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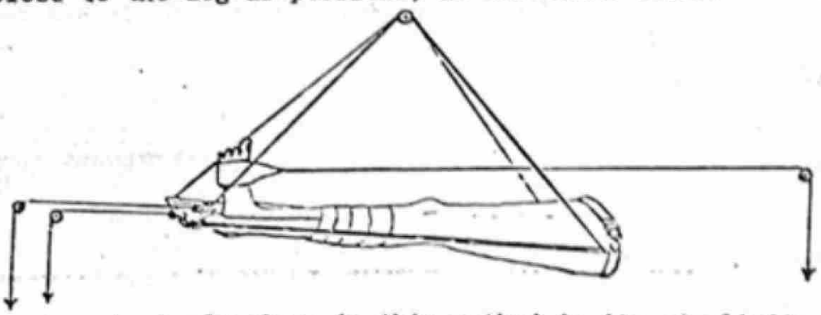
Prevention of contractures after bleeding into the calf muscles

Bleeding into the calf muscles is a common and serious event in the severe haemophiliac which may occur spontaneously or as a result of trauma. The muscle which is most commonly affected is the gastrocnemius. Resolving haematomata in this muscle cause fibrosis and contracture with shortening of the muscle body and an equinus deformity of the foot. In two fairly recent series the incidence of contractures in all muscle bleeds was 10% and 11%, whilst those involving the calf muscles alone resulted in an incidence of 36%. Because of the difficulties in treating this complication in calf muscles a variety of conservative and operative procedures have been used. These have usually involved the use of immobilisation in serial or hinged plasters, often over periods of weeks or months. Failure of this method producing chronic deformity has necessitated eventual surgical correction by extension of the tendo-achilles or gastrocnemius muscle slides.

A method of traction has been developed at this centre which appears to be much more rapidly effective, correcting such equinus deformities after severe calf bleeds within 3 days. The method employs the principle of traction/counter traction and has been used successfully in the treatment of six such bleeds. Haemostasis is achieved first by standard replacement therapy (usually over 2 - 4 days) and then traction applied. The affected limb is placed in a Thomas's splint (to which a nominal weight is added) with below knee skin traction of approximately 3 lb. A padded Cramer wire cradle is applied to the ball of the foot and balanced by counter traction of the same amount. It is essential that the traction should be parallel to the limb and that the traction cord should be as close to the leg as possible, as indicated below.



The important advantage in this method is its simplicity and rapid effectiveness with resultant avoidance of prolonged immobilisation and muscle wastage. We feel that this is achieved because (1) the system is dynamic, (2) the direction of traction is such that full dorsiflexion is produced and (3) the apparatus is easily removable and allows physiotherapy during the period of traction.

some responsibility for the enormous increase in bleeding frequency.

Following a meeting with the Headmaster, Dr Rainsford and Dr McHardy, it is ined that for the summer term even closer supervision of the boys will be ried out, both from the medical and teaching point of view. Football will be hibited and, furthermore, boys will be assessed clinically and, on this sessment, their ability to take part in various sports and leisure activities ill be determined. It is hoped that the bleeding frequency will fall with the ntroduction of these measures.

USE OF THERAPEUTIC MATERIALS

The breakdown of factor VIII containing materials used during the two terms is shown below. It is assumed that one bag of Cryoprecipitate is equivalent to 70 units and one bag of fresh frozen plasma equivalent to 200 units.

	Kryobulin	Elstree Lister	Hemofil	Cryo	F.F.P.	Totals
Autumn	177,663	49,650	-	217,140 (3,102)	4,000 (20)	448,363 units of factor VIII
Spring	119,589	46,200	99,924	175,280 (2,504)	5,400 (27)	446,393 units of factor VIII

In view of the increased bleeding frequency for the Spring term it is remarkable that the total consumption of units of factor VIII during both terms is very nearly the same. This may be explained by the fact that the Autumn term was some seven days longer than the Spring and that, during the Autumn term, some 40 extra prophylactic transfusions were carried out. In addition, the figures given are quoted for Treloar Haemophilia Centre and do not take into account fluctuations in Outpatient attendance.

