

Exhibit 1

A THP

MANCHESTER AREA HEALTH AUTHORITY
(TE)

1571198

HOSI

STICK
AT BOT

11 M5

1/10/89

ATTACH TO CASE NOTES.

11198

27M

14/92

CASE NOTES.

Antibody Screening: NEGATIVE.

Name	Hospital	Hospital No.
RONAN	MRI	GRO-C
First Name	Ward	Consultant
PATRICIA	HAEM	GSL
D.O.B.	Sex	Report Date
GRO-C 49	F	5.08.93

GRO-C

Specimen VB Lab. No. S93_17884 Date Rec'd 29.07.93

Virus	Test	Result
Hepatitis C ANTIBODY	(ELISA)	POSITIVE

GRO-C

North Manchester Regional Virus Laboratory, 061-741-5200

Booth Hall Childrens Hospital Manchester, M9 2AA. **VIROLOGY**

North Manchester Regional Virus Laboratory, 061-741-5200

Booth Hall Childrens Hospital Manchester, M9 2AA. **VIROLOGY**

North Manchester Regional Virus Laboratory, 061-741-5200

Booth Hall Childrens Hospital Manchester, M9 2AA. **VIROLOGY**Booth Hall Childrens Hospital Manchester, M9 2AA. **VIROLOGY**

Informed by letter	HTLV-3 antibody	Negative
	Consultant Virologists: MAURICE LONGSON & S	GRO-C
North Manchester Regional Virus Laboratory, 061-795 2200/MRI 71523		MOND

VIROLOGY 1

WITN3289031_0002

GSL/KJ/57/1198

6th June 1994
(clinic 25.5.94)

Dr M Sultan
Lower Broughton Health Centre
Great Clowes Street
Salford
Lancs

Dear Dr Sultan

RE: Patricia Ronan DOB: GRO-C 1949

GRO-C

I saw your patient with sever von Willebrands disease in the Haemophilia Centre on 25 May 1994. She remains well and has had no bleeds now for nearly a year. She is on oral contraceptive. She has no indigestion. She has a stiff right ankle, presumably the result of bleeds into this joint.

I told her that there was serological evidence of past infection by hepatitis C. (This is as a result of previous exposure to the virus as a result of treatment before 1985 with "non-heat treated" factor VIII. She knows that her liver function tests are borderline abnormal, suggesting chronic infection, although she has no symptoms attributable to this. She was understandably concerned to hear this, but appreciates no treatment is currently indicated and that we propose to monitor her liver function tests every 6 months.

Yours sincerely

Dr G S Lucas
ACTING HAEMOPHILIA DIRECTOR

MB/KJ/57/1198

8th June 1994

Dr M Sulton
Lower Broughton Health Centre
Great Clowes Street
Salford
Lancs

Dear Dr Sulton

RE: Patricia Ronan DOB: GRO-C 1949
GRO-C

I am writing to inform you of the following blood test results obtained on your patient.

Hepatitis A - Your patient is immune to this infection and does not require vaccination or immunoglobulin for foreign travel.

Hepatitis B - Your patient is immune to hepatitis B due to vaccination. She will require testing approximately 5 years after vaccination and thereafter yearly to check he is maintaining his immunity. Her next blood test is due in 1998.

Hepatitis C - Your patient is hepatitis C positive by a second generation test. This means she is probably a chronic carrier of hepatitis C. There is a slight risk of transmitting the infection through blood, and possibly semen. Hepatitis C carrier state confers an increased risk of long term liver disease such as chronic active hepatitis, cirrhosis or hepatoma, over a time span of 20+ years. Those most at risk seem to have a higher than average alcohol intake.

Liver enzyme results on your patient are mildly elevated. If drinking alcohol she should reduce her intake to decrease the risk of chronic liver disease.

If you require more detailed information on these results please

contact the Haemophilia Centre on 061-276-4810.

Yours sincerely

Dr M Bolton
CLINICAL ASSISTANT

CRMH/VLW/57/1198

8 January 1996
(Clinic Date: 4 January 1996)

Dr M Sulton
Lower Broughton Health Centre
Great Clowes Street
SALFORD
Manchester
M7 9RN

Dear Dr Sulton

Re: Patricia Ronan - DOB: GRO-C 1949

GRO-C

DIAGNOSIS: Severe Von Willebrand's Disease (Type III)
Chronic Hepatitis C

I saw Mrs Ronan today. She has no significant bleeding problems. Her menorrhagia is well controlled using the oral contraceptive.

She has chronic Hepatitis C with consistently mildly abnormal transaminases. This has been causing her a great deal of worry in recent months, partly because of this issue in the media. I feel sure that she is a candidate for Interferon treatment which we have discussed at length today and she is keen to try this. I will review her in 3 months time with a view to starting it. In the meantime, we will ask her Health Authority for permission to pay since we do not have a separate budget for Interferon.

Yours sincerely

Dr C R M Hay
Consultant Haematologist
Director Manchester Haemophilia Comprehensive Care Centre

CRMH/VLW/CLINICS/57/1198

12 April 1996
(Clinic Date: 4 April 1996)

Dr M Sulton
Lower Broughton Health Centre
Great Clowes Street
SALFORD
Manchester
M7 9RN

Dear Dr Sulton

Re: Patricia Ronan - DOB: GRO-C 1949

GRO-C

DIAGNOSIS: Type III Von Willebrand's Disease
Hepatitis C

This lady with modestly elevated LFT's came for review today. We have started her on Interferon - 3 megaunits 3 times a week and have warned her about the side effects. We will review her in 6 weeks time.

I have also arranged binding studies on her because she is almost certainly not a true type III but a compound heterozygote and may have the Normandy Von Willebrand variant.

Yours sincerely

Dr C R M Hay
Consultant Haematologist
Director Manchester Haemophilia Comprehensive Care Centre

CRMH/VLW/CLINICS/57/1198

7 November 1996
(Clinic Date: 7 November 1996)

Dr M Sultan
Lower Broughton Health Centre
Great Clowes Street
SALFORD
Manchester
M7 9RN

Dear Dr Sultan

Re: Patricia Ronan - DOB: GRO-C 1949

GRO-C

DIAGNOSIS: Von Willebrand's Disease
Hepatitis C

Mrs Ronan is not responding to Interferon. Her liver function tests were abnormal on the last 2 occasions. She is very keen to persist, however, and so I have increased the dose to 6 megaunits 3 times a week.

