablets and antibiotics. The patient suffered no complication and was discharged nine days later. In view of the patient's previous adverse reactions to plasma preparations, a change of treatment to include the usage of Kryobulin was discussed. It would avoid the need for prophylactic steroids, eminently desirable in view of the patient's hypertension and ulcerlike symptoms. Therefore appropriate arrangements were undertaken to change treatment. The patient and his wife were trained in the aseptic techniques necessary for the self-administration of factor VIII in the home situation. After completing the usual training period, he was issued with material to be kept at home and was entered into the Centre's Home Treatment Programme.*

1976: *During late 1976 Mr Devlin developed recurrence of ulcer symptoms. On this occasion a barium meal revealed the presence of an acute duodenal ulcer. Appropriate advice was given regarding maintaining a strict diet, the regular usage of antacids and the need for rest.*

1977: *In January at routine review the patient was well and had no further ulcer symptoms. He continued to be managed as an outpatient on his home treatment programme, which was only complicated by an episode of acute anxiety and depression in January 1977. He made an excellent recovery following a course of tricyclic antidepressant therapy.*

1978: *Recurrence of ulcer symptoms. Cimetidine (an H_2 antagonist) treatment was instituted and the patient made a prolonged and satisfactory response to treatment.*

1979: *Mr Devlin was admitted on 13 October following a severe car accident. His wife had administered appropriate factor VIII treatment within 1½ hours of the accident occurring. He sustained multiple injuries. He had a fractured left tibia and fibula, severe haemarthroses of the right elbow joint and the right knee joint; similar haemarthroses affected both ankle joints. Clinically he had a massive haemarthrosis of the left knee joint caused by the fracture involvement of the articular surface of the knee joint. His treatment was of long duration and intensive in nature. In view of the half-life of infused factor VIII varying between 8 and 14 hours, he was treated with 8-hourly infusions of factor VIII in the first instance for several days. Thereafter he was given infusions at 12-hourly intervals until 30 October. It was continued daily at a higher dose level until 17 November 1979. His factor VIII clotting activity level was maintained at the lower limit of normal throughout the period, namely approximately 60% factor VIII clotting activity. He was discharged on 17 November to continue treatment at home. Despite his horrendous injuries, he was able to walk again.*

1980-82: *Mr Devlin continued on his home treatment programme without complication.*

1983: *Admission for dental extraction of his remaining teeth. He was treated successfully with one injection of factor VIII and was discharged without complication.*

October. Prolonged admission for treatment of lifethreatening bleeding with his pseudotumour.

1984-89: *The remainder of the clinical admissions and progress is irrelevant as Mr Devlin had serocoverted by 1984.*

1981-85: ***Haemophilia and AIDS***

The first cases of AIDS occurring in haemophilic patients were published in December 1982 (MMWR 31, 644). Prior to that, cases of fatal pneumocystis pneumonia and Karposi's sarcoma had been described in American homosexual men. Usually such conditions are associated with a profound disturbance in the patient's immunological system. However, it was not until January 1983 that alterations in the immune system of some haemophilic patients were described by Jones et al. They found low T4 lymphocyte cells and altered T4/T8 ratios. The cause of the changes was undetermined.

1983: *Throughout 1983 the published debate regarding the relationship of the AIDS infection to thehaemophilic population continued: in January and March 1983 two editorials, one in the New England Journal of Medicine and secondly, one in the Annals of Internal Medicine, pondered if a change to treatment with Cryoprecipitate would be prudent, thus avoiding commercial factor VIII infusions which may or may not be responsible for the changes described in the immune system. In May 1983 French workers isolated a retrovirus known as LAV (lymphadenopathy associated virus) (Science 220, 868). In November the first United Kingdom case of AIDS developing in a haemophilic was reported by Daly and Scott. By the end of the year 21 cases of AIDS in American haemophilic patients had been reported. At this time the United Kingdom Haemophilia Reference Centre Directors met and discussed the problem. In June 1983 general recommendations on treatment policy were sent out to all Haemophilia Centres in the UK.*

NB The Royal Victoria Hospital is a designated Reference Centre.

