PENROSE INQUIRY – TOPIC C5 – PROFESSOR GORDON LOWE

(5a) THE INFORMATION GIVEN TO PATIENTS (OR THEIR PARENTS) ABOUT THE RISK OF NON A AND NON B HEPATITIS BEFORE THEIR TREATMENT WITH BLOOD OR BLOOD PRODUCTS

At the outset of this witness statement, I would refer the Inquiry Team to the Collective Response of past and present Haemophilia Centre Directors in Scotland on Topic C5. This comprehensive document has been prepared by myself, Professor Ludlam of Edinburgh Royal Infirmary and Dr Brenda Gibson of Yorkhill Hospital, and endorsed by the list of recipients comprising past and present haemophilia staff, appended to that document.

My own recollection, as a trainee doctor 1976-87, then Co-Director 1988-2009, is that patients attending Glasgow Royal Infirmary were routinely informed of the risk of hepatitis (B, and non A non B) before and after their treatment with blood or blood products by Centre staff (medical and nursing). This risk was reinforced in several ways –

(a) Nursing and medical staff taking precautions to avoid transmission during treatment (e.g. use of disposable gloves evolved, and careful disposal of needles, syringes, intravenous lines and blood or blood product packs).

(b) Educational/information leaflets (e.g. those issued by the UK Haemophilia Society) on haemophilia, its treatment and complications. Some examples are provided in Annex 3 of the Collective Response.

(c) Patients or parents requesting further information about NHS or commercial clotting factor concentrates would be given the information leaflets provided with such concentrates, which included the possibility that they might transmit hepatitis. (Annex 4 of the Collective Response).

(d) From the introduction of hepatitis B vaccination in the UK NHS in 1985, patients without natural immunity to hepatitis B were offered vaccination. Information given at that time would include that many patients would be naturally immune following hepatitis B exposure through blood product treatment; and that vaccination was protective only against hepatitis B, and not against hepatitis due to other viruses (including non A non B hepatitis) (Annex 5 of the Collective Response). Similar information would be given when hepatitis A vaccination was offered to patients from 1992. Parents of children with haemophilia, especially those on home treatment, were also offered vaccination, and advised on the risks of hepatitis from blood spills and needle stick injuries.

(e) From 1983, it was evident that patients receiving clotting factor concentrates (NHS or commercial) for the first time, had a high risk of developing non A non B hepatitis (Fletcher et al 1983). Accordingly, UKHCDO and others recommended that cryoprecipitate be preferred to clotting factor concentrates for patients with factor VIII deficiencies with no, or limited, previous exposure (UKHCDO 1983; Forbes et al 1984; Rizza and Jones 1987), until 1988 (UKHCDO 1988). This practice would be explained to relevant patients (or their parents) during this time period.

(f) From 1988, patients previously not exposed to clotting factor concentrates (or their parents) were given information on, and invited to participate in, a clinical trial of virally-inactivated SNBTS clotting factor concentrates whose aim was to demonstrate that such concentrates had a low risk of non A non B hepatitis/hepatitis C. The information sheet is provided in Annex 6 of the Collective Response. The results of this study were published in 1992, and confirmed a low risk of non A non B hepatitis and hepatitis C (B. Bennett et al 1993; Annex 7 of the Collective Response).

(g) Following the licensing of non-human-donor (recombinant) clotting factor concentrates in the UK in 1995, Haemophilia Directors in Scotland successfully lobbied the Scottish Health Department to make these available for treatment of patients with haemophilia in Scotland. The first priority was patients previously not exposed to clotting factor concentrates (Annex 8 of the Collective Response)

Information given to patients (or their parents) on the severity of non A non B hepatitis before their treatment with blood or blood products at Glasgow Royal Infirmary

The Inquiry's Preliminary Report has already summarised evidence that prior to 1985 non A non B hepatitis, while common, was generally thought not to be a serious illness either in the acute, symptomatic stage (jaundice) or in the more common chronic, asymptomatic stage. This information would be provided to patients (or their parents) during discussions about the risk of hepatitis. From 1985 it was increasingly realised that the chronic, asymptomatic stage of non A non B hepatitis could progress in severity, initially through research studies of serial liver biopsies, and thereafter through epidemiological studies of clinical complications (cirrhosis and liver cancer). From 1985 , however, patients (or their parents) would be informed that it was hoped that viral inactivation of clotting factor concentrates (NHS and commercial) would reduce, or eliminate, the risk of transmission of non A non B hepatitis. This hope was realised in time.