We will review her LFT's and will review her in 4 weeks and, if there is no immediate response, give up.

Yours sincerely

Dr C R M Hay
Consultant Haematologist
Director Manchester Haemophilia Comprehensive Care Centre

MJB/GA

Dr M Sultan
Lower Broughton Health Centre
Great Clowes Street
Salford
Manchester M7 9RN

9 April 1997

Dear Dr Sultan

Re: Patricia Ronan D.O.B. GRO-C/1949
Severe Von Willebrand's Disease, Hepatitis C Positive

Pat had a very unfortunate episode over Christmas when she was attending casualty for treatment to a nosebleed. Unfortunately despite showing her green card, the seriousness of her bleeding disorder was not appreciated and she was not given heparin in sufficient quantity until her fourth attendance. It is very difficult to know how to prevent such occurrences as the house officer involved had consulted with senior haematology staff who themselves unfortunately were moderately inexperienced in haemophilia treatment. However this only serves to emphasise the impossibility of Pat trying to get treatment anywhere other than MRI. As she still has a small blood clot in the right Little's area I have continued her on tranexamic acid 1g tds for a further week so there is a high chance still of re-bleeding.

Pat's liver function tests are showing some improvement, the ALT on 30 December 1996 being 56 units per litre. I am checking Pat's Hepatitis C PCR RMA today. If this is negative it is worth continuing treatment, but if she's still positive I really think she should stop and await further developments in Hepatitis C treatment in the future. I've arranged to see her in 4 weeks time.

Yours sincerely

Dr M J Bolton
Department of Clinical Haematology

CRMH/KJ/clinics/1999/feb03.doc/57/1198
10 February 1999
(dictated/clinic visit 3/2/99)

Dr M Sultan
Lower Brought Health Centre
Great Clowes Street
Salford
M7 1RD

57-01198

Dear Dr Sultan

Patricia Ronan dob: GRO-C 1949

GRO-C

Diagnosis: Type III von Willebrand's Disease

Patricia is very well. Her menorrhagia is well controlled by the oral contraceptive which continues. There are two other active problems at the present time.

Her first problem is pain in her right ankle. She works as a sewing machinist and so uses this right foot quite a bit to control the foot pedal of her machine. She apparently specialises in the tiny stretchy things people wear to go to discos! She has pain on walking and has to take Co-dydramol to control the pain. On examination there is actually very little movement in the ankle joint itself, there is some bony swelling. The other ankle looks normal, I think she has haemophilic arthropathy in this joint and might benefit from fixation. It is also possible that there might be a loose body because she definitely describes locking and sometimes it goes click and either seizes up or releases. I have arranged some fresh x-rays of her ankles and will review her in the next joint orthopaedic clinic.

The other problem is her hepatitis C. She had a more than adequate trial of Alpha Interferon in doses ranging up to 6 mega units 3 times a week which continued for at least 9 months back in 1996/97. Her LFTs did improve, but she remained persistently hepatitis C RNA positive. I have today discussed with her the possibility of trying Interferon again, this time combined with Ribivarin, which would improve her chances of responding. She is very receptive to this,

Consultants: Dr J A Liu Yin, Dr G S Lucas, Dr C R M Hay, Dr C R Shiach
Top Grade Clinical Scientist: Dr K Hyde (Email: KHYDE@)

Associate Specialist: Dr K I Cinkotai

GRO-C



Awarded for excellence



Investor in People

NHS

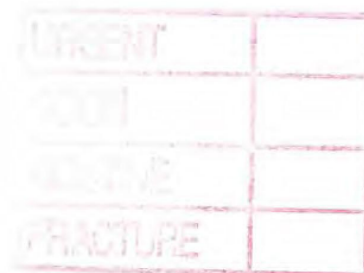
not least because she tolerated the Interferon very well, even in double dosage. I have explained the side-effects of Ribivarin to her briefly and will discuss it again with her when we see her in the joint orthopaedic clinic. She would of course have to come and see us fairly frequently to start with for checks of her blood count, since Ribivarin can cause haemolytic anaemia.

Yours sincerely

GRO-C

Dr CRM Hay
Director, Manchester Haemophilia Comprehensive Care Centre
Honorary Senior Lecturer in Medicine

Mr P Hirst
Consultant Orthopaedic Surgeon
Fracture Clinic
Phase II
Manchester Royal Infirmary



Consultants: Dr J A Liu Yin, Dr G S Lucas, Dr C R M Hay, Dr C R Shiach

Associate Specialist: Dr K I Cinkotai

Top Grade Clinical Scientist: Dr K Hyde (Email: KHYDE@

GRO-C



Awarded for excellence



Investor in People



MB/CW/M57/1198

Date: 26th November 1999
Clinic: 25th November 1999

Dr M Sultan
Lower Broughton Health Centre
Great Clowes Street
Salford
M7 9RN

Dear Dr Sultan

Re: PATRICIA BOLTON GRO-C 49

GRO-C

Diagnosis: Type II von Willebrand's disease

Patricia was worried today because of palpitations, which sounded innocuous, and passing blood PR. She takes Co-dydramol for relief of pain in her ankle, but says she is not constipated. However, she does have piles so I have given her Lactulose to encourage her to aim for a looser bowel motion. If the bleeding continues or worsens she will attend the haemophilia centre for further examination. I changed her pain relief to dihydrocodeine continus 1bd as she suffers pain during the night and when getting out of bed in the morning, she is on the waiting list for an ankle arthrodesis.

I have checked Pat's liver function tests today, we discussed Hepatitis C again, she seems to have a moderate alcohol intake, but this is probably a bit excessive in view of her Hepatitis C infection (a glass of wine and some other alcohol most nights). I suggested she cuts back quite sharply and we will see if this has any effect on her liver function tests.

