Dear Dr McIntyre

INTERMEDIATE FACTOR VIII CONCENTRATE: BATCHES 82 AND 90

Further to recent telephone conversations I now report that all remaining units from these batches have been withdrawn from clinical use.

These two batches of Factor VIII Concentrate were made in the last stages of departure from the Royal Infirmary and the quality control and finishing arrangements were carried out at the PFC at Ellen's Glen.

Each batch consisted of 72 bottles and, because of difficulty in assessing the rabbit pyrogen test, were included in a trial administration carried out over the period January to March 1975. In this trial a group of units of different batches, each having a different pyrogen response in rabbits, were sent to the Edinburgh and Glasgow Haemophilia Treatment Centres through the Regional Transfusion Centres. It was hoped that, by using the units in order of rising response, we could identify the rabbit response which would be safe for issue. Concurrently, the limulus test had been applied to each batch and there was a reasonable certainty that none of the batches contained dangerous levels of pyrogen.

The/
The result of this test series was negative in that, at both Haemophilia Centres, all the units were used without the recording of adverse reaction of any kind. The net result was to increase the impatience of clinicians for wider issue of the product.

Batches 89 and 90 were issued only to the Edinburgh and Glasgow Haemophilia Treatment Centres through the Regional Transfusion Centre. All units of both batches issued to the Edinburgh Centre have been used. The last of batch 90 was used on the 14th July 1975 by a patient, on home therapy. No adverse report has been received from Edinburgh on these, or any other, batches of the intermediate fraction.

The last bottle of batch 89 was used yesterday in Glasgow and, as you know, provoked a violent delayed allergic response in a young boy.

Two bottles of batch 90 were also administered yesterday to another patient in Glasgow with a few hours of delay between administrations. The second unit caused a reaction similar to the earlier adversity except, perhaps, the reaction was even more severe. The remainder of batch 90 (there should be eight units if my information is correct) has been withdrawn from clinical use by Dr John Davidson of the Glasgow Haemophilia Treatment Centre. If there are less than eight units in the withdrawal group one must assume that earlier administration of batch 90 occurred in Glasgow.

In joint discussion with Dr Ruthven Mitchell, Deputy Director at the Regional Transfusion Centre, Low Hospital and separately with Dr John Davidson it has been arranged to carry out a pyrogen test on a sample of the distilled water used to redilute the freezing units in Glasgow. This water is May and Baker product, "Water for injection", 200 ml, batch no. BT3374, expiry date July 1976. Also, a pyrogen test is to be carried out on batch 80 samples, one dissolved in May and Baker water and one dissolved in water prepared at the Transfusion Centre, Low Hospital. The original pyrogen test on the batch was done in the very way as the latter proposal and gave, in three rabbits, the individual temperature rise responses of 1.1°, 1.0° and 1.0°. This aggregate of 3.2° is well inside the 4.0° aggregate considered acceptable for this product.

I understand that you have now advised that the intermediate Factor VIII Concentrate be withdrawn, in the meantime, for use by patients on home therapy and agree that this is a reasonable precaution. However, it should be noted that the two batches implicated in the Glasgow reactions have a good history elsewhere; ten units of batch 90 have been infused in Edinburgh and two units have been infused in Glasgow without incident. It seems reasonable to suppose that some factor, such as the diluent or syringe used in Glasgow, comments both incidents may be implicated in this problem. Whilst possible, it is unlikely that two batches of Factor VIII Concentrate, each with a good clinical history, should be implicated in two incidents in one treatment centre within the one working day. To be logical, therefore, it would seem necessary to advise, at least temporarily, the withdrawal of the 'water for injection" batch no. BT3374 from clinical use. At the very least the manufacturer should be advised that the batch is under scrutiny.
I do not have details of how plasma fractions are stored or prepared for clinical administration at the Glasgow Haemophilia Treatment Centre but, having respect for the competence of all concerned at the Centre, I doubt the possibility of some serious technical lapse.

I feel that, apart from the very real clinical problem, the sensitivity of this situation can not be over-stressed. The intermediate fraction is employed widely throughout the world and is proving to be a very acceptable product. The version prepared by this Centre has been brought to clinical use by a team of people who are internationally respected for their careful technique and for the quality of the coagulation factor concentrates which they prepare. Haemophiliacs are a very apprehensive group of people who are likely to react by refusing to accept this product if any breath of adverse criticism becomes attached to it. The Protein Fractionation Centre, at this stage in commissioning, is exceedingly vulnerable to any hint of carelessness and, being still unlicenced, does not possess the protection of the existing legislation. Whilst coming close to it the techniques being employed still require to be "frozen" in standard forest. I believe that we could withstand very searching scrutiny of our operations but, doubtless, there is plenty room for criticism in a new unit only nine months into a commissioning programme.