1984: *In May 1984 Gallow and colleagues cultured a virus from two AIDS patients. It was termed HTLV3. Eventually it became clear that the French retrovirus LAV and Gallow's HTLV3 virus were identical. The name was changed subsequently to HIV1, namely human immunodeficiency virus 1. By June 1984 a British Medical Journal editorial accepted that AIDS was transmitted by blood products. In the USA one in a thousand haemophilics had AIDS but over 50% had detectable abnormalities of their immune system. The following month AIDS was reported in a haemophilic treated only with Cryoprecipitate (Canadian Medical Association Journal 131, 45). In September 1984 the first report of the HIV virus's fatal sensitivity to heat treatment was published. By December of the year the Scottish National Blood Transfusion Service had introduced heat treated material. Gradually all material for use in the treatment of haemophilia from all sources became heat treated. The UK Haemophilia Directors issued general guidelines as to the best treatment for haemophilics.*

December 1984:

During December 1984 plans were laid to interview all of the patients attending the Northern Ireland Haemophilia Centre. It was felt that the opportunity should be afforded to all to have frank discussions regarding the possibilities of becoming infected or already being infected by the AIDS virus. At that time a test was available to measure antibody to the HIV virus. There was no test available to test for the presence of the actual virus, i.e. there was no antigen test available. Therefore it was not possible to predict the consequences of finding a positive result. The arrangements took several months to complete, as patients were requested to come to the Centre in small groups to allow sufficient time for discussion and debate. Actual testing of samples commenced on 2 January 1985. Each sample

was coded. The prefix was BV (Belfast virus) and each patient's sample was allocated a sequential number commencing at BV1 up to and including BV396. When the results were available, they were entered into a confidential notebook retained by Dr Mayne and kept in a locked filing cabinet drawer in her office. Access was permitted only to two other people, the Chief MLSO in the Haemophilia Laboratory and Dr Mayne's personal and confidential secretary.

1985: In due time, on 25.3.85. Mr Devlin was sent his letter to attend for testing on 19.4.85. Patients, following counselling, were asked if they wished to be told the result. If they did not wish to be told, it remained confidential to the three people mentioned previously until such time, in the future, when it became vitally necessary to interview and inform patients of the results. If the result was positive, it required to be confirmed by a second sample and two other techniques. Thereafter in the cases of some of the regularly attending patients, it was possible to carry out retrospective testing to try and assess the time of seroconversion. These samples were available because, as often as possible, it had been customary to take a blood sample from the patient when he attended the Haemophilic Follow-up Clinic. The sample was required to test the patient for the presence of a factor VIII inhibitor which would alter his treatment, to test for anaemia in case of occult haemorrhage, to check liver function and, finally, to assess for virological infection with hepatitis. Thus the last aliquot of the sample was sent to the Virology Department. The consultant virologist stored any extra serum over and above that needed for the test, from each sample. He felt that, in the future, viruses other than hepatitis B cannot be isolated and

the retrospective samples would be helpful to detect infection in the patients. The virologist's prophecy has been fulfilled with the advent of a new test now available for hepatitis C (1989).

In the case of Mr Devlin, his sample of the 19.4.85. was positive. His last negative sample was 4.2.83. and his first positive was 10.1.84. He had another blood sample taken for Virology in November 1983 but on this occasion there was insufficient in the sample remaining after testing for storage. With hindsight, this would seem to have been unfortunate. If a November sample had been available, a more accurate date of seroconversion would have been obtained. However, it is known that Mr Devlin seroconverted during 1983. Mr Devlin received large quantities of commercial factor VIII treatment in 1979 on account of his car accident. It would seem unrealistic to consider that material as the source of his seroconversion.

1977: ***Choice of material for usage in N I H C:***

Policy was adopted in 1977. It concerned the usage of commercial factor VIII material. As far as was practical, "one brand" was used for the home treatment patients and a second brand for those unsuitable for home treatment. Depending upon availability and the patient's clinical situation, the policy would be maintained. If possible, a home treatment patient would continue on the same brand, even should he become an inpatient for emergency or planned surgery. Additionally it was felt important to try and treat all children with locally prepared Cryoprecipitate in the first instance to avoid hepatitis.

Kryobulin (Immuno Ltd, Vienna) was selected for the home treatment patients due to its ready solubility and ease of preparation. The decision taken at that time was the personal one of the Director who felt that it might be prudent to restrict heavy users to only one product. It was not possible to place all the haemophilic patients on home treatment, only those patients with good accessible veins, a reasonable intelligence and who had someone available at home throughout the 24-hour period to help with the administration of the material could be included. There was an almost equal number of non-home treatment patients who were treated with the second brand, Hemofil, manufactured by Travenol Ltd, USA. Hemofil was the first commercial product which entered the United Kingdom. It was used in the Northern Ireland Haemophilia Centre in the early 1970s and at that time had proven to be lifesaving. It had less good solubility than Kryobulin and thus was more suitable for hospital usage when professionals were available to carry out its preparation.