Pat is not keen to try Interferon and Ribavirin treatment and we have become less enthusiastic since in a small series of our own patients very few responded to this treatment.

We will therefore see her again in 6 months time.

Yours sincerely

Dr M Bolton
Clinical Assistant

Manchester Haemophilia Comprehensive Care Centre
Department of Clinical Haematology

Manchester Royal Infirmary
Oxford Road Manchester M13 9WL
Fax: 0161-276 4814

Ref: CRMH/LD/M57/1198
Date: 21 June 2000
Clinic date : 7 June 2000

Dr M. Sultan
Lower Broughton Health Centre
Great Clowes Street
Salford
M7 1RD

Dear Dr Sultan,

Re: Patricia Ronan dob: GRO-C49
GRO-C

Diagnosis: Type A von Willebrand's Disease
Hepatitis C


I saw this lady for review today. She is on the waiting list to have her ankle arthrodesed and clearly is getting quite a lot of pain from it. I am sure she will be much better once she has been operated on. We treated her hepatitis C with Interferon. This was unsuccessful, despite increasing the dose. Our experience would suggest that we are likely to have no success with Interferon combined with Ribavirin in such patients. Fortunately, her LFT's are intermittently abnormal, a biochemical pattern that has been associated with a good prognosis. We have agreed, therefore, just to keep liver under periodic review. She has no other problems at the present time. We have checked her LFT's today and we will review her in 6 months.

Yours sincerely,

Dr CRM Hay
Director, Manchester Haemophilia Comprehensive Care Centre
Honorary Senior Lecturer in Medicine

Consultants: Dr C R M Hay, Dr C R Shiach **Clinical Assistant :** Dr M.J. Bolton
Haemophilia Nurses : Sister Lorraine Birtwistle, Sister Paula Mohn, Sister Meg Openshaw (Counsellor) **Dentist :** Mrs Wilson

Secretary to Dr Hay : Ms Kim Jones

 GRO-C
E-mail : kimj@ GRO-C

Secretary to Dr Shiach : Ms Lynne Dewhurst

 GRO-C
E-mail : lynned@ GRO-C

C:\My Documents\Patient's\Patricia Ronan.doc

Manchester Haemophilia Comprehensive Care Centre
Department of Clinical Haematology

Manchester Royal Infirmary
Oxford Road Manchester M13 9WL
Fax: 0161-276 4814

Dr Charles RM Hay

E-mail : haemophilia@man.ac.uk

Secretary Ms Kim Jones - ☎ 0161 276 4812

E-mail : kimj@ [redacted] GRO-C

Ref: CRMH/JE/M89/03394 : Clinic date: 11/04/01
Date: 25th April 2001.

Dr M Sultan
Lower Broughton Health Centre
Great Clowes Street
SALFORD M7 1RD

Dear Dr Sultan,

Re: Patricia RONAN d.o.b. [redacted] GRO-C 49

[redacted] GRO-C

Diagnosis: 1. Type 3 von Willebrand's Disease.
2. Hepatitis C.

I saw Mrs Ronan today with her husband. She has recently had an ankle arthrodesis and already the pain is very much better than it was. When it settles, she should be pain-free. She is wearing a light walking plaster, which she will continue to wear for the next 5 weeks or so.

When she was in hospital, we discussed the possibility of treatment for her Hepatitis C using a combination of Ribavarin and Pegylated Interferon. We sent her away to think about this, and we discussed it again today. She previously failed to respond to ordinary Interferon, but the response rate to Pegylated Interferon is much better.

Today we have started her on Ribavarin 1 gram a day and PEG Interferon 0.45 mls of 1,200 mcg/ml. (based on her body weight of 75 kilos and making an allowance for the weight of her plaster). We will review her in one week's time.

We did her Hepatitis C genotype while she was in but the result is not back yet. I would anticipate that she will be genotype 1A or 1B.

Yours sincerely,

Dr CRM Hay

Director, Manchester Haemophilia Comprehensive Care Centre
Honorary Senior Lecturer in Medicine

Ms Lynne Dewhurst
Secretary to Dr Caroline R Shiach

Manchester Haemophilia Comprehensive Care Centre
Department of Clinical Haematology
Manchester Royal Infirmary
Oxford Road Manchester M13 9WL

Telephone: GRO-C

Fax: 0161 276 4814

E-mail: lynned@GRO-C

Ref: JR/LD/M57/1198
Wednesday, 13 June 2001

Clinic Date : 29th May 2001

REFERRAL

Dr Alistair J Makin
Consultant Gastroenterologist
Department of Gastroenterology
Manchester Royal Infirmary

Dear Dr Makin,

Re: Patricia Ronan dob: GRO-C/1949
GRO-C

Diagnosis: Severe von Willebrand's disease

I would be very grateful if you could arrange a colonoscopy as a day case appointment for this woman with von Willebrand's disease and hepatitis C.

She has recently been commenced on Pegylated Interferon and Ribavirin for the treatment of her hepatitis C and we have been checking her full blood counts weekly. Unfortunately, two weeks ago her haemoglobin dropped from a base line of 13 g/dl down to 7.8 g/dl. This could be partly due to the Ribavirin medication, however, she was also complaining of passing black, offensive smelling stools and was known to have previous duodenal erosions. She underwent upper GI endoscopy on 23rd May, which was in fact entirely normal. She is currently haemodynamically stable and her haemoglobin has increased to 12 g/dl. At the time of the OGD a lower GI investigation was recommended and so I would be very grateful if you could put her on the out patient list for a colonoscopy. Many thanks for your help.

