Personal Practice

Management of the Haemophilic Child

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Haemophilia is a hereditary and lifelong bleeding disorder which affects males and is transmitted by apparently normal females. Bleeding commonly occurs after trauma, and in the severely affected patient may occur apparently spontaneously. The haemostatic defect is due to total or partial deficiency of factor VIII (anti-haemophilic factor, anti-haemophilic globulin, AHG, AHF) and the severity of the bleeding is fairly well correlated with the level of the factor in the blood (Table I). Complete deficiency of factor VIII is found in severe classical haemophilia and is associated with spontaneous haemorrhages into muscles and joints with crippling. The patient with only partial deficiency of factor VIII is usually spared haemarthroses and may bleed only after injury or surgical operations.

TABLE I

Relation of Observed Blood Levels of Factor VIII to the Severity of Clinical Manifestations of Defective Haemostasis

Blood Level of Factor VIII (% of normal)	Level of Haemostatic Efficiency
50–100	Normal
25–50	Tendency to excessive bleeding after major trauma; often not diagnosed
5–25	Severe bleeding after minor trauma or surgical operations
1–5	Gross bleeding after minor injuries; some haemarthroses and 'spontaneous' bleeding
0	Severe haemophilia; haemarthroses and crippling; deep tissue haemorrhages

Incidence

Haemophilia is by far the commonest of the hereditary haemorrhagic disorders (Table II), though the total number of haemophiliacs in the

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*In the Personal Practice series of articles authors are invited to give their own views on some current practical problem.

community is small. There are thought to be approximately 3000 to 4000 severely affected haemophiliacs in the United Kingdom, and there may be as many again who are mildly affected with the condition. The age distribution of the 224 haemophiliacs treated at the Oxford Haemophilia Centre during the year 1969–1970 is shown in Table III. Approximately 25% of the patients are less than 10 years of age and 40% are less than 15 years of age.

TABLE II

Patients with Bleeding Disorders Registered at Oxford Haemophilia Centre (June 1969)

Diagnosis	No. of Patients	%
Haemophilia	623	61
Christmas disease	120	12
von Willebrand's disease	183	18
Others:		
Afibrinogenaemia	1	
Circulating anticoagulant	27	
Factor XIII deficiency	1	
Factor V deficiency	3	
Factor VII deficiency	2	
Factor X deficiency	4	
Factor XII deficiency	2	9
Factor IX deficiency	14	
Qualitative platelet defects	37	
Combined clotting factor deficiencies	5	
Total	1022	100

Inheritance

Haemophilia is transmitted in a sex-linked recessive manner. This mode of transmission is illustrated in the Fig. It can be seen from this diagram that in the case of a haemophiliac, all his sons are normal but all his daughters are carriers of the condition. In the case of these carrier daughters their sons have an equal chance of being normal or haemophiliac and their daughters have an equal chance of being normal or carrier.

Approximately one-third of haemophiliacs have no family history of the condition and presumably in these people the condition has arisen as a result

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TABLE III

Age Distribution of 224 Haemophiliacs Treated at Oxford During 1969–1970

Age Group (yr)	No. of Patients
0–5	19
6–10	36
11–15	35
16–20	27
21–30	49
31–40	25
41–50	14
51–60	12
61–70	3
71 +	4
Total	224

of a gene mutation in the patient or his mother. The alternative explanation is that the defective gene has been present in previous generations, passing down through the female members without manifesting itself in the male. This situation could come about if previous generations were composed mainly of females.

In general, haemophilia runs true to type in a given family with regard to plasma factor VIII level and clinical severity.

Factor VIII

It is generally accepted that the haemostatic and coagulation defects in haemophilia are due to absence of an essential clotting factor from the blood. This factor is variously known as anti-haemophilic factor (AHF), anti-haemophilic globulin (AHG), or factor VIII. Factor VIII is thought to be a glycoprotein with a molecular weight of at least 2,000,000. Its site of synthesis in the body is not known but it is made probably throughout the reticuloendothelial system. The factor is labile on storage and deteriorates at a variable rate in blood stored at +4 °C. The half-life of factor VIII transfused into a haemophiliac is of the order of 12 hours. This fact must be remembered when planning transfusion therapy for a patient undergoing surgery.