The preparation of this product at the level of clinical need is now well established and issue of substantial quantities has started in the present week, to be followed by weekly issues in excess of 50% of the total national need for anti-haemophilic factor. Proposed issue is at the rate of 4,000,000 units per year against an estimated national need of about 6,000,000 units. It is difficult to proceed, in the event of patient rejection, this provision could be easily switched to a different method of manufacture.

With kind regards

Yours sincerely

JOHN C. WATT
Scientific Director

c.c. Major-General R C Jeffrey
Dr J D Cash
Dr J Wallace
Dr J Cook
Dr B Lewis
Dr C Cameron
Dr J Davidson
IN CONFIDENCE

5 September 1975

To Regional Transfusion Directors

Dear

Further to our telephone discussion I have to confirm that reports have been received from Glasgow of fairly severe adverse reactions in two patients thirty minutes after receiving treatment with two different batches of Factor VIII produced at the Protein Fractionation Centre. These batches have all been recalled. Although these reactions occurred in association with the administration of Factor VIII an unequivocal causal relationship has not been established. However it has been decided as a precautionary measure to recommend that the use of PFC Factor VIII for home treatment be discontinued for the meantime. This recommendation relates only to home treatment.

I should be grateful if you would convey this recommendation to the clinicians concerned and also ask them to pay particular attention to the occurrence of any reaction, however minor, in patients who are receiving treatment in hospital with PFC Factor VIII. In the absence of General Jeffrey I should be grateful if you would let me know of any reports passed on to you.

Your help and co-operation in this matter is appreciated and I shall keep you informed of future developments.

Yours sincerely

[Signature]

[Name]

Copy: General Jeffrey (on return)
Mr J Watt
Dr. G. D. Forwell,
Chief Administrative Medical Officer,
Greater Glasgow Health Board,
351 Sauchiehall Street,
Glasgow, G2 3HT

Dear Dr. Forwell,

Factor VIII Concentrates (Intermediate)

As you will be aware the Scottish National Blood Transfusion Service, Protein Fractionation Centre in Edinburgh is now producing the above concentrates for the management of patients with haemophilia.

In the past we have evaluated a number of different batches of this product and found them to be satisfactory, but two recent batches have produced reactions in patients. I reported this to the Regional Transfusion Centre in Law Hospital who in turn reported this to the Protein Fractionation Centre in Edinburgh, who in turn reported this to Dr. A.D. MacIntyre in the Scottish Home & Health Department. Dr. MacIntyre telephoned me yesterday asking for details of the reactions and asked that I inform you of the incidents.

On 3rd September 1975 a haemophiliac was given a dose of batch 89 Factor VIII Concentrate (Intermediate). There was no untoward effect when the dose was given, but 30 minutes later he developed rigors and malaise. This responded to intravenous hydrocortisone and antihistamines.

On the same day another haemophiliac was prepared for E.N.T. surgery in the morning with a dose of Factor VIII concentrate (intermediate) batch 70. This caused no reaction but in the evening he was given a further dose of Factor VIII concentrate (intermediate) this time of batch 90, following which he developed a very similar delayed reaction to the patient in the morning. This patient also responded very promptly to treatment with hydrocortisone and antihistamines.
I have discussed the problem with Mr. J. Watt, Director of the Scottish National Blood Transfusion Service, Protein Fractionation Centre, and he tells me that no other reactions have been reported to these batches of Factor VIII concentrate. Batch 89 has now been completely used, but I have taken the precaution of withdrawing the rest of batch 90 which I hold.

The water used to reconstitute the Factor VIII concentrate is May & Baker Sterile Pyrogen free water for injection, lot No. DD 3374. Dr. McIntyre has advised that this batch of water for injection should also be withdrawn pending investigation. Samples of the water for reconstitute and of batch 89 and batch 90 Factor VIII concentrate (Intermediate) has been forwarded to the Regional Transfusion Centre at Law Hospital for further examination, and in particular Pyrogen testing.

I will keep you informed if there are any further developments.

Yours sincerely,

J.F. Davidson
Consultant Haematologist

O.c. Dr. MacDonald, Consultant Haematologist, Glasgow Royal Infirmary
Dr. C.R.M. Prentice, Ward 3, Glasgow Royal Infirmary
Dr. J. Wallace, Regional Director, Law Hospital
Mr. J. Watt, Director, Scottish National Blood Transfusion Service, Protein Fractionation Centre, Edinburgh.
Dear John,

Thank you for the copy of your letter of 4th September.