Yours sincerely,

Dr Jane Robertson
Specialist Registrar in Haematology

Dr Charles R M Hay
Director & Consultant Haematologist

Ms Kim Jones
Secretary to Dr Hay

Telephone: GRO-C

Fax: 0161 276 4814

E-mail: kjones@GRO-C

Manchester Haemophilia Comprehensive Care Centre
Department of Clinical Haematology
Manchester Royal Infirmary
Oxford Road Manchester M13 9WL

Ref: LD/M57/01198
NHS No. 452 884 7086
Date: 18 July 2001

Clinic Date 17th July 2001

Dr M Sultan
Lower Broughton
Health Centre
Great Clowes Street
Salford
M7 1RD

Dear Dr Sultan,

Re: Mrs Patricia Ronan dob: GRO-C 1949

GRO-C

Diagnosis: von Willebrand's disease
Hepatis C
On Peg Interferon and Ribavirin

Mrs Ronan has been tolerating her treatment quite well symptomatically but it has unfortunately caused quite severe neutropenia. This has necessitated a progressive reduction in the dose of Peg Interferon so we reduced her to 0.25 mls of the 160 µg/ml formulation last week. Since doing this, her neutrophil count has picked up from $0.59 \times 10^9/l$ to $1.13 \times 10^9/l$. She takes 400 mg of Ribavirin a day. I will review her in a further week in view of her neutropenia but if it remains stable the review interval will lengthen. She seems unusually susceptible to this particular side effect.

Yours sincerely,

Dr CRM Hay
Director, Manchester Haemophilia Comprehensive Care Centre
Honorary Senior Lecturer in Medicine

Dr Charles R M Hay
Director & Consultant Haematologist

Ms Kim Jones
Secretary to Dr Hay

Telephone: GRO-C
Fax: 0161 276 4814
E-mail: kjones@ GRO-C

Manchester Haemophilia Comprehensive Care Centre
Department of Clinical Haematology
Manchester Royal Infirmary
Oxford Road Manchester M13 9WL

Ref: LD/M57/01198
NHS No. 452 884 7086
Date: 4 October 2001

Clinic Date 24th September 2001

Dr M Sultan
Lower Broughton
Health Centre
Great Clowes Street
Salford
M7 1RD

Dear Dr Sultan,

Re: Mrs Patricia Ronan dob: GRO-C 1949
GRO-C

I reviewed this patient with type 3 von Willebrand's disease in the Haematology Department. She was recently admitted with upper GI bleed. The exact site and cause of bleeding was not found on either endoscopy or angiogram, though she did have some duodenal erosion on OGD. Her bleeding eventually stopped with aggressive platelet support and Haemate P infusion. She has had no bleeding since her discharge on 17th September and her blood count remains stable. She is not keen to carry on taking Peg Interferon and Ribavirin and this has been stopped. Currently, her platelet count has increased to $236 \times 10^9/l$, haemoglobin 11.4 g/dl and white cell $3.56 \times 10^9/l$ today (24/9/01).

Yours sincerely,

Dr Lian Lee
Specialist Registrar in Haematology

Manchester Haemophilia Comprehensive Care Centre
Department of Clinical Haematology
Cobbett House
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL

PA to Dr CRM Hay:- Ms Kim Jones

Direct phone / fax nos:- 0161 276 4812 / 8085

email: kim.jones@ GRO-C

Our ref: CRMH/ke/M57/01198
NHS No: 4528847086

MedisecNET ref: GRO-C

Dictated: 18 September 04
Typed: 18 September 04

Mrs Patricia Ronan

GRO-C

Dear Mrs Ronan

RE: Variant Creutzfeld Jacob Disease (vCJD)

"If you have problems reading or understanding English then please contact our Translation and Interpretation service on 0161 276 6342".

We have been asked to send the enclosed standard letter and patient information leaflet from The Department of Health, on 20/9/04, to **all patients with bleeding disorders** even if they have never been treated with blood or clotting factor concentrates made from UK plasma. This letter and information sheet are long and potentially confusing and so we are also writing to you to emphasise one or two points and to put the issue into perspective.

This letter and information sheet explains that some patients who have been treated with clotting factor concentrates manufactured from British plasma in the nineteen eighties and nineties may have been exposed to the vCJD agent and may have a slightly increased risk of passing on the vCJD protein to others in certain very specific circumstances. These include blood donation, tissue transplant donation and certain types of surgery such as eye surgery, neurosurgery and lymphoid surgery. It is important that affected patients and their carers are aware of this so that they do not inadvertently pass on vCJD protein to anyone else. It does not mean that the affected patients have or will develop vCJD themselves. It should be emphasised that during the 20 year period of theoretical risk, that no patients with bleeding disorders have developed vCJD and it is also now clear that fewer and fewer cases are being seen in the general population.

In the letter sent to you, you will have read that if you have been treated with an implicated blood product that there is an estimated extra 1% "public health risk" of you being able to pass on the abnormal vCJD protein to others and that this can only happen under unusual circumstances and not in normal everyday life. There are no recorded instances of patients with vCJD passing the condition on to any family members. To understand why this does not mean that you have a 1% risk of getting vCJD, it is necessary to understand a little bit about the condition.

Dr Charles RM Hay - Director, Manchester Haemophilia Comprehensive Care Centre, Honorary Senior Lecturer in Medicine

vCJD is caused by an abnormal cow "prion" protein getting into the body. This protein causes BSE or "mad cow disease" and is different from the abnormal human prion protein which causes the human equivalent disease, classical Creutzfeldt Jakob disease. In almost all cases reported so far this happened because the abnormal proteins were present in our food. Between 1980 and 1996 all of us in the UK were exposed to the vCJD protein when we ate meat or meat products. Despite the fact that we all ate the vCJD proteins over and over again, so far only 147 people in the UK had developed vCJD. Furthermore, rather than increasing, the number of new cases is getting smaller. New cases peaked in 2000 with 28 new cases reported in the year but there have been only 4 new cases this year so far. So, even though the entire population has been exposed to vCJD for over 15 years, only a tiny proportion have developed the disease. This lack of large numbers of cases and reducing number of new cases suggests that it is unlikely that many of us will ever be affected by vCJD. So coming into contact with the abnormal protein does not mean that a person will get the illness. In fact the chance of developing vCJD appears to be very small indeed.

Even though the abnormal prion protein rarely appears to cause problems in humans, it does not go away and may stay in our bodies for ever. However for an unfortunate small minority the protein multiplies, damages the nervous system and causes vCJD. No one knows why this happens but the process usually takes at least 5 to 10 years or more.

