PATRON: H. R. H. THE DUCHESS OF KENT

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THE HAEMOPHILIA SOCIETY

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NEWS BULLETIN

AUGUST 1974

TREATMENT OF HAEMOPHILIA

During the past few weeks there has been a good deal of correspondence in the "Lancet" which has highlighted how the financial troubles of the National Health Service are affecting the supplies of materials used for the treatment of haemophilia.

A detailed and comprehensive letter from Dr. Rosemary Biggs of Oxford stated that because of the shortage of material 90% of haemophilic patients in the United Kingdom are receiving less than the optimum treatment for their complaint. Essential but non--urgent operations are being postponed and delay is arising in putting patients on to home treatment. Other doctors have written giving their views, as has the Haemophilia Society. Some of these letters are reproduced on pages 3, 4 and 5 of this Bulletin.

To draw the attention of the Secretary of State of the Department of Health and Social Security, The Rt. Hon. Mrs. Barbara Castle, M.P., to the situation, questions were asked in the House of Commons on 9th July 1974 by Mr. Lewis Carter-Jones (Labour-Eccles) which produced the following statement from Dr. David Owen, the Parliamentary Under-Secretary of State:-

> "The supply of Factor VIII produced within the National Health Service is at present insufficient for the optimum treatment of haemophilic patients. I hope that it will be possible to increase our supplies and meanwhile product licences were issued last year to two firms to market imported FactorVIII in the United Kingdom. Adequate stocks, I understand, are held of this commercial material. It is not the Department's normal practice to make central purchases of health service supplies but central contracts were arranged to facilitate the purchase of this material by health authorities. I recognise the desirability of enabling these patients to receive treatment at home but progress in this direction is likely to depend largely on the extent to which production of Factor VIII within the National Health Service can be increased".

A further question from Hon. C. M. Woodhouse (Conservative-Oxford) produced a similar reply.

Surely it is ludicrous that a Minister should state that there are "adequate stocks" of commercially produced Factor VIII, imported under licences issued by the Government, in the knowledge that it cannot be purchased by most hospitals because the necessary money is not available.

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MEMBER OF THE WORLD FEDERATION OF HEMOPHILIA

The figure of £1-2 million which it is estimated would purchase sufficient commercially produced material to adequately supplement that made by the N.H.S. is a tiny drop in the ocean of the total expenditure which in the year 1972-3 reached almost £3,000 million. It is, for example, a small fraction of the amount it is estimated will be lost to the N.H.S. by the phasing out of private patient beds. Whether or not you agree with this it is a matter for speculation why, if money can be forfeited for what it is claimed is a point of moral principle, it cannot, apparently, be just as easily found for what, in this instance, might be the principle of saving a life or preventing the crippling of a young child.

The general discontent which is rife throughout the N.H.S. at the present time does not help in finding a solution to our problem. When the Haemophilia Society recently offered a hospital assistance in the form of voluntary workers to help in increasing the production of cryoprecipitate, we were told that such help might well be resented by the laboratory technical staff to such an extent that "industrial action" could be the result. Some may be shocked by this attitude but who can say they would not have similar feelings if, like so many in the hospital service, they were in a job in which they are overworked, underpaid, and feel they are being taken advantage of because they have more conscience about their responsibilities than other more powerful sections of the community.

If there is to be an answer to the problem affecting haemophiliacs then we must see to it that those in public office are aware of the facts. We therefore urge all members to write to their Member of Parliament, or if by the time you receive this Bulletin we are in the throes of a General Election, write to all your prospective candidates. Such pressure will ensure that all in the House of Commons will at least be aware of the present deplorable situation.

We can only hope that this knowledge will prompt some to take action which will contribute towards achieving a solution.

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The letters on Pages 3, 4 and 5 and the article on carriers on Page 5 are reproduced with grateful acknowledgments to the Editor of the "LANCET".

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We will be pleased to send a further copy of this News Bulletin to any member upon request.

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THE LANCET, AUGUST 3, 1974

BLOOD FRACTIONS FOR HÆMOPHILIA

SIR,—This Society wishes to endorse wholeheartedly the pleas made in your correspondence columns in the past few weeks for an increase in the supply of blood fractions for treating hæmophiliacs.