Information given to patients (or their parents) on alternative treatments to blood or blood products at Glasgow Royal Infirmary.

Patients and parents were advised that the only alternative treatment to blood or blood products for raising low levels of factor VIII to prevent or treat excessive bleeding was the synthetic drug, desmopressin. This was used in Glasgow Royal Infirmary from the late 1970s for patients with mild haemophilia A or von Willebrand's disease (factor VIII level at least 10% normal), for example to prevent excessive bleeding after dental extraction or other minor surgery. However, it had several limitations:

- Small and short lived effect
- Repeat injections were followed by a lower response due to exhaustion of stores of factor VIII (tachyphylaxis)
- Common vasodilator effects (e.g. flushing, fainting) so not tolerated by some patients

- Less common serious adverse effects (e.g. water intoxication, thrombosis leading to heart attacks) so contra-indicated in patients at risk.
- Desmopressin was ineffective in most patients with haemophilia A (severe or moderately severe patients) and in all patients with haemophilia B.

Hence most patients had no effective alternatives to treatment with blood or blood products until their replacement with non-human (recombinant) clotting factor concentrates during the 1990s.

General information given to patients (or their parents) about hepatitis, BEFORE OR AFTER their treatment with blood or blood products.

(a) It is my recollection that patients referred to Glasgow Royal Infirmary Haemophilia Centre from Yorkhill Hospital or other Haemophilia Centres had already been informed of the risk of hepatitis from blood and blood products.

(b) In the 1970s and early 1980s, when few patients were on home treatment and the majority attended the Haemophilia Centre for treatment of acute bleeds, patients (and parents) would get to know other patients (and parents) as they were all seen and treated in a single room 'Haemophilia Centre' at Glasgow Royal Infirmary. They would exchange information while they waited for treatment or while it was being infused. Thus information spread readily. Furthermore, some individuals had other family members with haemophilia from whom they would have learned about the condition and the complications of treatment, including hepatitis.

(c) The UK Haemophilia Society was very conversant with the risk of hepatitis. Their representatives were invited to the UKHCDO Annual General Meetings and the associated Scientific Meetings, at which the issue of hepatitis was repeatedly discussed, especially in the early 1980's. This information was disseminated to their members by way of the Haemophilia Society's regular information leaflets (Annex 3 of the Collective Response) and other publications for patients, relatives and

partners (extracts from Dr P Jones book on Home Treatment appended Annex 10 of the Collective Response), which were displayed to patients attending the Haemophilia Centres in Glasgow Royal Infirmary.

Local meetings of the Haemophilia Society were an opportunity for treatment and welfare matters to be discussed. For example, at a meeting of the Society in March 1980 at Glasgow Royal Infirmary, Dr Alistair Parker (Consultant Haematologist) reviewed treatment arrangements in Seattle, which he had recently visited, and the minutes record that hepatitis was discussed (Annex 15 of the Collective Response). At the same meeting Dr Forbes raised a number of initiatives focussing on welfare issues. Also, I recall an invitation to speak at a meeting of the West of Scotland Haemophilia Society in 1988, where during a review of changes in haemophilia care in the 1970s and 1980s I reviewed the risk of hepatitis, and measures taken to reduce the risk including desmopressin, vaccination, cryoprecipitate and heat treatment of factor concentrates – including the SNBTS clinical trial of their products in previously untreated patients which was about to start (Annexes 6 and 7 of the Collective Response).

(d) Within the Haemophilia Centre waiting and treatment rooms at Glasgow Royal Infirmary there were notice boards to advertise Haemophilia Society activities, and copies of the Society's information leaflets (including information on hepatitis) were available for patients to read and take away.

(e) Books about haemophilia were available to patients and relatives attending Glasgow Royal Infirmary in the late 1970s and 1980s and these discussed what was known about hepatitis. The best known was 'Living with Haemophilia' by Dr Peter Jones (1980) which was widely read by patients and promoted by the Haemophilia Society. It was in great demand and ran to several editions. Sections which gave information on hepatitis are appended (Annex 11 of the Collective Response).

(f) The leaflets accompanying the bottles of both NHS and commercial concentrate were received by patients (and relatives and partners who often assisted patients with preparing and administering treatment) about the concentrates

including the possibility that they might transmit hepatitis (Annex 4 of the Collective Response).