It will be noted that, in the Spring term, almost 100000 units of Hemofil were used whereas in the previous term this product was not administered. At the beginning of the Spring term, during the influenza outbreak, some seven boys had severe anaphylactic reactions to Kryobulin: GRO-A GRO-A . In the case of GRO-A GRO-A , this reaction was followed by collapse, with no detectable blood pressure or pulse. In ivew of the seriousness of these episodes it was felt unwise for the affected boys ever to receive Kryobulin again and they were restricted to Hemofil. The marketing company for Kryobulin was contacted and the Managing Director, Mr Norman Berry, arranged a meeting to discuss this problem at which the following people were present: Dr A. Aronstam, Prof. C. Kunz (Vienna University), Dr H.Eible (Immuno A.G.), Dr O.F. Schwarz (Immuno A.G.), Mr Norman Berry and Dr P.J.Kirk. It was decided that these episodes were true anaphylactic reactions to Kryobulin. However, as the reactions all occurred at about the same time and all those affected were Lord Mayor Treloar College boys, it was felt that there was some unknown contributory factor at the college. It was noted that other boys at Treloar Haemophilia Centre, Oxford and Sheffield had not reacted adversely to the offending batches.

Prophylaxis in haemophilia was also discussed at this meeting and it was felt that two boys, namely GRO-A and GRO-A could benefit from a thrice-weekly prophylactic regime. It is to be hoped that such a regime would not only reduce their bleeding frequency, but also have some beneficial effect on the cystic bone changes which these boys exhibit.

Dr Eibl of Immuno A.G. kindly offered to supply this material gratis and a preliminary protocol was drawn up and given to him to present to the Austrian Government, from whom approval is necessary for the export of this material.

It is perhaps relevant to mention GRO-A, who commenced at the College the beginning of the Spring term. In the past he has had very severe reactions cryoprecipitate, Elstree concentrate and Kryobulin. Since he has been stricted to Hemofil he has had no reaction of any description. Unfortunately e 14 days after receiving a transfusion with Kryobulin GRO-A developed hepatitis ich will be discussed under the appropriate heading.

PROPHYLACTIC TRIAL

During the Autumn term six College boys were placed on a prophylactic regime of twice-weekly transfusions. The boys were selected on clinical grounds, either because of a general severe bleeding tendency or, in two cases, where there was a particularly troublesome joint. One boy, GRO-A, had improved sufficiently with this regime by the end of the term that the prophylactic transfusions were discontinued. During the Spring term five boys were treated on the same regime: it would appear to have been of particular benefit to GRO-A during the second term as his number of bleeds was reduced from 12 to only 4. GRO-A and GRO-A all benefited to a lesser extent. GRO-A was maintained on this regime to enable full recovery of his right knee. This was very successful and prevented all bleeds up until the end of February. Unfortunately, he had a traumatic bleed into the right knee and required intensive treatment until the end of term. This case was interesting in that for some 2 - 3 weeks, despite there being no objective evidence of bleeding, there was a great deal of pain and muscle spasm in the right leg and the joint was virtually fixed at 70-80° flexion. At the suggestion of Mr GRO-A, he was given intravenous Valium with Fortral and complete relaxation occurred and full extension was achieved. After this, mobilisation proceeded quite quickly and he was able to go home on time wearing his block leather splint.

The trial has been concluded and the results are at present being evaluated by Dr Aronstam.

CLINICAL PROBLEMS

GRO-A : This boy was receiving twice-weekly prophylaxis during the Autumn term and, until the end of November, he had sustained only five bleeds. On 22.11.75 he had a traumatic bleed into his right elbow after a fall. Previous radiological evidence had shown the presence of a large cyst in the proximal end of the ulna, and the olecranon and the olecranon fossa are grossly enlarged. This episode was first treated conservatively by means of immobilisation and replacement transfusion. However, after some 24 hours he was still in considerable pain and it was felt necessary to aspirate the joint under general anaesthesia. Further replacement therapy was given and a P.O.P. cast applied and he recovered uneventfully.