Clinical Manifestations of Haemophilia

A child affected by haemophilia is born with the condition and the diagnosis of the clotting factor defect may be made by examination of blood taken by careful venepuncture from the umbilical cord. The liability to bleed excessively is therefore present from birth, but, in spite of this, bruising at birth is unusual as is excessive bleeding from the umbilical
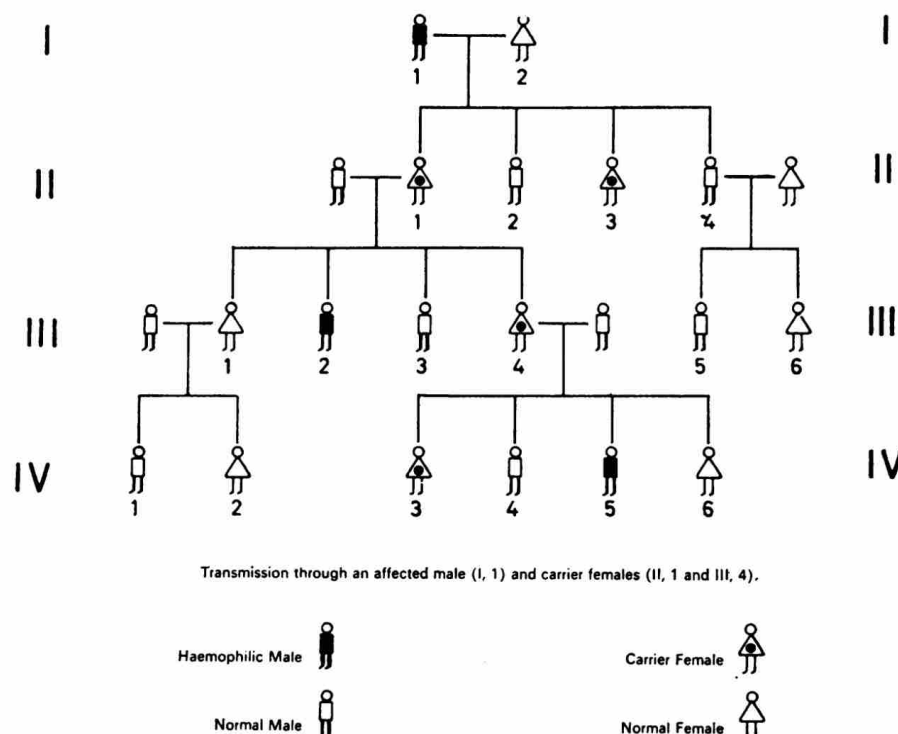

Transmission through an affected male (I, 1) and carrier females (II, 1 and III, 4).

Haemophilic Male   Carrier Female

Normal Male   Normal Female

FIG.—*The pattern of hereditary transmission of haemophilia and Christmas disease.*

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stump. Commonly, there are no signs of haemophilia until several months after birth unless of course the child undergoes circumcision or some other surgical procedure. This is possibly due to the fact that the child is not exposed to trauma in the early months of life. In the majority of cases of severe haemophilia the first signs of the condition are excessive bruising of the skin or persistent bleeding from the mouth after trivial injury. One or other of these signs has usually appeared by the age of 18 months and sometimes as early as 3 to 4 months. Excessive bruising may take the form of a lump or patch, and on occasion may track widely through the subcutaneous tissues and result in considerable loss of blood from the circulation. Such bruises usually involve the buttocks or the head in the region of the forehead or occiput. Lips, gums, or tongue may be injured by teeth or foreign objects and may bleed persistently and seriously. The occurrence and site of haemorrhages are usually related to the child's mobility and activity and exposure to dangerous situations. Increased activity may produce a fall from bed or settee, and attempts at standing and walking may result in bruises on buttocks and forehead should he fall. Very occasionally a fall on to the head may produce intracranial haemorrhage.

From the time of learning to walk, the joints and muscles are liable to strains and haemorrhage. In the young child the ankles are most commonly affected but later the knees take precedence (Table IV). In schoolchildren the elbows may suffer as commonly as the knee, perhaps as a result of leaning on them while writing.

TABLE IV

Incidence of Joints Affected at 440 Consecutive Attendances for Treatment of Haemarthroses in 88 Haemophiliacs

Knee	Elbow	Ankle	Shoulder	Other Joints
38%	26%	19%	9%	8%

Muscles are the next most common site of haemorrhage after joints, and bleeding into them may be spontaneous or may arise after some locomotory strain or as a result of direct injury. Muscle haemorrhages involving in particular the forearm and the calf may result in scarring and contracture of these muscles with consequent limb deformity. Furthermore, muscle haematomas, if large enough, may produce dangerous pressure effects on nearby vessels and nerves. Bleeding involving the iliacus muscle is a common and particularly important

form of muscle haemorrhage and may present with many of the features of acute appendicitis. Careful clinical examination in these patients may reveal a mass in the region of the iliacus muscle palpable just inside the pelvic brim and evidence of femoral nerve compression on that side. In addition there may be a progressive fall in the patient's haemoglobin if he continues to bleed into the muscle. These features, along with the rapid improvement of symptoms after AHG therapy, are important in differentiating between haematoma and appendicitis.

Bleeding of any severity from the gut, nose, or urinary tract is uncommon in childhood, though in adolescence and adulthood haematuria is the third most common form of bleeding.

The sites of haemorrhage which have been mentioned are those which are commonly encountered, but it should be borne in mind that in the severe haemophiliac, bleeding is possible into practically any site and any unexplained pain, swelling, loss of function, or indeed any obscure illness, should be considered as being possibly due to haemorrhage unless there is clear evidence to the contrary.

Excessive postoperative haemorrhage may follow any operation, and even the simplest procedure, such as removal of a loose deciduous tooth, without adequate replacement therapy may be followed by dangerous haemorrhage. Tonsillectomy is a common operation in childhood and because of this is sometimes regarded lightly. It should be remembered that tonsillectomy is a particularly severe test of haemostatic function not only in severe haemophilia but in the mildest form of the condition.

The life of the young severely affected haemophiliac is punctuated by a succession of bleeding episodes. These may be frequent, or few and far between; they may be severe, or not so severe. They may lead to marked crippling in some cases and surprisingly little crippling in others. Frequently they disrupt home and school life to a considerable extent so that there may be increasing disability not only physically but also socially and educationally.

Many factors influence the occurrence and outcome of bleeding episodes.

