NORTHERN REGIONAL HAEMOPHILIA SERVICE
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23rd February, 1988

Dr. L. Donaldson,
Regional Medical Officer,
Northern Regional Health Authority,
Benfield Road,
Walkergate,
NEWCASTLE UPON TYNE.

Dear Liam,

I enclose a historical record of the use of factor VIII preparations in the Northern Region since 1969. I hope this will help answer many of the questions raised both by the Regional Health Authority and Jim Cousins in his letter to you of 3rd December, 1987. These figures, taken with my comments below, should allay any worries that the Northern Region's use of factor VIII has been in any way untoward.

Before commenting on the figures could I just say that I hope in future any questions relating to the management of haemophilia, and specifically the incidence of HIV infection in my patient cohort, could be addressed directly to me and to no-one else concerned with HIV infection. If the original letter drafted by our Regional AIDS Co-ordinator had reached a Member of Parliament it would have given a totally erroneous impression.

Firstly, the figures. These are presented both in tabular and graphic form. Table A lists the use of factor VIII preparations from 1969 - 75. Between 1969 - 1974 the figures for Carlisle and Newcastle are incorporated. From 1975 the other Associate Centres in Sunderland, Middlesbrough and Whitehaven are included.

Between 1969 and 1975 much of the service depended on the use of fresh frozen plasma. Commercial concentrates were introduced in 1973 and quickly made up the shortfall in local Blood Transfusion Service plasma and cryoprecipitate. The sudden rise in NHS factor VIII concentrate usage in 1971 was caused by the treatment of one patient who suddenly developed high titre factor VIII antibodies and almost bled to death following dental extractions.

The relationship between the figures in Table A and the rest of the country is shown in graph form in Figure 1.

Table B shows the use of factor VIII between 1976 and 1986. Most of the fresh frozen plasma in these years was used for the treatment of factor V

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deficiency, the large quantity in 1979 being used to cover neurosurgery in one patient.

With the increasing use of home therapy and prophylaxis, cryoprecipitate usage declined over the years, and until recently was only used for small children and mildly affected patients. The supply of NHS concentrate to the Northern Region has been, to say the least, erratic and the inevitable gross shortfall has been made up with commercial concentrate. To the right of Table B I have worked out the percentages for the use of each of these products in comparison with the remainder of the United Kingdom.

The results in Table B have also been displayed graphically in Figure 1 and Figure 2.

Table C shows the number of patients treated in the Northern Region in comparison with the United Kingdom, together with the amounts of factor VIII used and the average amounts of factor VIII per patient per year for the past 10 years.

Within the past 6 years we have been responsible for treating between 5% and 8% of United Kingdom haemophilia A patients and the average per patient per year usage of factor VIII has been in accord with the rest of the country.

Figure 1 shows a cumulative graph of the use of the total factor VIII (and the products making up this total) between 1969 and 1986 for the United Kingdom. This graph is prepared annually by my colleagues in the Haemophilia Centre Directors Association; the figures are collected by the Oxford Haemophilia Centre and collated there with the help of a computer. I have super-imposed the Northern Region totals on the national picture and from this you can see that our rise in usage over the years has been entirely in keeping with that of our colleagues in other Regions.

Figure 2 reveals in more detail the discrepant usage of NHS and commercial concentrates. I have already referred to the erratic supply of the former; this has been particularly evident in the past two years with barely any NHS concentrate being available to us in 1985 because of changes in manufacturing practice, principally the introduction of dry heat treatment.

Taken together these figures should satisfy question 2 in your letter of 22nd December, 1987 and go some way to answering question 3. If you require any further details with regard to question 3 I am sure either Anne Collins or Huw Lloyd will be happy to help.

With regard to question 1, I can tell you that we started to use heat treated concentrates in the Northern Region in December 1984. Non-heat treated concentrates were rapidly phased out as people brought back their home therapy supplies. In view of the cost involved in changing from non-heat treated to heat treated material, an argument did ensue as to whether those people who were HIV antibody positive should continue to receive contaminated material. This argument resulted in both a letter to the Lancet and a meeting chaired by Mike Rawlins. A copy of the letter, which was not discussed with anyone involved in treating the patients before it appeared in print, and of the minutes of that meeting are appended.