We are most concerned, because the present situation is causing hæmophiliacs to suffer unnecessarily. In the past, such sufferings were inevitable because no effective treatment existed. Today, thanks to the work of doctors and research-workers, good treatment has been developed, but is not being made available for want of what is, proportionately, a small sum of money.

Treatment for hæmophiliacs varies from area to area. In some hæmophilia centres, supplies of clotting factors are adequate, and hæmophiliacs receive treatment based, as it should be, solely on the nature and extent of each hæmorrhagic episode; but in many centres these treatment criteria cannot be followed because the staff are virtually forced to ignore individual needs and to base treatment solely on the limited supplies of concentrates they have to hand. We have the greatest admiration and respect for the directors of the hæmophilia centres and their staffs and cannot but feel it is a ridiculous waste of their time that they should have to put such efforts into scrounging blood products from various sources in order to provide their patients with even this minimum of treatment.

Mention has been made of the cost of purchasing commercially produced material as an interim measure until the N.H.S.-produced concentrates are available in greater quantities, and of the cost of so increasing such N.H.S.-production. However, against this must be set the considerable savings that would result from better treatment. It would mean a reduction in the number of hospital attendances with a consequent saving in valuable bed space and in doctors' and their staffs' time, reduced social-security claims, reduced calls upon ancillary services such as the ambulance service, and a reduction in time lost from work and school. The most important advantage of adequate treatment is, however, one upon which no price can be placed, and it should be the major concern of the health authorities, for it is the goal for which all concerned with the welfare of hæmophiliacs are working—namely, the freeing of the hæmophiliac from the effects of his complaint. Those hæmophiliacs who are in receipt of adequate treatment demonstrate that with such treatment hæmophiliacs lead normal lives, holding down normal jobs and playing a full part in the community. For the N.H.S. to, in effect, prevent the medical profession extending such optimum treatment to all sufferers is a scandal that should not be permitted to continue.

Unfortunately, we are only too well aware in this Society of the shortcomings of the N.H.S. We are called on repeatedly by hæmophilia centres for funds to support their work; and, as well as providing funds for research, we have made grants which we know are, in effect, subsidising the N.H.S., being used as they are for the equipment and staffing needed to provide day-to-day treatment for hæmophiliacs. Despite criticism from some of our members of this, we are prepared to give support rather than see hæmophiliacs suffer unnecessarily, but we feel it is deplorable if we have now to consider providing money for the purchase of the actual products for treatment. Such products should be available in adequate quantities for the routine treatment of hæmophiliacs through the Health Service. Many other disorders need not dissimilar continuous routine care, and we cannot help wondering what would be the reaction if the N.H.S. decided it would not provide funds for the drugs already available for treating such conditions.

The purchase of commercially produced blood products will only be necessary until the N.H.S. and the Blood Transfusion Service can produce sufficient for hæmophiliacs' needs, but in the interim we must urge most strongly that funds are found to ensure that no hæmophiliac is being deprived of his entitlement to the treatment he needs.

Hæmophilia Society,
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16 Trinity Street,
London SE1 1DE.

JOHN L. PROTHERO,
Hon. Secretary.

THE LANCET, JULY 13, 1974

Hæmophilia Carriers

Mrs A has a hæmophilic brother, Mrs B's sister has a hæmophilic son. What is the risk that sons of these women will be hæmophilic too? Until quite lately their doctor could only have explained the inheritance of hæmophilia and pointed out the consequent risks; there was no way of finding out whether the women were carriers or normal. When a technique for estimating antihæmophilic factor (A.H.F., factor VIII) in plasma was devised, there were hopes that carriers would prove to be abnormal. But in practice not all obligatory carriers (i.e., the daughters of hæmophilic males) had A.H.F. levels below the rather wide normal range, and only a few other possible carriers had low figures. So the estimation did no more than enable a few carriers to be identified; the others had to be told that the usual risks still applied. Some two years ago an editorial [1] commented on research showing that hæmophilic plasma contained a material antigenically similar to A.H.F. but with no coagulant properties. In most hæmophilic patients the normal amount of active A.H.F. was almost totally replaced by this functionally inactive but antigenically similar A.H.F. There seemed a possibility that imbalance between A.H.F. clotting activity and the amount of functionally inactive A.H.F. in plasma might offer a means of identifying female hæmophilia carriers. A test based on this imbalance has now proved to be very practical.