Haemostatic mechanism. The process of haemostasis is still not fully understood and the mechanism may be more effective in one severe haemophiliac than in another or in the same haemophiliac at different times, depending on the state of the vessels, the platelets, or some other as

yet undefined plasma factors. There may be in some severe haemophiliacs traces of factor VIII difficult to detect, which are sufficient to decrease the incidence and severity of bleeding as compared with other severe haemophiliacs.

Physique. The boy who is naturally thin and whose joints are perhaps ill protected by muscles may be more liable to strain and bleeding than his sturdier haemophilic brother. And yet if the boy is overweight his knees will be more prone to stress and therefore more likely to bleed.

Accident proneness. Through temperament or by lack of education the boy may expose himself to potentially dangerous situations and as a result accidents may occur which result in bleeding. Accident proneness may be acquired in that an existing disability will increase the chances of accident, as when a sore, stiff, or weak knee causes a fall. Conversely, the boy who maintains good joint and muscle function may be more agile, better co-ordinated in his movements, and more likely to avoid and extricate himself from potentially dangerous situations.

Life and environment. Changes in environment may explain an alteration in the pattern of bleeding disorders. The family may move to a house with stairs, the affected child may start to travel by school bus, or he may be given a bicycle, or be studying for examinations, and in each case it is possible that a change in the pattern of bleeds may occur.

General Management of Haemophilia

Haemophilia is due to the absence of factor VIII from the blood and management consists primarily of replacing this missing factor by giving transfusions of normal plasma or plasma derivatives rich in factor VIII. Though replacement therapy is a very important aspect of treatment, management of haemophilia in the broadest sense requires much more than factor VIII replacement and involves consideration of the problems of education, recreation, employment, and other socioeconomic aspects of life. Presumably the problems of loss of time from school and work and the limitation enforced by haemophilia on the patient's interests and activities will become less as more potent preparations of AHG become more widely available.

The aim of management of the haemophilic child is to treat and control haemorrhage into any site, particularly into joints and muscles, as early as possible after the onset of bleeding. In this way

crippling may be prevented or minimized, and the child allowed to attend school to acquire the standard of education of which he is mentally capable. For this policy of early treatment to be successful it is essential for the patient to be able to get to hospital as soon as possible and to be given his dose of AHG as soon as possible thereafter. At the Oxford Haemophilia Centre the practice is for the patient to telephone the Centre to report that he is bleeding, then to telephone the ambulance service direct if he does not have his own car, and arrange for his own admission. In our experience most general practitioners with haemophiliacs under their care agree to this arrangement and the ambulance service for their part are usually prepared to accept calls from patients providing they have received a letter from the general practitioner or the hospital concerned explaining that the patient is a haemophiliac. The patient should be seen and treated as soon as possible after reaching hospital. He should not be expected to take his place in a queue in casualty department and end up by being seen by an inexperienced casualty officer. Ideally he should go to the ward or treatment area where he is to be given his dose and should be seen and treated by a doctor experienced in the management of haemophilia. In the case of children it is particularly important for the child to see the same faces at each visit. In this way the child soon loses his fear of attending hospital and may even request to be taken there as he comes to associate it with relief of pain in friendly surroundings.

Education. Because of his proneness to bleeding after minor injury the severely affected haemophiliac should not be employed in jobs which put severe strains on his muscles and joints. He should try as far as possible to find employment which requires him to use his brains rather than his muscles. A good education is essential if he is to find himself such a job. Unfortunately because of the recurrent episodes of haemorrhage the haemophilic child may lose much time from school. His problems are further added to by the fact that many head teachers are not willing to accept a haemophilic child into their schools because of the responsibility of supervising him and the fear that the child might suffer a severe haemorrhage while at school. This latter difficulty can usually be overcome by explaining to the head teacher that the boy is no more likely to bleed to death in the classroom than any other boy and that the commonest manifestation of the condition is bleeding into a joint or less commonly a muscle, and that the teacher's chief responsibility on such occasions is to arrange to

have the child admitted to hospital as soon as such a haemorrhage takes place. Having decided to take a haemophilic boy into the school most teachers are surprised at how little concern they cause.

The alternatives for the haemophilic boy are that he may attend an ordinary state school or its private school counterpart, or attend a school for physically handicapped boys, or have tuition at home. Attendance at an 'ordinary' school has the great advantage that the child mixes with normal boys and girls of his own age and starts to learn from an early age how to live and play with normal children. In addition, he starts to learn from experience the type and amount of physical activity he can undertake while living in a normal environment and the extent to which he must limit or avoid harmful activities.

For the boy who is severely crippled early in life and requires to use crutches or a wheel chair to get about there are advantages in his attending a school for handicapped boys provided there is easy access to a Haemophilia Centre for factor VIII replacement therapy. The Lord Mayor Treloar School near Alton in Hampshire is one such school. It deals with 150 physically handicapped boys from the age of 11 years and upwards of whom 50 have haemophilia or Christmas disease.

Games and other recreational activities.
The type and amount of physical exercise a haemophilic boy can take vary greatly from boy to boy and are best learned by the boy from personal experience. Attempts to limit a boy's physical activity by laying down strict rules almost invariably lead to frustration on the part of the child and the parents. The child with spirit will go and play rough games no matter what rules have been laid down. Unfortunately, if he does sustain a haemorrhage as a consequence of playing forbidden games he may tend not to mention this until it is quite advanced and he is in severe pain, for fear of being reprimanded. It is probably wiser and less stressful for all concerned to allow the child more freedom in his activities than has been the custom in the past. If the child then reports any injury or haemorrhage as soon as it occurs so that he can have early treatment the consequences are not likely to be too serious. Though games such as football, rugby, and boxing should be avoided, there is no reason why the haemophilic child should not swim or cycle if these activities are within his capabilities. Well-developed muscles about the various joints are an important factor in joint stability. This is particularly so in the case of the knee joint where wasting of the quadriceps muscle leads to weakness

of the knee with consequently increased disposition to bleed into the joint. The importance of exercises to regain quadriceps function after a period of immobilization is discussed later.