Nine of the 147 unfortunate people who developed vCJD were blood donors before they became ill. Two patients have now been reported to develop signs of vCJD following whole blood transfusion from these donors. This shows that vCJD can be transmitted from patient to patient by blood transfusion. The risk of developing vCJD from clotting factor concentrates is thought to be very much smaller than from transfusion of blood from an affected donor. Now that vCJD prion proteins have been eliminated from our food, the only way that vCJD can get into our bodies is by coming into direct contact with prions from an affected person, for example by blood transfusion or tissue transplantation. This is why the Department of Health have notified you about the possibility of having come into contact with vCJD prions from blood products made from British Plasma.

In just the same way as hardly any of us have developed vCJD from the food that we ate, it is very unlikely that you will develop vCJD from these blood products. Because the vCJD protein stays in our bodies, there is a very small risk that you could unwittingly pass the vCJD protein to someone else. This is why the information you have been sent lets you know that you have a "1% public health risk" of passing the protein on to someone else in certain narrow circumstances. This is not a "1%" risk of developing the disease but 1 in 100 risk of passing the protein on to another person under certain circumstances unless simple precautions are taken to prevent it. It is important that you, your immediate family, your GP and hospital doctors know whether you are considered to be of this small risk to others. This is to ensure that the correct measures can be taken to prevent unwitting spread of vCJD prions to someone else. The risk of passing the condition on to family members is negligible.

Please return the form at the end of the letter to me to indicate that you have received it. Some batches of British plasma products contain donations from patients who developed vCJD. Fill in the form to tell us if you wish to be informed whether or not you have been treated with a batch of concentrate from a batch which included a donation from a donor who developed vCJD. We have enclosed a stamped addressed envelope that you can use for this.

Should you wish for further information, please call the helpline on 0161 220 5581, Monday to Friday (inc.) 8am to 8pm, Saturday and Sunday 8am to 1pm. Do not use the Haemophilia Centre number, since this must remain open for normal clinical enquiries.

We will endeavour to see everyone personally over the next few weeks, but since we have been asked by DoH to write to patients with bleeding disorders of all types (most of whom are not implicated), we unfortunately cannot give priority appointments.

Yours sincerely

GRO-C

Dr CRM Hay
Director, Manchester Haemophilia
Comprehensive Care Centre
Honorary Senior Lecturer in Medicine

Yours sincerely

GRO-C

Dr P Bolton-Maggs
Manchester Haemophilia Comprehensive Care Centre
Consultant Haematologist

DRAFT
[Patient name]
[Address]

20th September 2004

IMPORTANT INFORMATION

Dear [insert name]

Variant Creutzfeldt-Jakob Disease (vCJD) and Plasma Products

This letter is being sent out to all patients and the parents of children with haemophilia, other bleeding disorders and congenital antithrombin III deficiency. It gives new information about certain plasma products available between 1980 and 2001, the possible risk of vCJD and the need for precautionary health care measures following certain medical procedures and surgical operations.

This information does NOT affect ALL patients.

- **PATIENTS AFFECTED** by this information are those with haemophilia, other bleeding disorders or congenital antithrombin III deficiency who received treatment between 1980 and 2001 with clotting factors or antithrombin manufactured by the UK Bio Products Laboratory (BPL) or the Protein Fractionation Centre (PFC) of the Scottish National Blood Transfusion Service (SNBTS) using plasma pools sourced from the UK. These include concentrates of factor VIII, factor IX, factor VII, factor XI, factor XIII and prothrombin complexes as well as antithrombin.
- **PATIENTS NOT AFFECTED** by this information are those who have only ever received recombinant products, DDAVP (desmopressin), clotting factors or antithrombin made with non-UK sourced plasma, or who have never been treated.

If you have ever received a blood transfusion or immunoglobulin this is treated differently and is not covered in this letter.

We realise this information creates uncertainty and may cause you concern.

It is important for everyone to read the rest of this letter and the enclosed 'Information for Patients' that has been prepared to help you understand this changing situation.

What has happened?

You may be aware of product recalls in 1997, 1999 and 2000 when donors who provided plasma used to make clotting factors or antithrombin were subsequently found to have vCJD. These previous notifications involved products made by the Bio Products Laboratory in England and the Scottish National Blood Transfusion Service. You may have been informed at the time.

We are writing to you now to give you further information about these and about further batches of clotting factors or antithrombin that have been made using plasma from donors who later developed vCJD; what action is being taken; and to offer you the opportunity to discuss this with us. None of these batches are now in use.

Who is looking into this?

The CJD Incidents Panel (the Panel) is an expert committee set up by the UK Chief Medical Officers to advise on incidents of possible transmission of CJD through medical procedures. These include treatment with blood or plasma products. When people are diagnosed with vCJD, any blood donations they have given are traced. The Panel has reviewed in detail all batches of plasma products known to date to have been made using plasma from donors who later developed vCJD. We refer to these below as 'implicated' products and batches.

What is the risk from these implicated products?

The Panel has used scientific evidence and expert opinion, together with information from the plasma product manufacturers, to examine the possible risks to health from having received implicated plasma products. This risk is on top of the general risk from eating beef and beef products that may have been contaminated by the agent causing Bovine Spongiform Encephalopathy (BSE or 'mad-cow disease').

The potential additional risk to health depends on the type of plasma product and how each batch was manufactured.

For most batches of implicated products the potential additional risk is so low as to be considered negligible. For example some batches of factor VIII, where only the albumin (which is used to stabilise factor VIII in the vial) has been sourced from a donor with vCJD, are extremely low risk. However, batches of factor VIII where the clotting factor (and not the albumin) has been sourced from a donor with vCJD, and other implicated products, which include factor IX and antithrombin, carry a higher risk.

What does this mean?

The potential additional risk of actually developing vCJD from receiving any implicated plasma product, on top of the general risk from eating beef, is unknown, but the chances of it happening are likely to be very low.

Some patients who have received certain implicated products do, however, have a greater chance of passing the agent that causes vCJD to others through surgical operations and some other medical procedures. For public health purposes steps need to be taken to prevent spread this way.

Unfortunately, it is likely that further cases of vCJD will occur in people who previously donated blood. This means that more batches of UK-sourced plasma products may be implicated in the future.

Who is affected?

