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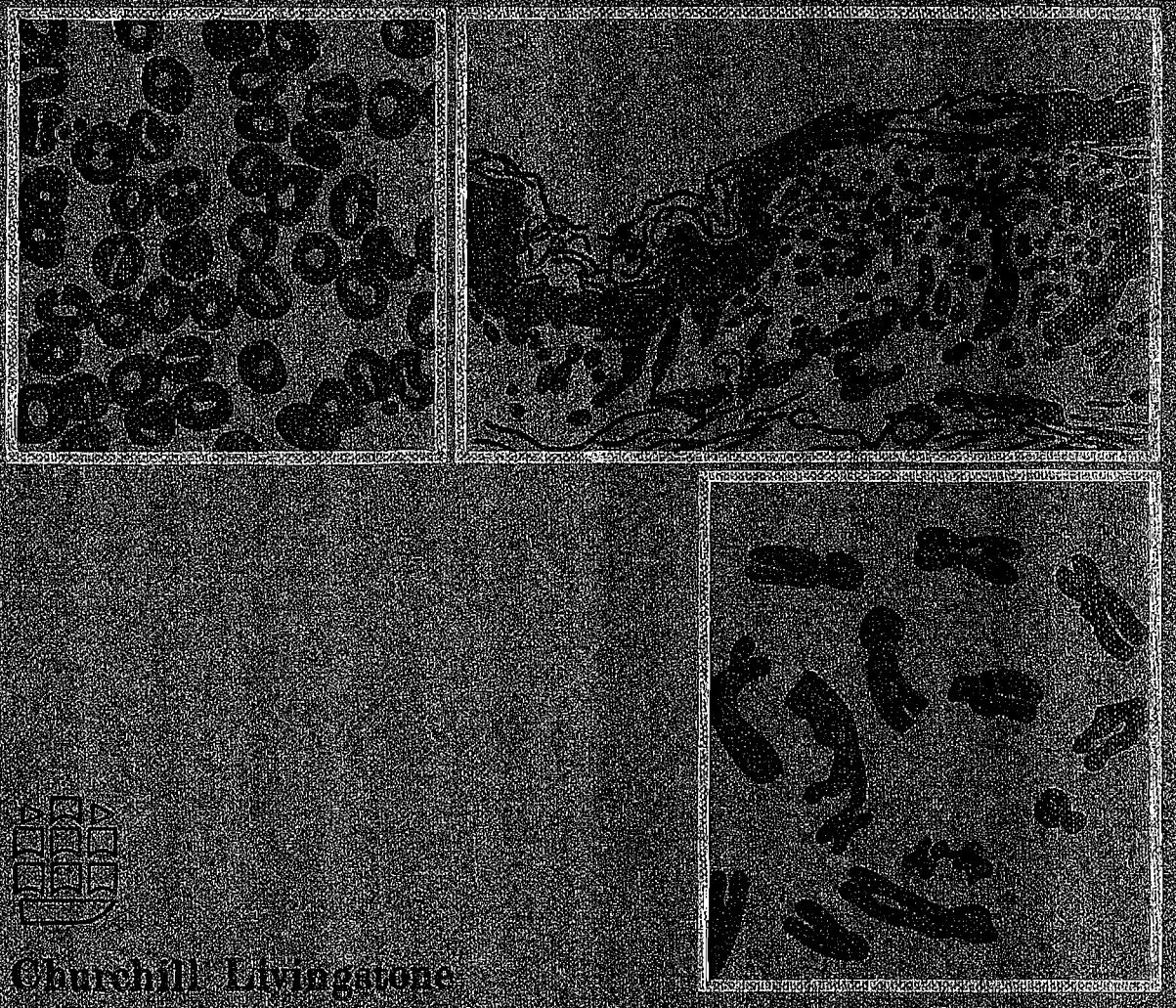
PAEDIATRIC HAEMATOLOGY



Churchill Livingstone

recurrent blood loss. The blood group should be determined and the serum screened for antibodies that might cause difficulty in cross-matching blood in an emergency. These results, as well as the exact diagnosis, are entered into the haemophilia card that the patient or his parents carry.

For further details of coagulation tests, their interrelation and interpretation the reader is referred to Hardisty and Ingram (1965). A good recent review of clinical and laboratory diagnosis of inherited bleeding disorders in children is that of Strauss (1972).