Management of Bleeding in Haemophilia
In this section we shall discuss the principles of replacement therapy, the therapeutic materials available for the control of bleeding in haemophilia, and the management of the commoner types of bleeding.

Principles of Replacement Therapy
The aim of replacement therapy in haemophilia is to raise the patient's blood factor VIII concentration by transfusion to a level which will promote haemostasis in the lesion being treated and to maintain this level until healing is well advanced. Lesions of different severity usually require different levels of factor VIII in the blood. For example, the level of factor VIII required to attain and maintain haemostasis after major abdominal surgery is higher than the level required for spontaneous haemorrhage into a joint. Table V shows the different levels of factor VIII regarded as necessary for the control of bleeding from different lesions. These recommended levels are intended only as rough guides and may be higher if the injured part is infected or being constantly moved, or conversely may be lower if the part can be easily immobilized.

TABLE V
Blood Levels of Factor VIII Required to Control Bleeding in Different Lesions

Lesion	Level of Factor VIII Required in Blood Immediately After Transfusion (% normal)
Spontaneous bleeding	5–20 (0–5)*
Dangerous haematomas, post-traumatic haemarthrosis, multiple dental extractions	20–40 (5–10)
Major surgery, serious accidents	80–100 (25–40)

*The figures in parentheses are the approximate levels to which the patient's factor VIII level will have fallen 24 hours after the dose.

Therapeutic materials available for treatment of haemophilic bleeding.
Whole blood. Because of the lability of factor VIII on storage at +4 °C, whole blood may be poor in factor VIII activity and should not be used for factor VIII replacement therapy. In addition to being low in factor VIII activity, whole blood can rarely be transfused fast enough to attain a reasonable haemostatic level in the patient's

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circulation. In the treatment of haemophilia whole blood should be given only to replace blood lost and not as a source of factor VIII.

Fresh frozen plasma. Plasma which is to be used for the treatment of haemophilia should be separated from the blood cells as soon as possible after collection and preferably within 3 to 4 hours of donation. After separation from the cells the plasma is rapidly frozen and stored at −20 °C to −30 °C. At this temperature there is very little loss of factor VIII activity in the plasma over 2 to 3 months. Plasma is effective in the control of spontaneous haemorrhages into muscles and joints, especially if given soon after the onset of bleeding. A dose of 10–15 ml/kg body weight (i.e. 7-10 units of factor VIII*) infused over a period of 45 to 60 minutes will raise the level of factor VIII in the patient's plasma to 15–20% of normal. When treating babies or small children it is wiser to use cryoprecipitate or a freeze-dried AHG preparation rather than plasma which could more easily overload the circulation.

Cryoprecipitate. When frozen plasma is allowed to thaw slowly at +4 °C a proportion of the plasma proteins remain insoluble in the cold. This cryoprecipitated fraction of plasma, which can be recovered simply by centrifuging the plasma after thawing, has been shown to be rich in factor VIII activity (Pool, Hershgold, and Pappenhagen, 1964) and has been found to be effective in controlling haemophilic bleeding (Pool and Shannon, 1965).

Cryoprecipitate is relatively easy to prepare and can be produced by most Blood Transfusion Centres. It is dispensed either in plastic bags which contain on average 75 units of factor VIII or in blood transfusion bottles which contain approximately 150 units of factor VIII. The material is stored deep-frozen and is reconstituted for transfusion by thawing at 37 °C and adding if necessary a volume (10–20 ml) of citrate saline, to ensure that the cryoprecipitate remains in solution and is easily injected through an average-sized needle. In our experience a dose of 10 units of factor VIII per kg body weight raises the level of circulating factor VIII by approximately 15% of normal. It follows that a boy weighing 30 kg will require 300 units of factor VIII, i.e. approximately 4 bags of cryoprecipitate to raise his factor VIII level to 15% of normal. As already mentioned, this level of factor VIII is usually sufficient to control an early spontaneous haemarthrosis or intramuscular haemorrhage.

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* Fresh frozen plasma contains on average 0·7 units of factor VIII/ml.

Freeze-dried AHG concentrates. Until the introduction of cryoprecipitate the only concentrated human factor VIII preparations were the various freeze-dried protein fractions prepared from human plasma by means of alcohol or ether fractionation. Though there has been a great increase in the production of lyophilized human AHG concentrates, especially in the United States, this material is still in very short supply and where available commercially is very expensive.

It has been our practice to reserve this material as far as possible for use in children or for adults who are allergic to plasma or cryoprecipitate.

Animal AHG. Because of the shortage of potent preparations of human AHG during the early 1950's, Macfarlane and his colleagues sought to prepare AHG from animal plasma. In 1955 (a, b) Bidwell described the preparation of potent AHG concentrates from both porcine and bovine blood, and in 1957 Macfarlane and his colleagues reported the successful use of these preparations in controlling haemorrhage in haemophiliacs undergoing major surgery.