The commercial companies were quicker off the ground to introduce heat treated material than Elstree, which was not able to supply product in small amounts

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until February 1985. It was the difficulty in introducing heat treated material which resulted in the failure of the National Health Service to supply factor VIII concentrate in any significant amounts to us in 1985.

Individual donor testing of the material used in the concentrates was of course not possible until the HIV antibody test had been developed and put through initial trials. Donor tested heat treated material was not available until September 1985 from the commercial companies and until February 1986 from Elstree. The Scottish Fractionation Centre in Edinburgh pre-dated Elstree in the supply of individual donor heat treated concentrates but they were, of course, only responsible for a population of 5 million, Elstree having to co-ordinate supplies to England and Wales.

With regard to HIV infection there are a number of points which I think are of relevance. Firstly, as I intimated to you in my letter of 2nd November (and for the reasons I set out in that letter) the percentage of cases in the Northern Region is equating with the percentage of cases in other Regions. The position in June 1987 referred to in Jim Cousins' letter did suggest an unusual focus for haemophilia and HIV infection in the North. However, the epidemiology of the disease in our Region is totally different from that in the rest of the country, when the overwhelming number of cases related to homosexuality in London are taken into account. The number of cases due to homosexual infection swamps the number of cases of haemophilia and HIV in London and skews the United Kingdom picture. The Northern Region figures show that from an estimated 1200 cases of HIV positive haemophiliacs in the United Kingdom, 87 are in the Northern Region, giving a percentage of 7.25%. The total of 87 includes a few visitors from other Regions and it is probable that the 1200 cases, although that was the figure used in our campaign for recompense last year, is an underestimate. By the end of September 1987, 1058 of these cases were known to CDSC.

To date 14 cases of overt AIDS in our cohort have been accepted by CDSC definitions, this figure accounting for 20% of the UK total (this figure is taken in comparison with that for the United Kingdom in January 1988). Eight deaths have occurred in the Northern Region with 54 in the United Kingdom as a whole, giving a percentage of 14.8 in comparison with the figure given by Jim Cousins of 27.5% for June 1987.

In Figure 3 I have superimposed the percentage of UK patients treated in Newcastle and the percentage of total factor VIII that we used in comparison with the United Kingdom on a bar chart of cryoprecipitate, NHS concentrate and commercial concentrate.

Retrospective testing of serum which had been stored down from a cohort of haemophilic patients now known to be HIV antibody positive shows that all were sero-negative in late 1980/mid 1981. From this and other data we think our patients became infected in late 1981/82 at a time when our average factor VIII usage was the same as that for the UK as a whole. This data fits both with information on retrospective sampling in other Centres and with the estimated incubation period between infection and overt disease.

The present position is that around 80% of our HIV antibody positive haemophiliacs show abnormal immunology with decreased T4 counts and, in most cases, abnormal physical findings. This high percentage of morbidity is in accord with figures presented from around the world for haemophiliacs, blood transfusion cases, homosexuals, intravenous drug abusers and those who have

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acquired the disease through heterosexual intercourse. The only factor which is now slowing progression is AZT; we have had no death nor severe opportunistic infection since August 1987, apart from one case of pneumocystis in a non-compliant patient.

Turning to the question of budgetting based on predictions for the future, I am sure that you will realise that it is virtually impossible for me to make an accurate prediction. The appended figures show that our use of factor VIII fell between 1985 and 1986. This fall can I think be expected to continue as more of our patients become sick and die of AIDS. However, this fall is unlikely to be reflected in price.