(g) Patients, relatives and partners received education before, and during, home treatment with factor concentrates (usually from the Haemophilia Centres' nurse specialists). This included education on the risks of hepatitis transmission, and the need to take great care with safe disposal of needles to avoid transmission by needlestick injury. (see excerpts from Dr. P Jones' book on Haemophilia Home Treatment, Annex 10 of the Collective Response).

(h) Some patients were generous in helping with undergraduate teaching of students either as in-patients or attending for 'clinical teaching' to a group of students. The patient would be party to all the clinical presentation which included much about haemophilia and the complications of treatment. Hepatitis was discussed on many occasions during these teaching sessions at Glasgow Royal Infirmary.

Clearly not all patients helped with clinical teaching. The results of blood tests would be discussed with patients if appropriate, i.e. if there was an unexpected abnormality or the patient enquired. Thus many individuals would get to know about the reason for these investigations and hence the possibility of these complications, particularly development of inhibitors and hepatitis as these are the commonest complications.

(i) During the 1970s and 1980s little was known about the risk of sexual spread of non-A non-B hepatitis although it was not considered a significant risk. Once hepatitis C testing became available in the early 1990s and sexual transmission was studied it was found to be uncommon (especially in the absence of other sexually transmitted diseases). Transmission of hepatitis B to a spouse was a known risk of either the presence of acute hepatitis B infection or from a chronic carrier of the virus – this occurs in about 5% of individuals following acute infection. Sexual transmission was routinely discussed with carriers of hepatitis B or C at Glasgow Royal Infirmary.

(j) By 1985 a hepatitis B vaccine (derived from chronic carriers of hepatitis B infection) was available and licensed. This was offered to patients who were susceptible to hepatitis B, i.e. patients who did not have antibodies to hepatitis B in their blood. In offering this vaccine there would have been a general discussion about different types of hepatitis.

(5b) THE TRACING AND TESTING OF PATIENTS WHO MIGHT HAVE BEEN EXPOSED TO THE VIRUS THROUGH THEIR TREATMENT WITH BLOOD OR BLOOD PRODUCTS

(1) Routine surveillance for hepatitis viruses and liver disease at Glasgow Royal Infirmary Haemophilia Centre, prior to hepatitis C testing from 1991 onwards.

When Dr. Walker and I succeeded Drs Forbes and Macdonald as Haemophilia Centre Co-Directors, we continued their policy of routine surveillance for hepatitis viruses and liver disease. As in any other chronic disease, management of haemophilia included regular monitoring (usually annually at clinic reviews) for complications of the disease, and complications of its treatment (including hepatitis). For example, Jones (1981), reviewing the organisation of a haemophilia service in a Chapter of the standard UK textbook, noted examination for hepatosplenomegaly (enlargement of liver or spleen, which might indicate liver disease due to hepatitis) and routine blood tests (Jones P, in Haemostasis and Thrombosis, edited by A.L. Bloom and D.P. Thomas. Edinburgh: Churchill Livingstone, pages 389-394) (Annex 1 of the Collective response). Routine blood tests included –

(a) Full blood count to measure haemoglobin, white count (including an assessment of the different kinds of white cells) and platelet count. This would be principally to make sure the patient was not anaemic due to occult bleeding (or in the early days of factor concentrate use that it had not led to a haemolytic anaemia – anaemia due to the premature removal from the recipient's circulation of red blood cells damaged following factor concentrate infusion).

(b) Assessment of blood chemistry consisting of -

i.) Liver function tests – to assess possible presence and possible degree of hepatitis

ii.) Urea and electrolytes to assess kidney function – haemophilia can lead to structural damage of the kidneys. Renal failure of any cause can lead to a bleeding state which would exacerbate the haemorrhagic state of the haemophilia.

(c) Assessment of clotting factor deficiency, e.g. factor VIII level and for presence of an anti-factor VIII inhibitor.

(d) Sample for virology for hepatitis B antibody and antigen.

As discussed by Dr. B. Colvin in his evidence to the Inquiry (8 March 2011) the diagnosis of non A non B hepatitis was difficult during the 1980's, prior to the identification of hepatitis C, for several reasons:

- Elevation of serum transaminases at routine clinic attendances (usually annually) provided an insensitive (weak) estimate of liver disturbance
- Elevation of serum transaminases was highly variable between and within individual patients
- Elevation of serum transaminases was insensitive to progression of liver disease
- Elevation of serum transaminases was nonspecific, reflecting liver disturbance due not only to viral hepatitis, but also to alcohol, other drugs, obesity and other causes; as well as disturbance to other body organs (e.g. skeletal or heart muscle).

Hence, interpretation of those blood "liver function tests" was difficult, as was information and advice given to patients.