Most patients become resistant to treatment with a particular animal AHG preparation within 7 to 10 days of starting treatment so that their factor VIII response after transfusion of the dose gradually diminishes. This 'resistance' does not seem to be due to the appearance of factor VIII antibodies since such antibodies have not been found at this stage of treatment. Moreover the patients still respond to the alternative animal AHG preparation and to human AHG. Both preparations of animal AHG are potentially antigenic and in addition can cause thrombocytopenia. Because of these drawbacks it is advisable to reserve bovine and porcine AHG for use in life-saving surgery when there is no cryoprecipitate available or for the treatment of patients with factor VIII antibodies who are bleeding disastrously. Animal AHG preparations are particularly useful in this latter situation since they are commercially available and also because of the fact that porcine and bovine factor VIII are in general less susceptible than human factor VIII to the action of factor VIII antibodies.

When considering replacement therapy to control haemorrhage in a given patient the doctor must assess the severity of the patient's lesion, decide on the level of factor VIII required in the patient's blood to obtain haemostasis, decide on the therapeutic material to use, and then calculate the dose of material required to achieve the desired factor VIII level. In the case of a patient undergoing surgery the doctor must also decide on the duration of replacement therapy.

(1) Severity of lesion. In general, spontaneous haemorrhages require a lower circulating level of factor VIII for their control than haemorrhages after obvious trauma. Most spontaneous haemorrhages into joints and muscles, especially if seen within 2 to 3 hours of onset, respond satisfactorily to plasma in a dose of 10–15 ml/kg body weight. This dose will raise the patient's level of circulating factor VIII to 15 to 20% of normal. If it is desired to use cryoprecipitate, the same level of factor VIII can be achieved in the patient by giving a dose of cryoprecipitate containing 10 units of factor VIII per kg of the patient's body weight, or if one wishes to express the dose in 'bags of cryoprecipitate' the dose is approximately 1 bag/10 kg body weight.

The approximate levels of factor VIII required in the blood to control bleeding in different lesions are shown in Table V. These figures serve only as rough guides to treatment levels required. If haemorrhage is not controlled, in spite of the circulating factor VIII level being at the recommended level, then a larger dose must be given to raise the level still higher or some surgical cause for the haemorrhage must be considered.

(2) Choice of therapeutic material. For most practical purposes the choice of therapeutic material rests between fresh frozen plasma and cryoprecipitate. Only rarely is lyophilized human AHG available. At Oxford we still commonly use fresh frozen plasma for the treatment of spontaneous or early haemarthroses or intramuscular haemorrhages in patients of 10 years of age or more. Plasma in a dose of 10–15 ml/kg of body weight is effective in the management of these minor or early haemorrhages. The disadvantages of plasma therapy are that it takes 30 to 45 minutes to thaw 450 ml of plasma at 37 °C, and a large volume of fluid is administered, which may take 45–90 minutes. The time factor may be of great importance to the patient sometimes and he may be reluctant to have plasma if he has experienced the convenience of cryoprecipitate in the past.

(3) Calculation of dose. Having decided upon the level of factor VIII necessary in the patient's blood for haemostasis and having decided on the therapeutic material to be used, it is possible by means of a simple formula to calculate the dose of factor VIII required. There are many formulae which may be used and the one which we have found useful is:

$$\frac{\text{Patient's weight (kg)} \times \text{Rise produced by dose in factor VIII (\% normal)}}{\text{Units of factor VIII in dose}} = K$$

The patient's weight is known, the level of factor VIII required in the patient's circulation has been decided, and K is a constant which is 2 if plasma is used, 1·5 if cryoprecipitate or lyophilized human AHG are used, and 1 if animal AHG is used. The following example shows the use of the formula. A haemophilic child with a factor VIII level of 5% and weighing 25 kg requires a dose of cryoprecipitate to raise his factor VIII level to 50% of normal. Using the above formula:

$$\frac{25 \times 45}{x} = 1\cdot 5$$
$$\therefore x = 750 \text{ units,}$$

i.e. 750 units of factor VIII are required. If it is assumed that there are about 75 units of factor VIII in each bag of cryoprecipitate then 10 bags of cryoprecipitate should be transfused.

Formulae such as the one shown above are of considerable value when calculating the first dose to be given to a patient about to undergo surgery but subsequent doses are best assessed on the basis of the patient's factor VIII response after his previous dose. The reason for this is that different patients may show different factor VIII responses after a given dose of AHG even after allowance has been made for differences in body weight. By assaying the patient's factor VIII level before and after every dose it is possible to 'tailor' replacement therapy to his needs, giving neither too much which is wasteful nor too little which is dangerous.

(4) Duration of antihaemophilic replacement therapy. The duration of factor VIII replacement therapy depends largely on the healing time of the wound. Small to moderate-sized haemarthroses in relatively undamaged joints require only 1 or 2 doses of plasma of the order of 10–15 ml/kg to control bleeding and bring about resolution. In more severe haemarthroses or if aspiration of the joint is undertaken, cryoprecipitate or freeze-dried human AHG concentrate should be given for 2 to 4 days in the first place and 1 or 2 further daily doses should be given when the patient starts active joint movement. A similar regimen is usually suitable for the management of haematomas of the iliacus muscle, forearm, or calf muscles.

For dental extraction it used to be the practice at Oxford to give cryoprecipitate or freeze-dried human AHG daily for a period of 7 to 10 days. There is now strong evidence that this regimen is not required providing epsilon-aminocaproic acid (EACA) is given in adequate doses. The management of patients undergoing dental extraction is dealt with more fully in a later section of this article.