GRO-A : On 6.11.75 this boy fell onto his right buttock and sustained a traumatic bleed into the right hip joint, which was confirmed by x-ray. In view of the possibility of necrosis of the femoral head, he was treated very conservatively on strict bedrest for a period of 2 weeks. He was mobilised very gradually and recovered uneventfully. Follow-up x-ray showed no evidence of permanent damage to the femoral head.

GRO-A : GRO-A commenced at the College at the start of the Autumn term and it was apparent immediately that he bleeds virtually every other day, mainly into his right shoulder and right elbow. The right shoulder contains a haemophilic pseudo tumour in the sub-glenoid portion of the scapula and there is a possibility of bone infarction of a portion of the humeral head. The ulna is similarly affected with a large subarticular cyst. To endeavour to cure the bleeding into this joint, he was immobilised in abduction in a P.O.P. jacket for a period of 5 weeks. During this time no bleeding occurred into this joint. However, he had several bleeds into the left shoulder joint which, unfortunately, also seems to be affected by haemophilic pseudo cysts, although not to the same degree.

st in the abduction splint he was also given a twice-weekly prophylaxis
ime and a marked improvement in his bleeding frequency was evident. There
e no further problems with the right shoulder until the beginning of February
en a bleed into this joint occurred, possibly precipitated by trauma.
llowing this the old pattern was resumed and he continued to have very frequent
aemarthroses into this joint. A block leather splint has been made which fitted
orrectly only at the end of the Spring term. It remains to be seen whether this
form of immobilisation will prevent bleeding. Next term it is proposed to put
Michael on prophylaxis three times a week in view of the apparently poor
prognosis of the right shoulder joint.

GRO-A : This boy continues to present problems at the College. He has a severely disabled right elbow and right knee and, in view of the marked muscle wasting and bone overgrowth of the right elbow, it was decided to fit him with a block leather splint for this joint. He has not settled down well at the College from a medical point of view and continues to report imaginary bleeds while, at times he failed to report those that are genuine. Some minor success was achieved for the last few days of the Spring term when he did appear to wear his splint as instructed.

GRO-A : This normally mild haemophiliac bled into his right iliopsoas muscle on 1.2.76. Despite very careful management he had a recurrence of this bleed on 8.3.76 which took some 2 weeks to resolve. Apart from these episodes, his bleeding frequency this term was much increased and was mainly due to trauma affecting both joints and muscles.

HAEMOPHILIA WITH FACTOR VIII ANTIBODIES

GRO-A : This boy received ten transfusions during the Autumn term. A particularly troublesome event commenced on 19.9.75 when a tooth socket started to bleed. This required not only large amounts of factor VIII concentrates for replacement therapy but it was also necessary to transfuse him with packed red cells. During the Spring term of a total of four bleeds only one, that into the left thigh, required replacement therapy. His inhibitor level at the end of this term was 7 Biggs units.

GRO-A : GRO-A had 13 bleeds during the Autumn term but was transfused for only two of these episodes, one involving his right gluteal muscles, the other a severe bleed into the right ankle joint. During the Spring term he was unwell for most of the time with upper respiratory tract infections. He had frequent epistaxes which were particularly troublesome at the beginning of February when he required transfusion with packed cells and replacement therapy. For the remainder of the term the epistaxes continued on and off, though to a much lesser extent. In view of the experience of Oxford Haemophilia Centre with cautery for recurrent nose bleeds, it was felt inadvisable to embark on this form of management.

GRO-A : At the beginning of November this boy had a bleed into his right iliopsoas muscle after returning from a Leave weekend. His management was complicated by the delay in treatment and it was 2 weeks before mobilisation was complete. His inhibitor level at that time hovered around the 100 unit mark and thus very large quantities of factor VIII concentrates were necessary to control this bleed. GRO-A improved in the Spring term until 6.3.76 when severe trauma caused bleeds into his right gluteal muscles, right shoulder and a laceration involving the nose. It was not possible to visualise the laceration and frequent packing, large quantities of factor VIII concentrates and a blood transfusion were necessary over a period of 14 days. He is no longer at the College and should he require treatment apparently he will attend the North Staffs. Royal Infirmary. Dr Giles, the Haematologist there, has been given all details concerning his current management.