In 1986 I drew attention to what I regarded as very poor scientific evidence that heat treatment could be relied on to completely eliminate HIV. This evidence was based on in-vitro work with spiked concentrates and the with the concept of 'log kill'. Since HIV has never been identified in any concentrate, despite the epidemiological evidence of infection, I have always believed the concept of log kill to be completely fallacious and, since early epidemiological evidence became available, refused to use the dry heated Armour product for patients in the North. Last year the Committee of Safety of Medicines withdrew Armour's licence, and notified their colleagues in the United States and Canada of their decision. Unfortunately the product continued to be used with the result there has been a recent breakthrough of infection in previously antibody negative haemophiliacs in Canada. In view of this evidence all dry heat treated material is being withdrawn from the market, the only exceptions being the NHS 8Y product from Elstree and the Scottish dry heat treated product from Edinburgh.

It has been calculated that every batch of commercial concentrate from 30,000 donations must be contaminated prior to anti-viral treatment and that some 1 in 30 batches of the National Health Service product will also be infected prior to heat treatment. It may therefore take many years for the epidemiological evidence of viral inactivation and safety in the NHS product to accrue, but if sero-conversion occurs in a single patient who has been treated solely with this material and who cannot have been infected in any other way, we will once again be entirely reliant on material from other sources (listed in Table D).

With regard to these sources I have already said that the dry heat treated material is being removed from the market. For the moment, dry heat treated Koate made by Cutter Laboratories is still available in this country and I am using it for the treatment of HIV antibody positive patients. Other products presently available are an Armour monoclonal product which has been licensed for use in North America and some European countries but has still not been granted a licence here. As this product is presently only heated to the same extent as the previously withdrawn product and as column fractionation is by itself notoriously unreliable, I would not prescribe it for any of my patients; this decision is shared by my colleagues in the Haemophilia Reference Centre Directors organisation. I am presently using a product heated in slurry form by the Alpha Company for HIV antibody negative patients who have already been exposed to commercial concentrates. However, this product is presently under scrutiny because there have been suggestions of non A non B hepatitis transmission and within the past week a possible case of HIV transmission in Germany. The Behringwerke product which is heat treated in the fluid form has recently been regarded as the safest (but most expensive) of the commercial concentrates. Because of shortages it has not been

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available to us and recent reports suggest viral transmission. The Immuno product is known to have transmitted hepatitis B.

The recombinant DNA story is that, to my knowledge, no product has yet been worked up to full fractionation. A pilot study on a patient in North Carolina has shown that the Travenol material produces the expected rise in factor VIII level in severe haemophilia, but even if this or the Cutter product are brought to full-scale production in the coming year it will be at least two years before either product becomes available for routine clinical use. Of course, when it does it will probably be unethical to use human donor material.

The only other product presently available to us is the solvent detergent preparation developed by the New York Blood Center and this is being slowly introduced into clinical trial in the Newcastle Centre for HIV antibody negative patients previously unexposed to multi-donor materials (whether NHS or commercial in origin). The evidence on the solvent detergent product looks extremely good, but only time will tell. On balance it appears safer to use on virgin patients than cryoprecipitate and I have started to phase this out.

With the help of my colleagues in the Centre Directors organisation I hope that I have been able to supply you with enough ammunition. I have sent copies of this report to Anne and Mike Rawlins for information. Obviously much of the information about individual products is confidential and I would not like it to appear in any minutes or in open meetings; it is provided to give you an idea of how difficult things are at present for the prescriber, let alone the patient. Continued uncertainty about future provision of anti-virals like AZT adds to this difficulty. If you require any further information please let me know.

Kind regards,

Yours sincerely,

GRO-C

PETER JONES
Director

cc. Professor M. Rawlins
Dr. A. Collins
Dr. P. Hamilton

TABLE A

PRODUCTS USED TO TREAT HAEMOPHILIA A PATIENTS 1969-75

NEWCASTLE SUPRA-REGION

	PLASMA	CRYO	NHS CONC	COMM CONC	TOTAL
1969	3,000	270,000	280	-	273,280
1970	45,000	266,000	7,000	-	318,000
1971	57,000	467,000	1,802,000	-	2,327,000
1972	3,000	174,000	350	-	177,000
1973	100,000	917,000	-	133,000	1,150,000
1974	80,000	991,000	-	432,000	1,503,000
1975	176,000	977,000	450	972,000	2,126,000