For patients undergoing laparotomy, 8-hourly dosage should be given for the first 3 to 4 days and 12-hourly dosage for the next 8 to 10 days, sufficient to keep the patient's factor VIII level above 30 to 40% of normal throughout the period of healing.

For operations involving much cutting of muscle or stripping of periosteum, or for the resection of haemophilic cysts, infusions may be required for 3 to 4 weeks. Similar treatment may be required for severe wounds and injuries complicated by infection or haematoma formation. Reopening or exploration of a wound may require a return to day 1 of a new course of treatment. On the other hand, if the site of operation or injury can be completely immobilized, a shorter period of infusion therapy may be safe.

Management of Some Specific Problems

Recurrent haemarthroses with the danger of crippling, and the need for dental extraction are perennial problems in haemophilia so that the care of joints and teeth is a very important aspect of the management of the haemophiliac. We shall therefore discuss here in some detail the treatment of acute haemarthroses and the care of the teeth in haemophilia. Also, the question of immunization and its hazards from the point of view of haemorrhage often causes much concern to parents and to doctors looking after haemophiliacs. This problem will also be discussed.

Acute haemarthroses. Because of the frequency of haemarthrosis, the severe pain which may be associated with the condition, the loss of time from school, the danger of severe joint damage and permanent crippling, it is important to treat bleeding into a joint as soon as possible after its onset, preferably within 1 to 2 hours of the child complaining of discomfort in the knee. The treatment of haemarthroses has 4 main objectives: (1) to stop bleeding into the joint; (2) to relieve pain in the joint; (3) to maintain or restore joint function; and (4) to prevent chronic changes in the joint.

When the haemarthrosis is small, spontaneous, and treated within 2 to 3 hours of onset, all of these objectives can be achieved by the transfusion of fresh frozen plasma, cryoprecipitate, or freeze-dried AHG concentrate. The dosage of these various therapeutic agents required to bring about haemostasis in such an early haemarthrosis has already been mentioned. Treatment of many haemarthroses may be carried out on an outpatient basis. The child is given his transfusion, rests for 1 to 2 hours, and may then return to school if the pain in the joint has settled. The majority of early spontaneous haemarthroses respond well to this treatment.

If the haemarthrosis is more severe, either because of trauma or because there was some delay in seeking treatment, there may be marked swelling of the knee with severe pain, muscle spasm, and loss of joint function. Such cases require the combined care of the haemophilia and orthopaedic service and should be admitted to hospital. Replacement therapy with cryoprecipitate or freeze-dried AHG is required and should be given daily for 2 to 3 days or until pain and muscle spasm diminish. In addition, immobilization of the joint is advisable and this alone often leads to rapid diminution of pain. In a small proportion of cases with very tense, swollen, painful joints, aspiration under full AHG 'cover' may be required. Immobilization of the knee, elbow, ankle, and wrist is obtained by means of padded plaster of Paris splints. The joint in the first instance is immobilized in the position of maximum comfort. Within 24 to 48 hours the acute pain has usually settled, and it is then possible to dispense with this temporary splint and start to encourage periodic joint movements or if necessary continue immobilization with another splint with the limb in a more functional position. In this latter situation static muscle exercises should be started as soon as the child is free of pain. It is especially important in the case of haemarthrosis of the knee to start static quadriceps exercises as soon as possible since the quadriceps muscle atrophies very quickly after a haemarthrosis, and prolonged immobilization leaves the knee unstable and prone to further bleeding. From static quadriceps exercises the child should proceed to straight leg raising, then to gentle flexion exercises, and then to partial and full weight bearing. It is probably wise to give factor VIII replacement therapy during the first 2 or 3 days of weight bearing, especially if the haemarthrosis has been severe and there has been much muscle wasting.

With patients now seeking treatment for haemarthroses early and with effective therapy with cryoprecipitate and AHG concentrate becoming more widely available, aspiration of blood from the joint is rarely required. The following factors should be considered before carrying out joint aspiration. (1) *Size of haemarthrosis and degree of pain and tension in it.* A large, tense, and very painful haemarthrosis should probably be aspirated if only to relieve the severe pain in the joint. (2) *Time interval between onset of haemorrhage into joint and admission to hospital.* If there is a delay of more

than 24 hours, aspiration of the joint is often difficult and it is seldom possible to empty the joint completely. This is presumably due to the blood in the joint having clotted. (3) *Type of joint involved.* The knee joint is the joint most commonly affected by haemorrhage and may contain up to 200 ml of blood. Such large volumes of blood may take many weeks to be reabsorbed and even then resolution may not be complete. For this reason the knee joint is the joint most frequently aspirated. Haemarthroses in the elbow or ankle joints are usually relatively small, are absorbed rapidly, and so rarely require aspiration. (4) *Presence or absence of antibodies to factor VIII in the patient's circulating blood.* Aspiration should never be carried out if it is known that the child's blood contains factor VIII antibodies. The risk of serious haemorrhage as a consequence of puncturing the joint are high and more harm than good may be done.

Care of teeth. The main aims of dental management in haemophiliacs are: (1) to prevent gingival disease and dental caries and so preserve the teeth; (2) to carry out dental extraction when this becomes necessary, as safely as possible.