It is likely that special public health precautions will need to be taken for many patients with bleeding disorders or congenital antithrombin III deficiency, because they will have received clotting factors or antithrombin that either are currently implicated (which include particular batches of factor VIII, factor IX and antithrombin) or that may be implicated at a later date. Therefore, **ALL patients with bleeding disorders or congenital antithrombin III deficiency¹ who have received clotting factors or antithrombin derived from UK-sourced plasma² between 1980 and 2001 are considered 'at-risk' of vCJD for public health purposes.**

This time period of 1980 to 2001 has been chosen as the most cautious: it runs from when BSE is thought to have entered the human food chain to the last possible expiry date of any product manufactured in the UK that was sourced from UK donors until 1998. Since 1998, plasma for manufacturing plasma products has been imported from the United States.

Am I 'at-risk' of vCJD for public health purposes?

If you have received any UK-sourced plasma derived clotting factors or antithrombin between 1980 and 2001, even if you have not received a currently implicated batch, you are 'at-risk' of vCJD for public health purposes.

If you are not sure whether you [your child] have [has] received UK-sourced plasma derived clotting factors or antithrombin between 1980 and 2001, and therefore whether you [your child] are [is] 'at-risk' of vCJD for public health

¹ congenital and acquired haemophilia (Haemophilia A and Haemophilia B), Von Willebrand Disease, other congenital bleeding disorders and congenital antithrombin III deficiency.

² factor VIII, factor IX, factor VII, factor XI, factor XIII and prothrombin complexes, as well as antithrombin.

purposes, please contact your Haemophilia Centre. You can do this using the reply form at the end of this letter.

What special precautions should I take?

If you are 'at-risk' of vCJD for public health purposes:

- you should not donate blood,
- you should not donate organs or tissues,
- you should tell whoever is treating you before you undergo medical, surgical or dental treatment, so that they arrange any special procedures for the instruments used in your care.
- It would be best if you tell your family about this in case you might need emergency surgery in the future.

If you are 'at-risk' of vCJD for public health purposes then a note of this will be made in your hospital medical records and will be recorded on the National Haemophilia Database. We will also tell your GP of your 'at-risk' status who will record this in your GP medical notes.

Does this affect my care?

If you are 'at-risk' of vCJD for public health purposes, your clinical care should not be compromised in any way. Healthcare professionals need to know you are 'at-risk' so that if any surgical instruments are used in your care they can be treated differently.

How does this affect my family?

If you are 'at-risk' of vCJD for public health purposes you do not need to take any special precautions in normal life. There is **NO** evidence that vCJD can be passed on between people by:

- living in the same house,
- sharing utensils,
- kissing,
- sexual contact,
- from mother to baby through childbirth or breastfeeding.

Can I find out if I have been treated with an implicated batch?

We are currently checking our patients' records to determine who was treated with UK-sourced clotting factors or antithrombin between 1980 and 2001, which of them have received implicated batches and the extent of their exposure. We will record this in patients' hospital medical notes.

If you would like to find out whether you [your child] have [has] received any of the implicated batches, or you wish to discuss this further with us, please indicate this on the reply sheet. We expect the process of identifying who has received those batches to take some time, as it may involve hand-searching records from many years ago, and liaising with other Centres. We are sorry for this unavoidable delay. We will arrange an appointment for you once we have the information.

If you do not wish to find out whether you [your child] have [has] received one of the implicated batches, please be aware that this information needs to be recorded in the hospital notes. Despite our best intentions, it is possible that this information may become apparent to you [your child] inadvertently, when, for example, looking at your [your child's] medical records.

Whether or not you have received any of the implicated batches or choose to discuss this with us should **NOT** affect your care, as the same special precautions will be taken for **ALL** patients with bleeding disorders or congenital antithrombin III deficiency who received UK-sourced clotting factors or antithrombin between 1980 and 2001.

How can I decide whether to find out if I have received implicated products?

At present there is no known case of a patient with haemophilia developing vCJD through treatment with blood products. There is no diagnostic blood test for vCJD and there is no treatment or cure for this condition. In addition, the same special precautions will be taken for **ALL** patients who have received UK-sourced plasma derived clotting factors or antithrombin between 1980 and 2001, whether or not they have received an implicated batch.

In the light of the above, you may wish to consider carefully whether or not you wish to know if you have received any of the implicated batches.

How can I find out more?

I enclose an information sheet about vCJD developed by the Health Protection Agency alongside the Scottish Centre for Infection and Environmental Health, clinicians' representatives and patients' groups, which I hope will go some way to answering your first questions.

I do appreciate that this information creates uncertainty that may worry and concern you. Do contact the Haemophilia Centre on [give telephone number] if you wish to talk about this.

Yours sincerely

[NAME]

Variant Creutzfeldt-Jakob Disease and Plasma Products Patient Reply Sheet

Name of patient/child*:

Date of birth:

National Registration Number (if known):

Telephone:

Address:

1. I would like confirmation of whether I/my child* received UK sourced plasma derived clotting factors or antithrombin between 1980 and 2001. These include: factor VIII, factor IX, factor VII, factor XI, factor XIII and prothrombin complexes as well as antithrombin.

IN PERSON / IN WRITING

2. I would like to know if I/my child* received an implicated batch.

YES/NO/DON'T KNOW

3. I would like to have a specific consultation with [the team] to discuss the implications of this issue. Please contact me to make an appointment.

YES/NO

4. I understand that my/my child's exposure to an implicated batch will be recorded in my/my child's hospital and GP notes, and on the National Haemophilia Database.

Signature _____

Date _____

Print name _____

Department of Clinical Haematology
Orange Zone, Cobbett House
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL

Mrs Tracy Hudd Tel: 0161 276 8090 Fax: 0161 276 8085 Email: tracy.hudd@GRO-C

Our ref: PBMA/tah/M57/01198 MedisecNET ref: GRO-C Clinic Date: 05 May 05
NHS No: 4528847086

Typed: 09 May 05

Dr M Sultan
Lower Broughton Health Centre
Great Clowes Street
Salford M7 1RD

Dear Dr Sultan

Re: Mrs Patricia RONAN - DOB GRO-C 1949

GRO-C

Diagnosis: Severe Type III vWD

I was pleased to review this 55 year old lady who has recently been free from trouble with her vWD. She has not had any treatment with blood products for some time. She told me she had been on iron tablets since her last visit but in fact at that time her Hb was normal as was her ferritin so she could now relax on this front. Her LFT's are nearly normal despite her chronic Hepatitis C infection. I know that she has been tried with Interferon and Ribavirin in the past but she could not tolerate it.