1969 - 74 Two Haemophilia Centres included: Carlisle and Newcastle

1975 Other Associate Centres included.

FACTOR VIII UNITS USED FOR TREATMENT OF HAEMOPHILIA A PATIENTS 1976-1986

TABLE B

COMPARISON OF UK AND NEWCASTLE USAGE

	UK				NEWCASTLE				NEWCASTLE % OF UK			
	PLASMA	CRYO	NHS CONC	COMM CONC	PLASMA	CRYO	NHS CONC	COMM CONC	PLASMA	CRYO	NHS CONC	COMM CONC
1986 *	7,000	1,620,000	31,221,000	53,448,000	-	205,142	660,764	5,720,856	-	12.5%	2%	10.5%
1985	5,000	2,244,000	22,644,000	50,275,000	-	163,090	188,098	6,408,997	-	7%	1%	13%
1984	3,000	3,357,000	39,832,000	33,864,000	-	107,324	1,188,908	4,391,736	-	3%	3%	13%
1983	2,000	3,299,000	29,558,000	35,747,000	-	167,446	1,034,179	3,260,956	-	5%	3.5%	9%
1982	1,000	3,907,000	23,608,000	45,656,000	-	35,000	980,000	3,604,000	-	1%	4%	8%
1981	-	6,328,000	22,174,000	34,870,000	-	186,000	1,439,000	3,234,000	-	3%	6.5%	9%
1980	1,000	6,980,000	14,368,000	34,749,000	-	67,000	623,000	3,524,000	-	1%	4%	10%
1979	32,000	9,934,000	15,057,000	26,172,000	1,000	452,000	926,000	4,356,000	3%	5%	6%	16.5%
1978	5,000	10,932,000	14,768,000	19,353,000	-	598,000	959,000	3,672,000		5.5%	6.5%	19%
1977	1,000	13,699,000	11,665,000	14,201,000	-	579,190	1,677,164	2,301,620		4%	14%	16%
1976	15,480	15,716,710	6,915,323	11,068,609	-	676,050	82,800	1,649,240	-	4%	1%	15%

* UK figures for 1986 are provisional only.

FACTOR VIII UNITS USED FOR TREATMENT OF HAEMOPHILIA A PATIENTS 1976-1986

TABLE C

	UK TOTAL	PATIENTS	AV/PT/YR	NCLE TOTAL	PATIENTS	AV/PT/YR
1986 *	86,296,000	2,273	37,966	6,586,762	145	45,426
1985	75,168,000	2,231	33,693	6,760,185	119	56,808
1984	77,056,000	2,259	34,111	5,687,968	125	45,504
1983	68,606,000	2,106	32,576	4,462,581	117	38,142
1982	73,172,000	2,251	32,506	4,619,000	144	32,076
1981	63,371,000	2,217	28,584	4,859,000	143	33,979
1980	56,098,000	2,107	26,625	4,214,000	166	25,386
1979	50,655,000	2,257	22,444	5,735,000	145	39,552
1978	45,058,000	2,078	22,000	3,672,130	171 ‡	21,474
1977	46,223,000	2,084	22,180	4,557,974	115	39,635
1976	33,716,122	2,061	16,359	2,608,090	153	17,046

* UK figures for 1986 are provisional only.

‡ Not adjusted for duplicates

TABLE D

BLOOD PRODUCT CHOICE FEBRUARY 1988

Haemophilia B: NHS IX HT (D) CONC

Haemophilia A:

> 2% VIII DDAVP

< 2% VIII options are:

1. NHS volunteer donor cryoprecipitate
2. NHS volunteer donor VIII HT (D) Conc
3. Cutter (Koate) paid US donor HT (D) Conc
4. Armour (Monoclate) paid US donor HT (D) Conc
5. Alpha (Profilate) paid US donor HT (slurry) Conc
6. Behring (Hoechst) paid donor HT (W) Conc
7. Immuno (Kryobulin) paid donor HT (steam) Conc
8. NYBC Tri-n-Butyl Phosphate (solvent)
   Sodium Cholate (detergent)
   Paid US donor Conc