ZIMMERMAN, RATNOFF, and LITTELL [2] developed an immunoassay for A.H.F. that estimated the plasma-level of both coagulant and antigen activity; this, combined with the usual assay for A.H.F. coagulant activity, enabled them to estimate the amounts of active and inactive A.H.F. in a group of women who were known to be hæmophilia carriers. These women were daughters of hæmophilic males, mothers of more than one hæmophilic male, or mothers of a single hæmophilic male who had other relatives with the disease. They tested 25 such carriers and 22 normal female controls; 23 out of the 25 carriers proved to have in their plasma both functionally active A.H.F. and antigenically detectable but functionally inactive A.H.F., and the ratio of A.H.F. activity to inactive antigen was only about half that found in the normal women. BENNETT and RATNOFF [3] have used the same methods with more varied groups. They tested 42 known female carriers and detected the carrier state in 40. In addition they tested 34 daughters of known female carriers and found that 17 of them were carriers too. This is impressive because it fits in with the expected 50% distribution. In a group of 10 women who had hæmophilic sons but no previous family history of the disease, 7 gave a positive carrier test. In one family the maternal grandmother was tested and was a carrrier, but in another family the grandmother was normal; presumably this represents a mutation in one of the female X chromosomes. In one family where the mother was not a carrier, BENNETT and RATNOFF were surprised to find that her two daughters were also normal, thus raising the possibility of a mutation on the X chromosome of the male.

These results are very encouraging. ZIMMERMAN et al. write that they were able "to identify 92% of carriers correctly at a level of certainty that would misclassify less than 1% of normal individuals as carriers". The position therefore now is that we can tell almost every woman who is a carrier about her state, and if the test is negative we can tell her that she has about a 90% chance of really being normal. In any biological estimate of this kind, complete certainty is not practical, especially when mutations may occur; and this may well be as near to certainty as we can hope for. These results apply only to classic hæmophilia; the identification of female carriers of Christmas disease (factor-IX deficiency) may be rendered more difficult by the number of genetic variants being found.[4]

1. *Lancet*, 1972, i, 729.
2. Zimmerman, T. S., Ratnoff, O. D., Littell, A. S. *J. clin. Invest.* 1971, 50, 255.
3. Bennett, B., Ratnoff, O. D. *New Engl. J. Med.* 1973, 288, 342.

ANNUAL DRAW

We regret it has not been possible to organise a special Meeting for the Annual Draw on 22nd September. It has therefore been postponed to take place at the Annual General Meeting of our North-East (Leeds) Group on the afternoon of Saturday, 28th September 1974. The venue is The Handicapped Centre, Hanover Square, Leeds.

We thank all those who have supported the Draw and ask that the counterfoils of tickets sold be returned as soon as possible.

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CHRISTMAS CARDS

Enclosed are leaflets and order forms in respect of this years Cards. So as to clear stocks two of last years designs have been included in the selection. We also still have packets of "MICE-A-BED" at 6 for 20p and "FLOCKS BY NIGHT" at 6 for 16p, if any member would like some of these.

We have calculated an average postage charge but on orders for more than 10 packets of cards we will be pleased to forward an invoice showing the actual postage paid. We hope this will avoid anyone paying a disproportionate amount for postage on large orders as happened in a few instances last year.

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CHRISTMAS PARTY

The Society's Christmas Party will be held in the Concert Hall at the Centre for the Handicapped, 10 Warwick Row, London, S.W.1. on the afternoon of Sunday, 8th December 1974.

As will be recalled last year's Party was cancelled because of the petrol crisis - we are hoping for better luck this year so please make a note of the date.