I have just heard the results of the pyrogen tests on batch 89980 and have temporarily withdrawn the rest of the intermediate concentrate pending further investigations and advice from yourself and the SCB TA.

We are all very sorry about this, and hope the problem can be rapidly resolved.

Kindest regards,

[Signature]
8th September, 1975

Mr. J. Watt,
Scientific Director,
Protein Fractionation Centre,
Royal Infirmary,
EDINBURGH, EH3 9HB

Dear John,

I enclose the results of the pyrogen testing on Intermediate Factor VIII batch No. 89 and 90. You will see that both batches were pyrogenic in each of the three rabbits. We also checked the May & Baker water and for your interest I enclose the report showing that this is clearly a pass at a 0.2°C rise in three rabbits. Since the patient who received batch 89 was group AB and the patient who received batch 90 was group A, we performed Anti-B and Anti-A allo-antibody titres.

Batch 89 gave the following results:

- at 4°C against Al cells 1/256
- at 4°C against B cells 1/64
- at 4°C against patients AB cells 1/128
- at 37°C against Al cells 1/64 saline, 1/512 IAGT
- at 37°C against B cells 1/32 saline, 1/2048 IAGT
- at 37°C against patients AB cells 1/32 saline, 1/2048 IAGT

The results with batch 90 were as follows:

- at 4°C against Al cells 1/256
- at 4°C against B cells 1/64
- at 4°C against patients A cells 1/16
- at 37°C against Al cells 1/128 saline, 1/512 IAGT
- at 37°C against B cells 1/256 IAGT
- at 37°C against patients A cells 1/8 saline, 1/32 IAGT

You will see these agglutinin titres are much higher than one would expect. I am not suggesting that the patients had a haemolytic secondary transfusion reaction but you may have seen the recent letter to the Landet by
8th September, 1975

Mr. J. Watt,

Maycock and his group reiterating the well known dangers associated with high titre antibodies.

It is difficult for us to think of any other immunological test which we could do since the material is of such a large pool of donors there will be considerable mixing. I shall obtain back from Dr. Davidson all of batch 90. There are no other units of batch 89 available. All of the 105 units of factor VIII concentrate which was sent to us are from batch 99. I will arrange to have this pyrogen tested as soon as possible.

Meanwhile I understand from Dr. Davidson that Dr. Howard Davis will be testing some batches by clinical use. I think that Dr. Davidson is very reluctant to use Interate until this matter is cleared up.

Yours sincerely,

Ruthven Mitchell, B.Sc., M.B., Ch.B., M.R.C.Path,
Deputy Director.
Glasgow and West of Scotland
BLOOD TRANSFUSION SERVICE
TELEPHONE Nos. WISHAW 73315/8
TELEX No. 779483

REGIONAL DIRECTOR
JOHN WALLACE B.SC., M.D., F.R.C.P.G., F.R.C.PATH.

AT LAW HOSPITAL,
CARLUXE,
LANARKSHIRE.
MLS 5ES

8th September, 1975

Dr. A.D. McIntyre,
Scottish Home and Health Department,
St. Andrew’s House,
EDINBURGH.
EH1 3BE

Dear Dr. McIntyre,

Intermediate Factor VIII Concentrates

I thank you for your letter of 5th September, 1975. The occurrence of severe adverse reactions in two recipients of Intermediate Concentrate of Factor VIII has created a worrying situation for all concerned. I think it is most important to avoid a panic situation and to review the matter calmly. Following your recommendation the use of the new Intermediate Concentrate of Factor VIII has been discontinued in the West of Scotland. I agree that this is a wise precaution, but clearly a decision will have to be taken about future policy.

Investigations are being continued at this Centre and written reports will be provided. I have however informed Dr. John Davidson, Consultant Haematologist, Glasgow Royal Infirmary by telephone that the sample of May & Baker Sterile Pyrogen free water for injection, lot No. DD 3374 submitted for pyrogen testing gave perfectly acceptable results. This will be confirmed in writing to Dr. Davidson, but I felt that he should be informed immediately of our finding.

At this stage my feeling is to proceed cautiously. I would suggest that certain batches of Intermediate Concentrate of Factor VIII might be released for cautious clinical use. It has been noted when pyrogen testing this product that some batches give an extremely small rise in temperature. Indeed the results are similar to those found in testing non-protein solutions. I feel that if these batches are otherwise satisfactory that the material should be issued with confidence.