GRO-A : This boy continued to be interesting from the point of view of factor VIII inhibitor. During most of the Autumn term no detectable inhibitor was found and he was treated as an uncomplicated case of haemophilia. He sustained 13 bleeds for which he required 14 transfusions. He returned to the College at the start of the Spring term with a presumed retroperitoneal bleed which had been treated at Oxford. From the end of January until the end of February he received no replacement therapy and on 24.2.76 his inhibitor level was found to be 4 Biggs units. It is interesting to speculate as to whether the frequent factor VIII replacement therapy that he normally receives actually suppresses the development of factor VIII antibodies. Further work between ourselves and Oxford is proceeding.

GRO-A : This boy receives very little treatment and over the last few months no detectable factor VIII antibodies have been found. He did require treatment around the middle of March and it remains to be seen whether the inhibitor will reappear.

HEPATITIS STUDY

This started at the beginning of the Autumn term and the conditions for entry and other requirements are recorded elsewhere in the Protocol. The boys were restricted to a particular type of factor VIII replacement material and this is shown in Table VI.

Seventeen cases from Oxford Haemophilia Centre were included from November 1975 whilst two Edinburgh patients joined in February 1976. It is apparent that in conducting a survey of this type it is difficult to ensure the collection of frequent blood samples unless the patients are readily available. Furthermore, limiting patients to particular replacement materials also creates problems because of the overall shortage of factor VIII products. It is inevitable that some patients will receive, and have received, materials other than their specified product. The nursing and laboratory staff are to be congratulated on the careful and thorough way that specimens have been collected, separated and despatched to the Virus Reference Laboratory. The work of Dr Hugh Platt and the Chemical Pathology Department of Basingstoke District Hospital has been invaluable in processing large numbers of liver function tests which has been accomplished quickly and efficiently. The assays for 5'NT have been particularly helpful in assessing the relevance of the high alkaline phosphatases which occur inevitably in a population of this age group.

So far no patients from Newcastle have registered on the study but it is to be hoped that 12 patients restricted to Hemofil will be included in the near future.

Since the start, three of the College boys have contracted hepatitis:

GRO-A, GRO-A entered the study on 2.10.75 with normal liver function tests. He was restricted to Kryobulin and, on 29.10.75, his S.G.O.T. was just abnormal at 54 I.U. By 12.11.75 this had risen to 331 units and remained elevated until 12.3.76. For most of the Autumn term GRO-A was generally unwell. He complained frequently of tiredness, anorexia and nausea. He was never jaundiced and his bilirubin always remained normal. Both liver and spleen were slightly enlarged. At the start of the Spring term he was still complaining of anorexia, abdominal pain and pains in his joints; his liver was just palpable and tender. He was admitted to Sick Bay for a period of 2 - 3 weeks and his symptoms gradually disappeared. His HBsAg has always been negative and his HBsAb always positive. Provisionally he has been labelled as a case of anicteric non-B hepatitis.

GRO-A : This boy showed clinical and laboratory evidence of hepatitis soon after being entered on the Hepatitis study. On 26.1.76 his liver function tests were normal. By 30.1.76 he was feeling generally unwell with nausea and high temperature. He was tender in the right costal margin but his liver was not palpable. His blood picture was typical of infectious mononucleosis and, indeed, his monospot was positive. However, this was not confirmed by EB virus studies which were normal. This case is interesting in that the probable source of the

active material can be identified: 17 days prior to becoming ill he was infused with Kryobulin 09M 12375 and 09M 12975. This was his first exposure to large pool concentrates and other evidence would indicate that 09M 12975 is the offending batch. On the four occasions when he has been tested, his HBsAg has been negative, while his HBsAb (IEOF) is persistently positive. This would appear to be another case of non-B hepatitis.

GRO-A : This mild haemophiliac has infrequent transfusions. On 15.2.76 he received 278 units of Hemofil, batch 190875. Some 32 days later his S.G.O.T. became abnormal and just prior to leaving at the end of term, the S.G.O.T. had risen to 640 units (30.3.76). As he suffers from hereditary spherocytosis, his bilirubin is outside the normal range and is usually between 20 - 30 UM. This has risen to 42 UM. His HBsAg results have not yet been received, but prior to this term he has always been negative for antibody. Therefore he is at risk of developing hepatitis B. He will be investigated further in the summer term.