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"LIVING WITH HAEMOPHILIA"

This most excellent book by Dr. Peter Jones, Director of the Newcastle Haemophilia Centre, has now been published.

It covers all aspects of haemophilia and is available to members of national haemophilia societies at a reduced price of £3. To purchase a copy or to obtain one on approval for 14 days write to:-

MTP Medical and Technical Publishing Co.Ltd.,
P. O. Box 55, St. Leonard's House,
Lancaster, Lancs.

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V.A.T. BURDEN LIFTED

Following an energetic campaign by the National Fund for Research into Crippling Diseases, the Government has zero rated "The supply of medical and scientific equipment purchased with charitable or voluntarily subscribed funds for donation to designated non-profit making hospitals or research institutes, solely for use in medical research, diagnosis or treatment".

Our grateful thanks go to the National Fund for the efforts on behalf of all medical charities. This will make a considerable difference to the grants we are able to make from our Research Fund.

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Letters to the Editor

SUPPLY OF BLOOD-CLOTTING-FACTOR VIII FOR TREATMENT OF HÆMOPHILIA

SIR,—The treatment of hæmophilic patients involves the replacement in their blood of an essential substance which they lack. In this respect, the disease resembles diabetes or pernicious anæmia. Factor VIII to a hæmophilic patient is literally his expectation of life. Hæmophilia differs from diabetes or pernicious anæmia in that the missing factor VIII can only safely be provided from human blood. The hæmophilic patient is thus indebted to society and in turn is the responsibility of society in rather a special sense.

Without treatment, before the middle of this century, few patients reached adult life and those who did were helpless cripples. Over the past 12 years, blood products containing factor VIII have gradually increased in amount. In the early part of this time, medical attention was centred on the cure of life-endangering bleeding and on protection during essential major surgery. As more material became available, patients were treated for particularly dangerous muscle hæmatomas and hæmarthroses in the hope of reducing somewhat the severity of crippling and delaying the age of onset of deformity. The present, but still modest, objective is to treat all developing musculoskeletal bleeds as early as possible, hopefully to prevent the occurrence of severe deformity in all patients. This form of therapy is called " on demand " treatment. Very many of the patients treated on demand arrive at the hospital on crutches, in ambulances, and with painful swollen joints. Most such episodes of musculoskeletal hæmorrhage resolve with treatment, but there can be no doubt at all that in the long term these patients will have arthritic joints long before those in the normal population. An extension of on-demand hospital therapy to the home (home therapy) so that treatment is given by the patient to himself, by a relative, or by a general practitioner would undoubtedly reduce the damage and also the anxiety under which patients and their families now live. It should be noted that even home therapy is a modest objective when comparison is made with prophylaxis. In prophylaxis, treatment would be given to prevent the occurrence of bleeding altogether. Prophylaxis is, of course, the rule for patients with diabetes or pernicious anæmia; its application to hæmophilic patients would treble the present estimated requirements of factor VIII.

Those who treat hæmophilic patients in the United Kingdom have in the past of necessity tolerated the chronic undertreatment of their patients and have put much time and effort into spreading the inadequate amounts of therapeutic material thinly so that deprivation should be least damaging. Essential but non-urgent operations have been postponed and are still being postponed. Economy has also been achieved by calculating the dose for each lesion for every patient to give the absolute minimum dose. In addition, patients have not been put onto home therapy who would greatly benefit by this treatment. Even with dire economy, some centres have been hard pressed to maintain minimum treatment. For example, the treatment of the boys at the Lord Mayor Treloar College at Alton in recent years has been maintained against a background of begging and borrowing from other centres from one week to the next. Were the school not supplemented in this way, it is calculated that there would be a deficit of about 260,000 factor-VIII units annually. There is, in fact, evidence that 90% of hæmophilic patients in the United Kingdom receive less (and in some cases much less) than optimum treatment for their complaint. The consequences of this undertreatment include subjecting the patients to unnecessary, painful, and destructive bleeding into joints and muscles. Ancillary effects of undertreatment include loss of educational time and inability to hold continuous employment.