She and her husband have discussed Hepatitis C transmission and her husband is now keen to be screened for this and I have arranged this today.

She has been treated with NHS-sourced blood products in the past and therefore must be regarded as 'at risk' for the transmission of prion disease by surgery. We discussed this issue in as much detail as was necessary. She did not particularly want to think about this. There is no evidence to suggest that patients who have received British plasma products have themselves developed vCJD but the Health Protection Agency have decided that patients may transmit the agent at a slightly increased risk over the rest of us who have merely eaten infected beef (probably) in the last 20 years. It is important that Surgeons or Endoscopists in particular are aware that she is one of our 'at risk' patients.

I arranged for her to have her usual array of blood tests and will write to you and her with the results in due course when they are through.

With best wishes.
Yours sincerely

Dr P Bolton-Maggs
Consultant Haematologist

PA/Medical Secretary to Dr Paula Bolton-Maggs, Dr John Burthem & Dr Caroline R Shiach
Consultants: Dr P Bolton-Maggs, Dr J Burthem, Dr C R M Hay, Professor J A Lin Yn, Dr G Lucas, Dr K Ryan, Dr C R Shiach

Department of Clinical Haematology
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PA/Med. Sec. to Dr P Bolton-Maggs:- Miss Kim Jones Direct Phone / Fax:- 0161 276 4812 / 8085 E-Mail: kim.jones@ GRO-C

Our ref: CRMH/kj/M57/01198
NHS No: 4528847086

MedisecNET ref: GRO-C

Dictated: 19 February 09
Typed: 20 February 09

Mrs Patricia Ronan

GRO-C

Dear Mrs Ronan

Re: Transmission of Variant Creutzfeldt-Jakob Agent by British manufactured blood products during the period 1980 - 2001

We are sending you the enclosed information at the request of the Department of Health to provide you with further details of a patient who died in his seventies who was found at post-mortem examination, to have microscopic evidence of the agent thought to cause variant Creutzfeldt-Jakob Disease (vCJD) in his spleen but in no other part of his body. It is thought most likely that he had contracted this from FVIII concentrate treatment given eleven years before. The significance of this finding is unknown since the patient had no evidence of vCJD, died from an unrelated cause and since there are no cases of vCJD reported in patients with bleeding disorders at this point in time.

We are informing you of this at this time because, as previously notified, you were treated with British manufactured blood products during the period 1980 - 2001. This new information does not affect the way you will be treated.

If you have any questions about any of this information, please contact the Haemophilia Centre.

With best wishes

Yours sincerely

GRO-C

Dr CRM Hay
Director Haemophilia Comprehensive Care Centre
Honorary Senior Lecturer in Medicine

Department of Otolaryngology
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL

Secretary to Mr S Freeman and Mr T Woolford Tel 0161 276 4639 Fax 0161 276 5003

Our ref: CG/am/M57/01198
December 13
NHS No: 4528847086

MedisecNET ref: GRO-C Clinic Date: 27

Typed: 08 January 14

Dr M Sultan
Lower Broughton
Health Centre
Great Clowes Street
Salford
M7 1RD

Dear Dr Sultan

Re: Mrs Patricia RONAN - DOB GRO-C1949

GRO-C

I saw this 64 year old lady who has been referred from Accident and Emergency. She presented in A&E with sudden onset of dizziness. About two months back she had an ear infection. I understand you gave her Amoxicillin. It did clear the infection but over the last six weeks or so she has been feeling extremely dizzy, so much so that she is not even able to walk. She has gone extremely unsteady over the last few days. She also feels quite light headed. Her co-ordination has reduced. She denies any sickness. She denies any fullness in ears. Having said that she does feel like she has some popping sounds in the ears. There is no associated dizziness with head movements. She is known to have Von Willibrand's disease. On examination ear, nose, throat, cranial nerves, cerebella were normal. She could not do Romberg's or Untenburger's and her gait was very unsteady. She has got a nystagmus on right gaze which is predictable. Her pure tone audiometry shows bilateral symmetrical sensorineural hearing loss on the higher frequencies. I am unsure as to the nature of this dizziness. It could be due to labyrinthitis given the nature of the nystagmus. At the same time I am keen to rule out retrocochlear pathology especially as her dizziness is really bad. I am requesting MRI scan brain, IM. At the same time I have also given her safety tips on preventing falls. We will see her again in due course and keep you posted. I have explained this to the patient and have requested the scans urgently.

Yours sincerely

Mr C Gadepalli
Senior Fellow in ENT

DRAFT COPY

Department of Clinical Haematology
Purple Zone, Third Floor
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M13 9WL

PA/Medical Secretary to Professor Hay and Dr Thachil Tel/Fax 0161 276 3360/8085 Email

GRO-C

Our ref: JVT/cj1/M57/01198
NHS No: 4528847086

MedisecNET ref: GRO-C

Dictated: 03 March 14
Typed: 03 March 14

Re: Mrs Patricia RONAN - DOB GRO-1949

GRO-C

I have gone through the notes for this lady and we have a diagnosis of von Willebrand's disease made from 1976. This was of a severe type which means that her factor VIII levels and von Willebrand's antigen, Ristocetin cofactor levels were very low. Again through the notes the information is available that she has had problems with gastrointestinal bleeding since at least 1990.

She has also received Cryoprecipitate which is a concentrate of von Willebrand's factor during her pregnancy in 1974. Diagnosis of von Willebrand's disease was made 1957 when she would have been between the age of 7 and 8 years old. She had haemorrhagic tendency since the age of 2 ½ and was frequently in hospital. She had about 11 blood transfusions at that time. There was a blood transfusion record after a tooth extraction in 1956 and 1957 the diagnosis was made of anti haemophilic globally deficiency although there was no family history.