Apart from these three cases of acute hepatitis a number of boys have permanently elevated liver function tests. At present work is directed at determining the significance of these findings for it is important to ascertain whether they are suffering from chronic hepatitis and, if they are, whether this is benign or an aggressive process. Four boys have had liver scans which all show mild, but very definite, abnormalities. It is proposed to do further scans next term on other indicated boys. Regarding the problem with the acute hepatitis cases, it is important to exclude other causes of hepatitis apart from hepatitis B, namely: hepatitis A, cytomegalovirus and EB virus. Hepatitis A work is unsatisfactory at present because a suitable test has not yet been devised which is uniformly satisfactory. It is likely that in the near future a reliable test will become available, and testing of the stored serum samples will then be feasible. The testing of samples for antibodies to the subtypes d and y of hepatitis B by haemagglutination substantially increases the work load of the Virus Reference Laboratory. The reagents for this assay are flown from America and are stable for only one week. Consequently very large numbers of samples must be processed in a short time. It is to be noted that Drs Vandervelde and Vossart have worked very hard to ensure the efficient and rapid reporting of results.

CLINICAL ASSESSMENT

A new method of recording bleeds and joint function was brought out during the Spring term. On presenting with a bleed, joint function is measured with a goniometer and the improvement in joint movement is evaluated daily until normal function is restored. Thus a precise and reliable method of determining morbidity for a single bleeding episode is possible. This method will be developed further during the summer term and will allow more objective evaluation of different treatment regimes.

HAEMOPHILIA ARTHROPATHY and RHEUMATOID DISEASE

Dr Rainsford, who has now been appointed by the Area Health Authority as Honorary Consultant in Haemophilia, is continuing his work - under the auspices of the Arthritis and Rheumatism Council - into the immunology of arthritis and its relation to rheumatoid disease. He has been examining the synovial membranes of patients suffering from these conditions and in two out of the five cases of haemophilia that have been tested, an antibody has been discovered which appears to affect the coagulation mechanism. An apparently similar antibody has been detected in the synovia of four out of seven cases of rheumatoid arthritis which was not demonstrated in the one case of osteoarthritis which has been tested so far.

ACQUIRED INHIBITORS OF COAGULATION IN GLANDULAR FEVER

The stimulus for this work resulted from a four-year-old child with presumed glandular fever who presented with an acquired bleeding tendency. An antibody which appears to act against the coagulation pathway was found and detailed assays were performed to determine its site of action. A summary of the work to date is as follows: The antibody would appear to have the following characteristics:- it is heat stable, it appears to belong to the IgG class of immunoglobulins, the KCCT was prolonged and was not corrected by the addition of normal plasma, it does not appear to affect factors VIII, IX or fibrinogen, and although immediately acting it is not a heparin-like anticoagulant. The prothrombin time was normal. However, on the one-stage factor II assay, a value of 50% of normal was found. We have been unable to demonstrate activity against phospholipid. Dr Edwards at the Virus Reference Laboratory, Colindale, has kindly supplied us with sera from patients with definite evidence of glandular fever. Of 18 cases tested so far, four have had a detectable antibody. This complication of glandular fevere had not been described before and it is hoped that, in the near future, the findings will be published.

HOME TREATMENT

Four of the outpatients registered at Treloar Haemophilia Centre are now on home treatment. The training of the College boys continues satisfactorily and up to date 8 boys are receiving materials from their home centres for this purpose.

Finally, acknowledgement must be made to the Army Blood Supply Depot at Aldershot, under the direction of Colonel John Winwick, for their continued help both in the supply of therapeutic materials in an emergency and the provision of normal plasma for use as standards in the variety of coagulation tests performed at this Centre.

Our thanks are also due to the Solent Group of the Haemophilia Society who have provided funds for the provision of an alarm system which has been fitted to the fridge and deep-freeze at the College where therapeutic materials are stored. Any interruption in the electricity supply will now be apparent immediately and emergency measures taken to prevent wastage of expensive stocks.

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