The prevention of gingival and dental disease is based on educating the patient from an early age about the necessity for oral hygiene. He should be instructed to brush his teeth regularly and at least twice each day, to avoid sweets and excess carbohydrates and to make 6-monthly visits to his dentist to have dental inspection and any necessary fillings carried out. These procedures can be undertaken by the family dentist without factor VIII therapy and in most instances without any local anaesthesia. If local anaesthesia is required this should be achieved by papillary infiltration. Anaesthesia by means of nerve block should never be attempted because of the danger of bleeding into the soft tissues of the neck and floor of the mouth.

When the preventive measures fail and dental extraction is required the child should be admitted to hospital to have this carried out. Dental extractions are carried out under general anaesthesia with the patient intubated via the mouth. With regard to factor VIII replacement therapy it was our practice until recently to give the patient a transfusion of cryoprecipitate or AHG immediately before dental extraction sufficient to raise his blood factor VIII level to 30 to 40% of normal and thereafter to give daily doses of cryoprecipitate for 7 to 10 days until healing was complete. During the past 4 to 5 years there have been reports that the antifibrinolytic agent epsilon-aminocaproic acid (EACA, Epsikapron) is effective in reducing blood loss after dental extraction in haemophiliacs (Tavenner, 1968). We have confirmed this work (Walsh *et al.*, 1971) and our regimen of treatment for haemophiliacs undergoing dental extraction is now as follows.

On the morning of operation the patient is given a transfusion of cryoprecipitate sufficient to raise his factor VIII level to 50% of normal. This is followed by intravenous EACA in a dose of $0 \cdot 1$ g/kg body weight. After extraction the patient is given EACA by mouth in a dose of $0 \cdot 1$ g/kg every 6 hours for 7 to 10 days. The patient is also given penicillin by the oral route in a dosage of 250 mg 6-hourly for 7 to 10 days. No further doses of cryoprecipitate are given unless the patient bleeds. This regimen of treatment has proved very effective in controlling bleeding and has led to a great saving of cryoprecipitate and AHG. In addition the risks of the patient getting transfusion hepatitis are reduced.

Deciduous teeth are commonly shed without excessive bleeding. If a deciduous tooth is forcibly loosened, persistent bleeding, which is aggravated by movements of the tooth, may occur from the gum and the tooth should be extracted. A single dose of AHG followed by oral Epsikapron $0 \cdot 1$ g/kg body weight, 6 to 8 hourly for 4 or 5 days, should control bleeding.

Extraction of firmly fixed deciduous teeth should follow the plan used for permanent teeth.

Injections and immunization. A skilfully performed venepuncture which does not unduly traumatize the surrounding tissues is generally free from bleeding complications in the severe haemophiliac if pressure is afterwards maintained on the puncture site for a continuous period of 3 to 4 minutes. After a venepuncture at the elbow the limb should be kept straight and not flexed over a swab.

The main problem in venepuncture is often related to whether one attempt, or 3 or 4 attempts at venepuncture are necessary, since this can involve a difference in the time the child is upset from a few minutes up to half an hour or even longer. In difficult cases it is helpful to sedate them adequately, say with trimeprazine, and occasionally it may even be necessary to give a short anaesthetic to provide ideal circumstances for successful puncture. On the whole these measures are uncommonly used, and for an experienced operator who is prepared to look carefully at all the possible puncture sites beforehand and then to immobilize

the part concerned, there is usually little trouble. The obese haemophilic infant is not always as difficult to transfuse as might be anticipated since suitable veins for the short duration infusions which are used in treatment may often be found on the foot, the back of the hand, or the scalp. Where repeated venepunctures are necessary for treatment one may find that with time one becomes familiar with the child and with the veins which have been used with success, so that the procedure becomes easier. The converse may of course occur and it may become more necessary to sedate the child as time goes on.

Medications may be given by mouth, or by intravenous or subcutaneous injection, applying pressure on the injection site and keeping the volume of drugs given by the subcutaneous route to a minimum. Intramuscular injections commonly produce serious haematomas and are not recommended. Subcutaneous injections should be made horizontally into the base of a fold of skin and subcutaneous tissue raised between forefinger and thumb, thus avoiding damage to underlying muscles.

Immunization can be carried out safely in haemophiliacs using intracutaneous or deep subcutaneous injection which, in most instances, is quoted as an alternative to intramuscular injection.

Home treatment of haemophilia. Some severely affected haemophiliacs attend hospital very frequently for treatment of bleeding episodes. They spend much time in travelling, lose time before treatment can be started, and occupy the services of ambulance and hospital staff to a disproportionate extent. If a suitable AHG preparation is available and a child's parents have the necessary intelligence and aptitude to learn to carry out venepunctures efficiently, they may be able to treat their child successfully at home at the earliest sign of trouble. In other cases, the general practitioner may be willing to give the child his injections. Home treatment can be much less traumatic psychologically than treatment in hospital and may prove to be more economical in terms of material used since a smaller dose of AHG than would be used in hospital, given early, will often arrest haemorrhage.