Pending

9. DNA: Baxter Hyland (Travenol)
   : Cutter

FIGURE 1

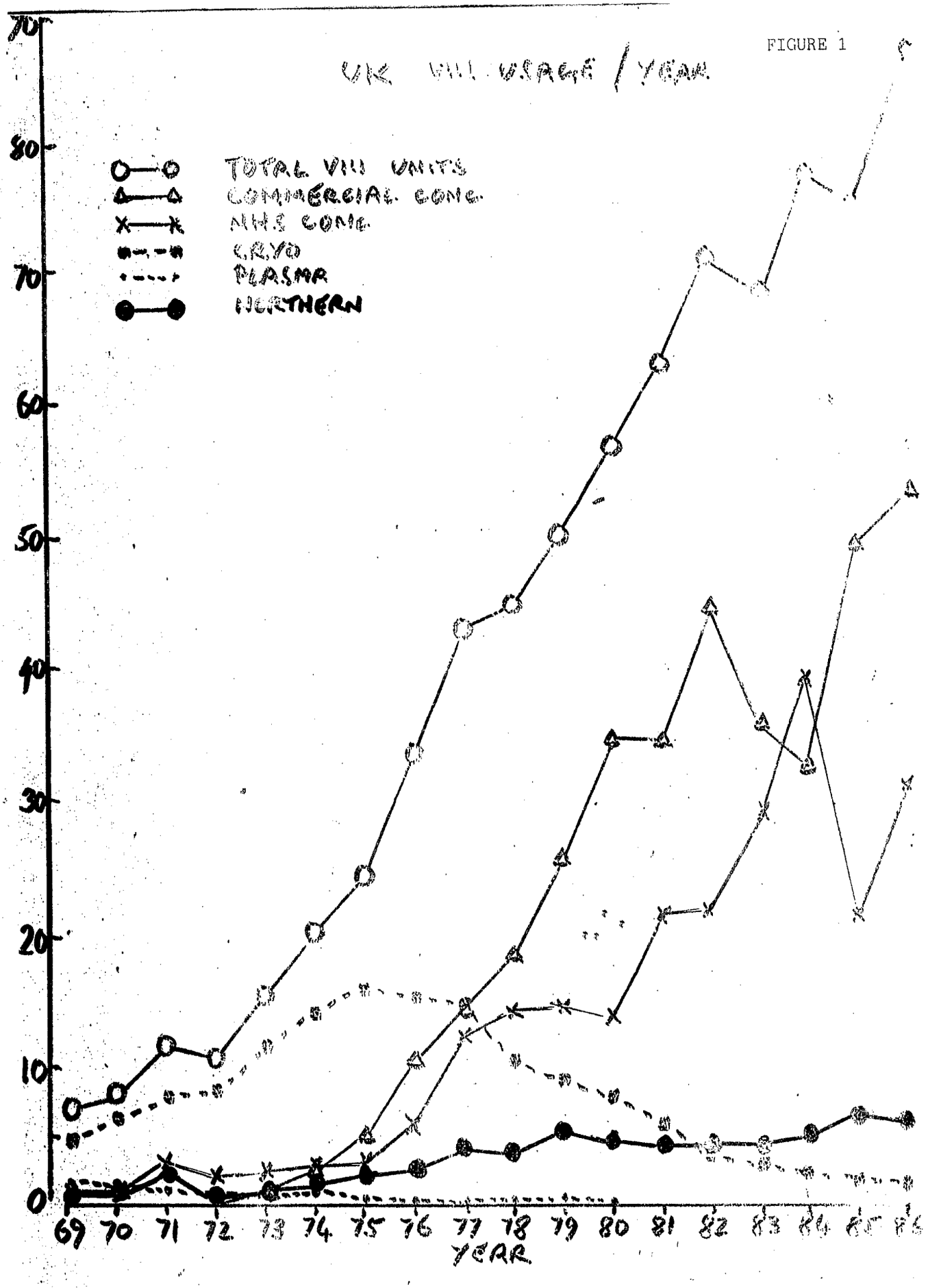