The question that arises is for how long should this shortage of factor VIII be considered to be a reasonable feature of hæmophilia treatment? Two things, in my view, make continued limitation both unnecessary and unethical. The first of these is the fact that three commercial companies are now licensed to sell good-quality human factor VIII in this country and they have between them amounts of material adequate to supplement the present provisions of the National Health Service. In fact, at the time of writing, one commercial firm has over 1,000,000 units of factor VIII awaiting use.

The second consideration which renders adequate provision of factor VIII both feasible and desirable is the fact that blood can now be collected in plastic containers, which makes it possible to use the red cells for patients who are anæmic and the plasma for patients who lack some plasma components. The blood donated in the United Kingdom is freely given by responsible citizens; the best use of this valuable resource clearly lies in the best use of all parts of the blood. With regard to the provision of factor VIII by the N.H.S., we can say with certainty that we have the skill, experience, and capacity in this country to provide factor VIII of very high quality in the amounts required.

Why, then, is there still a chronic shortage of factor VIII in the clinics where patients are treated? The reason is that factor VIII is expensive, whether bought commercially or made by the N.H.S. Over the country as a whole, a supply of commercial human factor VIII sufficient adequately to supplement that made at present by the N.H.S. would cost an annual £1–2 million. It is claimed that a sum of money of this order cannot be found from current allocations to the N.H.S. without reducing money spent on other necessities. To make increased amounts of factor VIII in the N.H.S. is also likely to be expensive since it would require substantial expenditure on organisation of blood-supplies, on staff, apparatus, and buildings for fractionation. Set against this financial argument, it must be remembered that poorly treated hæmophiliacs also cost a lot of money in their role as hospital inpatients and in receipt of social-security benefits. But of course the financial argument takes no account of the misery and anxiety attached to frequent painful episodes of bleeding and inability to hold a normal place in school and society. In the long run it will probably be found cheaper to pay for these patients' treatment rather than to pay for the inevitable consequences of undertreatment.

When, as a direct outcome of years of research, lifesaving therapeutic materials suddenly become available to a population of patients previously chronically undertreated, there surely should be some means of assimilating this welcome advance, otherwise it is stupid to undertake the research in the first place. How this should be achieved is an administrative and political problem rather than a medical one. Perhaps there should be a special fund in the N.H.S. set aside every year for the practical implementation of research discoveries. Perhaps an organisation should be set up to collect money on a charitable basis to supplement the N.H.S. funds available for the introduction of new treatments. Whatever solutions there may be for problems of this sort in general, some immediate solution should be found for the ridiculous impasse of large available stocks of therapeutic materials locked up in stores because no-one will buy them and, on the other hand, patients in dire need of this same material.

Oxford Hæmophilia Centre,
Churchill Hospital,
Headington,
Oxford.

ROSEMARY BIGGS.

THE LANCET, JULY 6, 1974

BLOOD FRACTIONS FOR TREATMENT OF HÆMOPHILIA

SIR,—I write to support Dr Biggs's plea (June 29, p. 1339) for a realistic supply of blood fractions for treating hæmophilia. For 20 years we have been able to make a precise diagnosis, and for 10 years the preparation of appropriate blood fractions has been possible. We know that treatment material is being provided within the Health Service in increasing amounts, but it is still far short of what we need. Until the N.H.S. provision is adequate, it is cruel not to make good the shortfall from the large supplies of good commercial material which, as Dr Biggs says, are now available.

The predominant symptom of hæmophilia is severe episodic pain, from the extravasation of blood into joints or tissues. The treatment of each episode is the prompt intravenous administration of the appropriate blood fraction, to stop the bleeding. At present, patients suffer much delay through having to attend a hæmophilia centre for each treatment. The longer the delay, the more severe the pain becomes and the greater the risk of ultimate crippling. When freeze-dried material is provided for immediate treatment at home or work, much suffering and the consequent need for analgesic drugs will be avoided. Therapeutic material now exists. Money must be found so that sufficient may be purchased until N.H.S. resources are adequate for the needs of patients with hæmophilia.