Rabiner and Telfer (1970) have recently described their experiences with a home transfusion programme involving 18 patients. They concluded after 18 months that treatment at home with cryoprecipitate was practical and safe and that the number of days lost by the patient from work or from school was diminished. There was,

however, an increase in the amount of antihaemophilic factor used. We have recently embarked upon a programme of home treatment in certain severely affected haemophiliacs using freeze-dried AHG as the therapeutic material. So far only 7 patients are receiving this form of treatment but if it proves to be useful and enables the patients to lead a more normal life it seems reasonable, providing enough AHG becomes available, to extend the programme to include as many patients as might benefit from this form of treatment. At present our criteria for giving home treatment are as follows. The patient must be severely affected; must be having frequent haemorrhage, i.e. at least once every 2 weeks; must be co-operative: must have a co-operative parent or relative who shows an aptitude for carrying out venepuncture; must have good veins; must live at a considerable distance from the Haemophilia Centre or have difficulty in getting there for treatment; and must not have factor VIII antibodies.

Certain safeguards should be enforced when a patient is receiving treatment at home. A careful record is kept of materials issued, used, and returned, of adverse reactions to treatment, and of bleeding episodes and their time of recovery. Periodic assays are carried out to check that the patient's response after a dose is adequate, and that he is not developing an antibody to factor VIII.

Ideally, the parent should phone the doctor at the Haemophilia Centre to report a suspected bleed and ask permission to give a dose, or in some circumstances to check whether it would be better to proceed to the Centre for further assessment. Parents treating their child should ensure beforehand that their general practitioner can be contacted for advice in the unlikely event of a reaction to the AHG preparation.

Possible complications of factor VIII replacement therapy. Transfusions of plasma or AHG concentrate are not entirely without danger though in general the risks of therapy are slight compared with the danger to life or limb of uncontrolled haemorrhage. The complications of replacement therapy are here briefly discussed.

Hypervolaemia. This complication rarely arises when concentrated AHG preparations are used but is a well-known complication of treatment with whole plasma. Plasma in a daily dose of 10 to 15 ml/kg body weight is usually well tolerated. Larger and more frequent doses of plasma tend to cause overloading of the circulation.

Pyrogenic and allergic reactions. In a proportion

of patients infusion of AHG concentrate, cryoprecipitate, or plasma is followed by a reaction which may produce headache, backache, rigor, and pyrexia, or an urticarial eruption, occasionally accompanied by breathlessness and bronchospasm.

In general, pyrogenic reactions come on an hour to an hour and a half after starting the dose and though they may be unpleasant for the patient and worrying to the observer they are not usually dangerous. A strong narcotic analgesic may be required for control of severe headache. Allergic reactions usually occur while the dose is being given though sometimes they may be delayed for several hours. On the whole, the earlier they occur the more seriously they should be regarded. If a reaction occurs during a dose, the rate of administration is reduced and an antihistamine such as chlorpheniramine maleate is given intravenously in the maximum dose recommended for the patient's weight. If the reaction is more severe, and especially if there is breathlessness and bronchospasm, the infusion should be changed for one of normal saline, and if necessary subcutaneous adrenaline and intravenous hydrocortisone should be given.

Transfusion hepatitis. Most severely affected haemophiliacs receive large numbers of transfusions of blood or blood derivatives and are therefore exposed to the risk of transfusion hepatitis. The risk of hepatitis is probably greater with freeze-dried AHG concentrates than with plasma or cryoprecipitate since the dried concentrates are usually prepared from pools of plasma obtained from several hundreds of donors. A patient receiving a single dose of a given batch of AHG concentrate may therefore have 'contact' with 400 to 500 donors. Because of this risk it is advisable when planning to give a course of freeze-dried AHG to a patient, to try as far as possible to give him material from the same batch of AHG and not to mix batches.

During the year 1969, 228 patients with haemophilia or Christmas disease were seen at Oxford and of these, 208 were treated with plasma, cryoprecipitate, freeze-dried human AHG, or, in the case of the Christmas disease patients, factor IX concentrate. Of the 208 patients transfused, 7 (3·4%) developed clinical jaundice. The incidence of subicteric hepatitis in those patients is not known. The figure of 3·4% for the incidence of jaundice may seem large but when one considers that on average each of the 208 patients had 'contact' with 630 blood donors during the year it is not so surprising.

Factor VIII antibodies. Approximately 6% of the haemophiliacs registered at the Oxford Haemophilia Centre have antibodies to factor VIII in their blood. These antibodies make the treatment of haemophilia extremely difficult since they rapidly destroy factor VIII transfused into the patient. The antibodies presumably appear as a consequence of treatment with factor VIII-containing materials but at present there does not seem to be any clear relation between the development of antibodies and the type or amount of factor VIII used in the replacement therapy.

In many patients, the level of antibody in the blood diminishes spontaneously over the course of 1 to 2 years providing factor VIII-containing material is not given to the patient. Unfortunately, the antibody usually reappears within 5 to 7 days of the giving of factor VIII.

With regard to the management of haemophiliacs who have factor VIII antibodies it is the policy at Oxford to withhold replacement therapy in cases of minor haemorrhage. In the case of muscle haemorrhages which are threatening to compress nerves or blood vessels, or in the case of haemarthroses which are large, tense, and painful and presumably causing serious joint damage, large doses of cryoprecipitate are given in an attempt to achieve haemostasis and promote healing. For example, a child might be given up to 1 bag of cryoprecipitate per kg body weight twice daily. A similar regimen might be used in the management of life-endangering haemorrhage but in this situation if there was no improvement within 12 to 24 hours of starting treatment or if the patient's condition deteriorated, it would be justified to use bovine or porcine AHG. Both preparations are available commercially* and in large amounts, and have the added advantage that bovine and porcine factor VIII are usually much less susceptible than human factor VIII to the action of factor VIII antibodies.

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