From time to time when emergencies occurred the quantities of material needed and the likely duration of the period of treatment had to be considered. It was difficult to maintain large stocks of material. In general there was more Hemofil in stock than Kryobulin, as the much of the latter material was distributed in the home treatment patients' own refrigerators throughout the Province. Thus in 1979 Mr Devlin was treated with Hemofil rather than Kryobulin. An unforeseen difficulty occurred in late 1982 and in particular throughout 1983. Due to increased demands for European origin Kryobulin on a worldwide basis, standing orders were unable to be met and as a consequence a third brand of material was introduced to the Haemophilia Centre in the Royal Victoria Hospital. The third material was

Factorate produced by Armour Ltd, USA. Mr Devlin used Factorate during his home treatment from 15 February 1983 to 30 August 1983. He received three doses of Factorate batch no V60812 and 48 doses of Factorate batch no W80005. In view of using this material for most of 1983, it was continued throughout his prolonged and almost catastrophic illness which commenced in October 1983. The only other admission he had during 1983 was early in the year, in February, for the extraction of his last remaining three teeth. For that admission he only required one dose (3236 IU) of Hemofil, batch no 810313 A024C and was discharged without complication.

1983: Mr Devlin's admission commenced on 4 October 1983. He had been seen by Dr Mayne on 15.9.83. when he had complained of feeling unwell, had had many episodes of severe diarrhoea, complained of nausea and fatigue. The diarrhoeal illness had affected the entire family but Mr Devlin felt that he himself had not recovered. In addition his pelvic swelling was painful. He was admitted on 4.10.83. having made no progress on outpatient management. On examination his pseudotumour had increased in size and had reached the size of a full term pregnancy. The pseudotumour had become infected and had sustained an extensive internal haemorrhage (see CT scan report October 1983). The scan revealed that the tumour had destroyed almost the entire right side of Mr Devlin's pelvis. He was treated with continuous intravenous antibiotics and regular factor VIII infusions until the tumour burst and drained 2½ litres of chocolate-coloured fluid. The drainage site healed satisfactorily. During this admission consideration was given to the possibility that Mr Devlin might have developed the AIDS syndrome. However, on clinical examination there was nothing to support this supposition. There was no lymphadenopathy, no skin lesions, no candidiasis and no splenomegaly. In

terms of laboratory investigations, although he had a very high ESR, greater than 150mm/1 hour, he had been pyrexial for many days following admission. He also had a raised IgG and IgM. There was alteration of his OKT4 and OKT8 lymphocyte ratio and he had one result of significant lymphopenia. However, subsequently his ESR reduced to 58mm/1 hour, his lymphocyte count returned to normal and the patient had a complete clinical recovery. It was felt at that time the changes in his blood test were probably related to an alteration in his immune mechanism caused by receipt of multiple transfusions of blood products. Such changes had been reported during 1982/83, hence the final comment in the patient's discharge summary for that admission.

During 1983/84 there were suggestions in the literature that a reversal to treatment with Cryoprecipitate might be appropriate for the safety of patients. However, in Mr Devlin's case it was decided that this would seem to be a retrograde step as he required steroid cover for almost all Cryoprecipitate treatment in the past. Reintroduction would have been inappropriate in view of his ulcer history and hypertension. Additionally the volume for infusion would be excessive for his cardiac status.

In conclusion, Mr Devlin seroconverted during 1983. It is regretted that there was no test available retrospectively in November 1983 as this would have been of considerable help in establishing a more precise date of seroconversion. It is clear that the prompt administration of factor VIII by his wife at the time of his road traffic accident was instrumental in saving his life. His pseudotumour problem was thought to be a terminal event in 1983. During that admission he was seen by two experienced haemophilia physicians who happened to be visiting the Haemophilia Centre. Both felt that

a successful outcome was unlikely and that if the patient did survive, he would be chair-bound for the rest of his life. After his admission in 1979 and again after the admission for his pseudotumour, Mr Devlin was unable to walk at the time of discharge. However, due to his perseverance and courage on each occasion, he became mobile, thus providing his amazing resilience.

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