Department of Hæmatology,
Louis Jenner Laboratories,
St. Thomas's Hospital,
London SE1 7EH.

G. I. C. INGRAM.

THE LANCET, JULY 13, 1974

TREATMENT OF HÆMOPHILIA

SIR,—I am prompted to write in support of Dr Biggs' main theme (June 29, p. 1339). Surely in this day and age the hæmophiliac patient should be as entitled to proper prophylaxis by treatment with blood-clotting-factor VIII as the diabetic patient is with insulin or the patient with pernicious anæmia with vitamin B_{12}. It is estimated that to reach this goal for the hæmophiliac patient would treble the present estimated requirements for factor VIII. This aim should be prosecuted without delay.

Those of us in charge of hæmophiliac patients no longer feel that we can tolerate the undertreatment of these patients. Also galling is the fact that major research in the United Kingdom, resulting in the acquisition of knowledge to treat hæmophiliac patients properly by modern standards, cannot be fully implemented presently for reasons outside the control of hæmophilia-centre directors.

Finally, in spite of the relative rarity of hæmophilia, research into the nature and production of factor VIII in the United Kingdom has benefited directly and indirectly large numbers of patients with a wide variety of congenital and acquired hæmorrhagic and thrombotic states.

E. K. BLACKBURN,
Ad-hoc Chairman,
Hæmophilia Centre Directors
of the United Kingdom.

Hæmophilia Centre,
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THE LANCET, JULY 20, 1974

Letters to the Editor

BLOOD FRACTIONS FOR HÆMOPHILIA

SIR,—I strongly support Dr Rosemary Biggs's proposal for a special allocation of funds for the purchase of commercial factor-VIII concentrate (June 29, p. 1339). In the long term this country must provide all its own blood products, but if a special grant could be made for freeze-dried concentrate so that hæmophilic boys at Lord Mayor Treloar College could be adequately treated at the college and for patients suitable for home treatment, this would go a long way towards easing the situation.

From this centre 24 hæmophilic patients or close relatives have learnt to administer cryoprecipitate. 19 of these are on regular home treatment. Although these families are all very grateful to the North London Blood Transfusion Centre for making cryoprecipitate available, and although they have all done remarkably well, they are always on a knife edge of anxiety about their supplies. Patients, including one family in which there are 2 hæmophilic boys, ring up continually to find out whether we have had a large enough delivery to be able to let them have another few bags.

As Dr Biggs so rightly points out, there seems little point in national support for research through the Medical Research Council unless the Government are prepared to develop the successful outcome of such work.

Hæmophilia Centre,
Royal Free Hospital,
London WC1X 8LF.

KATHARINE M. DORMANDY.

SIR,—In this centre it takes two days to train an experienced hæmophilic patient to treat himself at home with small-volume intravenous injections of factor-VIII concentrate as soon as he, or his parents, know that bleeding has started. With immediate treatment hæmophilic bleeding stops. So does pain, loss of function, and long-term crippling.

The expense of home therapy is considerable. However, like Dr Biggs, we believe that to withhold such treatment is unethical, and we think that, in purely economic terms, the cost will be largely offset by savings in hospital and ambulance time.

For years the daily struggle to obtain enough factor-VIII-containing material (usually cryoprecipitate) to meet the needs of hæmophilic patients has been a therapeutic nightmare. Although in the Newcastle area we have received an excellent service from our Regional Transfusion Centre the needs of growing children and the increasing use of surgery have meant that demand has often outstripped supply. Like Lord Mayor Treloar College we have had to turn to other centres for help, but in spite of this we know that some patients, particularly in the periphery, still receive suboptimal treatment during acute bleeding episodes.

It is nowadays thankfully rare to read words like " cruel " (Professor Ingram, July 6, p. 56), " deprivation " and " misery " (Dr Biggs, June 29, p. 1339) applied to the care of the physically handicapped in the United Kingdom. The majority of hæmophilic patients only become physically handicapped because of inadequate treatment over the years. With adequate supplies of factor VIII concentrate there can be no excuse for this. The resources must be made available.

Newcastle Hæmophilia Centre,
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PETER JONES.