Yours sincerely,

[Signature]

Regional Director

C.C. MAJOR-GENERAL H.C. JEFFREY,
MR. J. WATT,
DR. J. DAVIDSON,

Dr. G. MacDonal,
Dr. C. Prentice,
Dr. G. Forwell.
Rabbit pyrogen test results of NY batches.

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Glasgow and West of Scotland
BLOOD TRANSFUSION SERVICE

TELEPHONE NOS. WISHAW 73315/8
TELEX No. 779483

REGIONAL DIRECTOR
JOHN WALLACE B.SC., M.D., F.R.C.P.G., F.R.C.PATH.

AT LAW HOSPITAL,
CARLUKE,
LANARKSHIRE,
MLS 5ES

RM/MC
11th September, 1975

Mr. J. Watt,
Scientific Director,
Scottish National Blood Transfusion Service,
Protein Fractionation Centre,
21 Ellen's Glen Road,
EDINBURGH.
EH17 7QT

Dear Mr. Watt,

Factor VIII Intermediate Concentrate

Further to my telex number 779483 of 9th September, 1975
Dr. Wallace and I have been discussing what future action we may
contemplate. As promised we are retesting batches 92, 98 and 99
this week. It seems to us however that since we have a small
remainder of 76, 81, 83, 85 and 90 that some of these might be
cautiously re-issued provided we could re-assess the original
work which was done on them.

We asked our Mr. Alastair Watt to prepare for us the enclosed
cumulative list of Factor VIII pyrogen tests over the last few
months. We noted that some batches have clearly passed with flying
colours, whereas others are distinctly pyrogenic in rabbits. I
wonder if it is possible for you to check the temperature responses
in batches 76, 81, 83, 85 and 90 and let us know if there would be
any objection to our re-issuing these. Lastly do you wish us to
send you any of the batches which we have re-called?

Yours sincerely,

Ruthven Mitchell, B.Sc., M.R., Ch.B., M.R.C.Path.,
Deputy Director
Dear Ruthven

FACTOR VIII INTERMEDIATE CONCENTRATE

I thank you for your letter of 11th September and am looking forward
to the results of the re-testing of batches 92, 98 and 99. It seems
to me that, in many respects, all our future progress and particularly
the re-introduction of this product are dependent on these tests.

I have carried out a fairly careful re-assessment of all existing
batches of this product and am of the opinion that batches 76, 81, 83
and 85 could be re-issued with caution. However, I would be reluctant
to agree to the re-issue of batch 90 since this batch has already been
implicated in a reaction. In any event, I would like you to carry out
another pyrogen test on batch 90 and I would wish that the remainder of
the batch be returned to the PFC so that we can repeat the whole of the
quality control programme.

I realise that the Pharmacopoeia is quite clear on the criterion for
considering that a pyrogen test has been passed or failed when conducted
in rabbits but, particularly in relation to products containing protein,
I continue in my reluctance to accept the pass or fail status without a
careful assessment in conjunction with other assessment data. Obviously,
the decision on failure is fairly simple but the attainment of a low
temperature rise is not necessarily clear indication of a pass.

During/
Dr Ruthven Mitchell  
Deputy Director  

During the course of my investigation of the pyrogen testing status of all batches of this fraction I became aware of an apparent relationship between the weight of the rabbit and the temperature rise response. There is also, when the test results are listed in chronological order, for the results to occupy a fluctuating pattern. I felt that these casual observations had to be spurious in a test which is carried out under random conditions insofar as the timing of arrival of any particular fraction for testing happens to coincide by chance with the animals which are available for the test itself. However, to test the impression I have carried out some analyses of the responses in individual rabbits correlated with the weight of the animal and with the size of the injected dose. Correlation is, as one would expect, far from absolute and, indeed, the heaviest rabbit used showed a nil response. However, there is a relationship between weight and response and it does appear that there should be an upper limit for the weight of the test animal as well as the statutory lower limit. I intend to meet with Dr Derek Bangham in the course of the next few days and shall take the opportunity to discuss this observation with him. Almost certainly this is a coincidence unrelated with our present problems but, nevertheless, it may be part of the case against current regulations for pyrogen testing of biological substances.

With kind regards

Yours sincerely

JOHN G WATT
Scientific Director
Dear Mr. Watt,

Further to my Telex No. 779483, you will have by this time received the protocols. We had a discussion here on Friday concerning these results and we were particularly perturbed by your suggestion that the temperature responses might be related to body weight, with "pass" results being obtained in animals less than 1.9 kg. and "fail" results in animals greater than 2 kg.

We will repeat batch 90 as requested and look forward to hearing from you.