Further on she has been in hospital many times with problems of gastrointestinal bleeding on many occasions where she has required both blood transfusions, also receiving factor VIII and Tranexamic acid in the early 1990s. The GI bleeding had been thought to be due to duodenal erosions from non-steroidal tablets. Meanwhile there is also an entry in the notes that she would have contracted hepatitis C from blood transfusions. The diagnosis of hepatitis C was made in 1994 which confirmed hepatitis C positivity by a second generation test. At the time suggesting that she is a chronic carrier of hepatitis C. She did have abnormal liver function tests when hepatitis C was planned to have treatment with Interferon.

However she did not respond to this treatment on a clinic letter entry in November of 1996 when the liver function tests were continuously abnormal. This was thought to be milk ----- as homeopathic remedy which she had been taking to detoxifying the liver. There are further entries in the notes saying that she has remained consistently hepatitis C PCR positive despite 9 months of Interferon the last 3 months being 6 mega units for this reason this was stopped.

Her GI bleeding episodes had reduced quite a bit in the years of 1998 but she developed problems of arthritis in her right ankle which was arthrodesis in March 2000. Peri-operative stage was covered with Haemate-P which is a considerate of intermediate factor VIII and von Willebrand's factor the arthrodesis was March 2001. Further on she started developing further GI bleeds in May 2001 and underwent a GI endoscopy. There was an episode of right rectus abdominus muscle haematoma in 2002 which was treated with factor VIII concentrate.

Her GI bleeding symptoms continued to occur to summarise her 6th episode of GI bleeding which occurred in 2003 the first episode was in 1989. 1993 and 1997 she had melena and an endoscopy showed duodenal erosions on both occasions but in 2001 her upper GI endoscopy was normal with a ----- which was also normal. She also had an episode where she developed palpitations due to atrial ventricle ectopics in July 2003. A colonoscopy was within normal limits.

She was sent a VCJD letter on the 18th September 2004 and the letter sent to her would read that she has been treated with an implicated blood product and that there is an estimated 1% Public Health Risk of her having a normal VCJD protein. Another GI bleed occurred in August 2006. A medial capsule endoscopy showed actively bleeding lesions of the proximal bowel which is thought to be due to angiodysplasia confirmed on endoscopy.

Neutropenia and lymphopenia was thought to be due to active SLE, she also had a Hickman line infection in 2007. She has had in total over 15 endoscopies for which no source could be located, however a capsule endoscopy did show half a dozen angiodysplasia in the small bowel mainly located mid-jejunum. She has also had a Port-A-Cath infection in 2007.

She currently had some Tamoxifen which reduced her requirement for blood transfusions from the bleeding from her angiodysplasia. She continued to have anaemia but this settled and repeat endoscopy showed the angiodysplasia had improved. Throughout the period of GI bleeding she has had multiple doses of von Willebrand's factor replacement with Haemate-P.

The last episode of her hospital stay started on the 6th January. This was when she was admitted with 6 weeks history of left ear pain. This was first treated around December time as a middle ear infection but this became progressive and she was unsteady on her feet requiring assistance. She was also confused, had visual hallucinations and was agitated. On examination she had -----, left-sided weakness and decreased coordination. A CT scan of the brain ruled out infarction or haemorrhage but the MRI scan showed a suspected cortical lesion. Initially this was thought to be due to withdrawal of analgesic medication which was commenced for the ear infection and also as a side effect.

She was treated with Haemate-P because her haemoglobin had dropped but she continued to be confused. Her husband reported the confusion had started before Christmas and was worse on the ward round on the 8th January. She was seen by the Neurologist on the 8th January at 2.30 who made a suggestive diagnosis of cortical problem seen in CJD. This was also suggested for an MRI scan which was not perfect because of movement, the neurologist suggested transfer of the patient to Salford Royal Hospital.

She did have a lumbar puncture and further investigations done at Salford Hospital further details would be available from Salford Royal Hospital.

Von Willebrand's disease is a condition whether it is an inherited bleeding disorder which is inherited as autosomal recessive. This could cause spontaneous bleeding but can be associated with angiodysplasia. The reason this lady has had multiple blood transfusions would fit in with the possible duodenal erosions from non-steroidal for her several related conditions and also angiodysplasia which can be associated with this condition. This also required treatment with cryoprecipitate factor VIII and Haemate-P more latterly.

The query with respect to whether a possible diagnosis of sporadic CJD is linked to a blood transfusion is not entirely confirmatory. It is only our understanding from medical literature that this is not the case but I would be happy to be contacted in respect of any questions or queries.

Yours sincerely

Yours sincerely

Dr Jecko V. Thachil
Consultant Haematologist

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GRO-C

Our ref: CRMH/cj1/M57/01198
NHS No: 4528847086

MedisecNET ref: GRO-C

Dictated: 07 April 14
Typed: 06 May 14

Professor Rob Will
Professor of Clinical Neurology
The University of Edinburgh
The Bryan Matthews Building
Western General Hospital
Edinburgh
EH4 2XU

Dear Professor Will

Re: Mrs Patricia RONAN - DOB GRO-C 1949

GRO-C

Many thanks for copying us into James Ironside's neuropathology report. This is very helpful.

The only point I would make is that whilst the family are maintaining that we never told Patricia her CJD status, it is actually very well documented that we did. She was counselled about variant CJD and was offered the opportunity to be told whether or not she had received an implicated batch of factor VIII concentrate. She did not wish to know whether she had an implicated batch though, in actual fact, she had not. She subsequently showed a reluctance to discuss the matter and I suspect that she never discussed it with her family. This would account for their ignorance of the issue since she usually attended outpatient clinics on her own.

With best wishes,

Yours sincerely

Professor CRM Hay
Professor of Thrombosis and Haemostasis

cc: Dr M Sultan
Lower Broughton
Health Centre
Great Clowes Street
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M7 1RD

Re: Mrs Patricia RONAN - DOB [GRO-C] 1949

GRO-C

Dr Thachil
Consultant Haematologist
MRI