The few patients at Glasgow Royal Infirmary in the 1970s and 1980s with clinically suspected acute hepatitis (jaundice and/or other symptoms) would be routinely admitted to the local infectious disease unit at Belvidere Hospital for investigations, symptomatic management, and follow-up.

The few patients with symptomatic chronic liver disease (cirrhosis) would be referred to the Glasgow Royal Infirmary Gastrointestinal/Liver Disease Clinic (Dr. Robin Russell, Dr. John Mackenzie) for investigation, management, and follow-up.

The few patients who were carriers of hepatitis B were advised of the high risk of transmission by blood or sex; and that special precautions were required to avoid such transmission, including practising safe sex, and informing sexual partners of the risk and that they should practice safe sex and seek medical advice, including testing for carriage of the virus and vaccination. As discussed above, from 1985 all patients with haemophilia who were not immune to hepatitis B were advised to have hepatitis B vaccination, as were those assisting them with home treatment, who were at risk of needlestick injuries.

As discussed above, from 1992 all patients with haemophilia were routinely tested for antibody to hepatitis A, and if not immune were advised to have hepatitis A vaccination.

(2) Advice to patients and sexual partners on sexual transmission of hepatitis viruses at Haemophilia Centres, prior to hepatitis C testing from 1991 onwards

As discussed above, the few patients who were carriers of hepatitis B were advised of the high risk of transmission by blood or sex; and that special precautions were required to avoid such transmission, including practising safe sex, and informing sexual partners of the risk and that they should practice safe sex and seek medical advice, including testing for carriage of the virus and vaccination.

For patients with suspected non A non B hepatitis (usually, asymptomatic intermittent or persistent elevation of serum transaminases) no advice about the risk of sexual transmission, or testing of sexual partners, could be given, prior to the identification of the hepatitis C virus and the introduction of hepatitis C testing in NHS Scotland from 1991. Following however the identification of the risk of AIDS and the identification of the causative HIV virus, from 1985 all patients who had received treatment with blood products were advised to discuss sexual transmission of bloodborne viruses with their partners and to practice safe sex (e.g. use of

condoms), regardless of their HIV blood test results. (see evidence submitted by Prof Forbes on Topic B5). This advice continues to this day, and is clearly relevant to the (uncommon) risk of sexual transmission of HCV which was clarified during the 1990s, and also to potential sexual transmission of other pathogens.

(3) When did they start testing their patients for HCV?

Following the identification of the hepatitis C virus and the development of tests for exposure (antibody tests) and carriage (PCR tests), UKHCDO recommended in 1990 and 1991 that testing for hepatitis C be added to established routine surveillance for hepatitis/liver disease in patients with haemophilia (history-taking, clinical examination, liver function tests, hepatitis B testing, and from 1992 hepatitis A testing).

Accordingly, Dr. Walker and I added HCV testing to routine surveillance for hepatitis/liver disease from 1991, following discussion with the Regional Virus Laboratory at Ruchill Hospital and with our gastroenterology/hepatology colleagues.

(4) In what circumstances were blood tests carried out during the periods 1990-1995 and from 1995 onwards? Were patients tested individually or as a group? Were fresh blood samples taken for the purpose of testing or were stored samples used? Who carried out the HCV tests?

From 1991 to 1995, and from 1995 onwards, fresh blood samples were taken from all individual patients who had previously received blood or blood products, when they attended for routine review at the Haemophilia Centre. Blood was sent to the Regional Virus Laboratory, Ruchill Hospital, who were routinely testing patients for hepatitis B and hepatitis A.

(5) Did they tell their patients that HCV tests were being carried out? What did they tell their patients about HCV testing? Did they obtain consent from their patients before carrying out HCV tests?

Patients were routinely informed that HCV tests were being carried out. They were told that hepatitis C was a recently-discovered virus which was thought to be the commonest cause of non-A non-B hepatitis; that the antibody tests available from 1991 probably indicated exposure to the virus; and that most patients who had received blood products before 1985 would have a positive test result (as previously observed for hepatitis B in the 1970s). As with other routine blood tests (including liver function tests and hepatitis B tests), verbal informed consent was obtained. UKHCDO and Haemophilia Centre directors were advised by their medical defence societies in 1990 that hepatitis C testing could be undertaken on the same basis as other liver function tests (i.e. HIV type counselling was not necessary) (see Annex 16 of the Collective Response).