Yours sincerely,

Ruthven Mitchell, B.Sc., M.B., Ch.B., M.R.C.Path.,
Deputy Director
TO DR RUTHVEN MITCHELL
FROM MR JOHN WATT

RE INTERATE FACTOR VIII CONCENTRATE

I HAVE NOT SEEN THE RETEST RESULTS OF BATCHES 92 98 99 AND FEEL THAT THESE ARE SUFFICIENTLY LIKE THE ORI9INALS TO ALLOW A CAUTIOUS REINTRODUCTION OF THE PRODUCT USING THESE BATCHES FIRST.

ISSUE OF FACTOR VIII FROM THE PFC SHOULD CONTINUE AT THE PREARRANGED LEVELS AND DISTRIBUTION PATTERN.

GEN JEFFREY WILL RETURN FROM LEAVE THIS WEEK AND WILL BE EXAMINING THE WHOLE EPISODE WITH A VIEW TO FURTHER ACTION. I SHALL BE BACK FROM PARIS ON WEDNESDAY AND I CONSIDER THAT SHORTLY THEREAFTER IT WOULD BE WISE TO HAVE A MEETING TO DISCUSS EPISODES OF THIS TYPE AND THE PROPER ACTION WHICH SHOULD BE TAKEN.

I HAVE HAD MEETINGS WITH DR MAYCOCK AND DR BANGHAM TO DISCOVER THEIR REACTION TO THIS TYPE OF PROBLEM. DR BANGHAM HAS OF THE OPINION THAT THIS WAS NOT A TRUE PYROGEN REACTION ESPECIALLY ON THE POINT THAT BOTH BATCHES HAD ALREADY HAD A FAIR HISTORY PRIOR TO THE POINT OF TROUBLE. BOTH HE AND DR MAYCOCK SEEM TO CONSIDER THAT THIS TYPE OF EVENT IS LIKELY TO ARISE FROM TIME TO TIME AND EVEN WITH MORE SERIOUS CONSEQUENCES.


IN MY OPINION THE INTERPRETATION OF THE RABBIT TEST ON ICC PROTEIN DEFIC INTERATE AND SOME OF THE DEFIC PRECURSOR SOLUTIONS IS VERY DIFFICULT IF NOT IMPOSSIBLE. OF ALL MATERIALS COMING FROM THE PFC ONLY PPSB ALBUMIN DISTILLED WATER SALINE AND TRIS BUFFER ARE READILY TESTED BY THE RABBIT SYSTEM. SIX OF THE MATERIALS WE WISH TO TEST, INCLUDING THE CELL FREEZING SUPPORT SOLUTIONS CANNOT BE TESTED BY THIS SYSTEM.

THE LIMULUS TEST IS NOT A COMPLETE ANSWER TO OUR DILEMMA SINCE WE DO NOT KNOW ENOUGH ABOUT FALSE NEGATIVE RESULTS AS YET WITH THE EXCEPTION OF PPSB AND CAPRYLIC ACID SOLUTIONS WE CAN SAY QUITE CONFIDENTLY THAT IT DOES NOT PRODUCE FALSE POSITIVE RESULTS. THE TWO EXCEPTIONS ARE KNOWN TO INHIBIT THE RESPONSE OF THE LYSATE TO KNOWN ENDOTOXIN. THIS INHIBITION WAS ONCE DETECTED IN RELATION TO INTERATE AS WELL BUT WE COULD NOT REPRODUCE THIS EFFECT FOR FURTHER STUDY.

REGARDS+++

PLEASE NOTE ERRORS... PPF...OUR DILEMMA
Dear Mr. Watt,

Factor VIII Intermediate Concentrate

Many thanks for your letter of 16th September and your telex number 72425 of 21st September. Since I last wrote to you we have completed the pyrogen testing on another bottle of batch 90. This assayed at a total of 3.8°C for three rabbits. I note all that you have said concerning these batches and in discussion with Dr. Wallace we will take a long hard look at the possibilities of re-issuing batches 81, 83, 85, 92, 98 and 99. This should certainly release a considerable stock of the intermediate fraction, although I am afraid we are nowhere nearer solution to the cause of the reaction experienced by the two patients at Glasgow Royal Infirmary.

When I heard about your analysis of temperature data in terms of rabbit body weight I had our Mr. Alastair Watt analyse the figures that we have. Our interpretation is that there is no relationship between temperature response and total body weight in the rabbits used.

We were particularly interested in the comments of Dr. Maycock and Dr. Bangham and I am sure that Dr. Wallace will be writing to General Jeffrey with the latest position so far as this region is concerned.

Yours sincerely,

Ruthven Mitchell, B.Sc., M.B., Ch.B., M.R.C.Path.,
Deputy Director