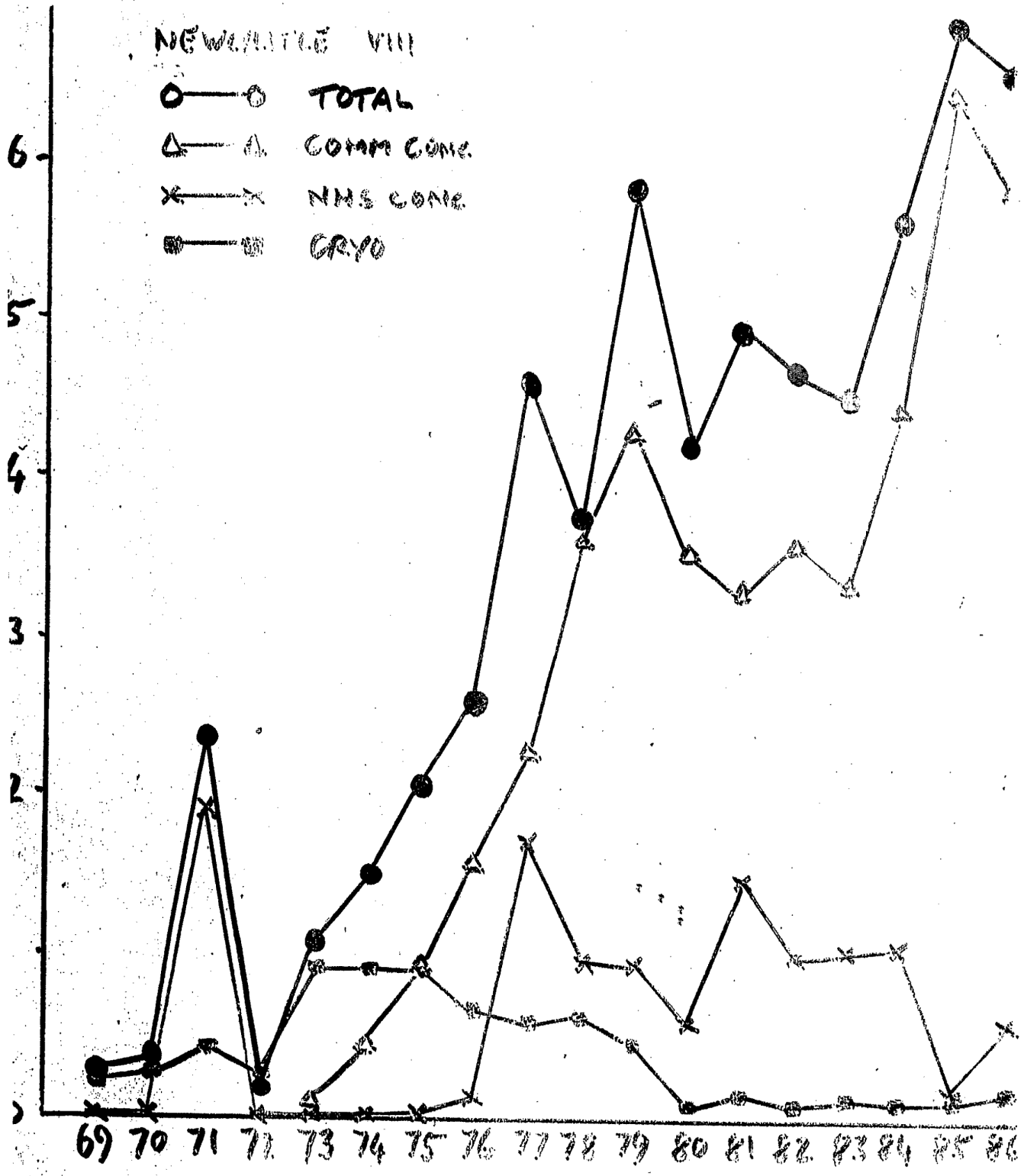


FIGURE 2



NORTHERN REGION AS % UK VIII USAGE