The first tests for hepatitis C antibody (available in NHS Scotland from 1991) were unreliable, and were replaced by the more specific RIBA-2 test in 1992. All patients who had received blood products attending the Haemophilia Centre were tested with the RIBA-2 test from 1992. From about 1994, testing for carriage of the hepatitis C virus (PCR viral tests) became available in NHS Scotland, and was routinely performed in all patients attending the Haemophilia Centre who had received blood products.

(5c) THE INFORMATION GIVEN TO PATIENTS WHO MIGHT HAVE BEEN INFECTED, OR WHO WERE FOUND TO BE INFECTED, AND THEIR FAMILIES

(1) What was their practice in relation to telling their patients of an anti-HCV positive test? Did they inform their patients immediately upon receiving their results? If not, why not? What arrangements were made for patients to be told of positive test results?

Patients with positive (or negative) anti-HCV positive tests were informed of their test results at their next clinic review. It was not appropriate to inform patients immediately, as no immediate action was required, but rather at a clinic, in a private room where the implications of positive (or negative) tests could be fully discussed and patients' questions answered, within the available emerging knowledge about HCV and HCV tests. At the clinic, patients' previous case records and treatment

records were available and could be reviewed to answer the frequently-asked question; when might they have been first exposed to the HCV virus (which would usually have been their first treatment with clotting factor concentrate).

(2) What did they tell their patients about the implications of HCV?

Patients with positive hepatitis C antibody tests were informed that they had probably (given that the initial tests were unreliable) been previously exposed to the hepatitis C virus through treatment with blood or blood products – most likely their first treatment with clotting factor concentrate, or their first several treatments with cryoprecipitate/fresh frozen plasma. They were informed that, as with hepatitis B, positive antibody tests were common in patients treated with blood products, but did not necessarily mean that the patient was a chronic carrier of the hepatitis C virus, or that they would develop chronic liver disease. They were advised that further tests, including hepatitis C PCR tests and serial liver-function tests would be required for this purpose. They were advised to avoid excessive alcohol consumption.

Patients with positive hepatitis C PCR tests were informed that they were probably chronic carriers of the hepatitis C virus, and had a risk of developing chronic liver disease (cirrhosis or cancer). They were advised to continue to attend the Haemophilia Centre for regular clinical review and blood liver function tests, for detection of these complications. They were advised to avoid excessive alcohol consumption.

Patients were advised that there was emerging evidence that hepatitis C could be transmitted sexually, although this appeared uncommon, and that they should continue to practice safe sex (e.g. use of condoms), as advised since 1985. They were advised to discuss this risk with sexual partners, who should be advised that hepatitis C testing could be performed (e.g. by their general practitioner, at an infectious disease or sexually transmitted disease clinic, or if they preferred at the Haemophilia Centre).

Patients were also informed that the antiviral drug interferon was being evaluated in clinical trials for treatment of hepatitis C; and that liver transplantation was a possible treatment for serious liver disease. They were advised that in due course they would be referred to a liver clinic for monitoring of hepatitis C and discussion of possible future treatments.

Patients were given current educational information leaflets published by the UK Haemophilia Society and/or the British Liver Trust, which reinforced the above advice, and included current estimates of the risk of complications. An example from 1993 is included in Annex 3 of the Collective Response.

The UKHCDO's first guideline on hepatitis C was published in 1995 (Annex 14 of the Collective Response). By that time it is my recollection that its recommendations had generally been followed in Glasgow Royal Infirmary, including referral to the Glasgow liver clinics of all carriers of hepatitis C for management by consultant hepatologists. (Dr. John Mackenzie, Dr. John Morris). A hepatitis C nurse specialist (Sister Margaret Neilson) was appointed about 1995 and attended the Haemophilia Clinic to give further information to all patients about hepatitis C and its management. Patients co-infected with HIV had their hepatitis C testing and management performed by the consultants in infectious disease who were already managing their HIV (Dr. Alan Pithie, Dr. Andrew Seaton) at Ruchill Hospital, then at Gartnavel General Hospital.

(3) Were there any written guidelines or policies on communicating positive results to patients produced by their unit at this time?

I do not recall any written guidelines or policies before the UKHCDO guideline on hepatitis C was issued in 1995. However, the above policy was fully discussed by Dr. Walker and myself with our medical and nursing colleagues.

(6) Were there any written guidelines or policies on HCV tests produced by their unit at this time?

I do not recall any written guidelines or policies. However, the above policy was fully discussed by Dr. Walker and myself with our medical and our nursing colleagues.

Gordon Lowe
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