MANAGEMENT

This is a broad subject including not only the prevention and treatment of haemorrhage and deformity, but also support and explanation of the disease to the parents, and consideration of the patient's education, recreational activities and future employment. Recent articles covering certain aspects of particular relevance to the paediatrician include 'Management of the haemophilic child' (Rizza and Matthews, 1972) and 'Haemophilia: A challenge to social work' (Miller, 1973). The management of musculoskeletal problems is the subject of an outstanding monograph by Duthie, Matthews, Rizza and Steel (1972). Comprehensive accounts of all aspects of management are available in the text books of Hardisty and Ingram (1965) and Biggs and Macfarlane (1966). Shorter recommended reviews include 'Haemophilia today' (Rizza and Biggs, 1971), 'Management of hereditary coagulation disorders' (Mason and Ingram, 1971), 'Diagnosis and treatment of inherited bleeding disorders' (Strauss, 1972) and 'Treatment of haemophilia' (*Lancet*, 1973A).

At initial interview with the mother after diagnosis has been established a Haemophilia Card should be issued and an outline of future problems should be discussed, based upon one's assessment of the severity of the defect in the particular patient. The pattern of inheritance is usually well known to parents at this stage but confirmation of the probabilities of future offspring being affected or carriers may be sought and genetic counselling requested. The mother must not be allowed to feel a social Pariah as a result of the publicity given to genetic counselling concepts. The following points need emphasizing both to parents and to the general practitioner:

1. No intramuscular injections must ever be given to the child by any doctor or nurse. Immunizations can be given using intracutaneous or deep subcutaneous injections (25 size needle) which, in most instances, is an acceptable alternative.
2. Aspirin should never be given. Paracetamol (Panadol) is a safe alternative.
3. At the first sign of pain or swelling in a joint immediate attendance is necessary at the hospital (day or night) so as to have IV cryoprecipitate, given as an outpatient. This point was forcibly made by Ali, Gandy, Britten and Dormandy in 1967 but is still not widely acted upon.
4. Prophylactic dental care should be instituted, by regularly attending a dental surgeon experienced in the management of haemophilia.
5. The future importance of a good education should be stressed.

Finally, they should be informed of the existence and objects of the Haemophilia Society.

Later, when the boy is going to school, the importance of good attendance and encouragement in school work should be reiterated. This is especially important if there are unavoidable spells in hospital. Intellectual pursuits and hobbies such as music are to be encouraged. Advice as to which sports are suitable will be needed. As with all physical activities the maximum that can be undertaken without the development of bruising or injury should be encouraged. This level of activity can only be determined by each individual patient by trial and error, although reasonable suggestions can be made from a knowledge of the severity of his disease and past performance. If there are difficulties at school the hospital social service can be of great help.

CORRECTION OF THE COAGULATION DEFICIENCY

Infusion replacement therapy of the missing factor is the cornerstone of treatment. Fresh or fresh-frozen plasma is effective in all the congenital coagulation deficiencies; cryoprecipitate in haemophilia and von Willebrand's disease but not in Christmas disease. Appropriate concentrates of Factor VIII, Factor IX and the prothrombin complex (II, VII and X) have also become available in recent years and are of use in particular circumstances.

One unit of Factor VIII or IX is defined as the activity present in 1 ml of fresh pooled normal plasma. A recipient's plasma volume is 40–50 ml per kg body weight. Therefore in haemophilic patients without inhibitors infusion of

1 unit/kg body wt raises Factor VIII approx. 2 per cent.

The same *in vivo* dose response and disappearance rate occurs regardless of the source of Factor VIII (Abildgaard, 1969).

A lower *in vivo* recovery of Factor IX is found after infusion of plasma or concentrate in Christmas disease:

1 unit of Factor IX/kg body wt raises the level 0·5–1·0 per cent

(Gilchrist *et al.*, 1969; Hoag *et al.*, 1969).

This is partly because it is distributed in a larger extravascular space averaging 2·7 times the plasma volume.

In the presence of fever, continuing haemorrhage or circulating inhibitors less than the expected recovery is found. Occasional patients show poor recovery without explanation (Abildgaard, 1969).

The disappearance curve of these infused factors in the deficient patient is biphasic. There is a rapid initial fall with a $T\frac{1}{2}$ of around 8 hours compounded both of diffusion into a depleted extravascular compartment and of the catabolic half-life. This is followed by a slower fall with $T\frac{1}{2}$ of approximately 14 hours for Factor VIII and 30 hours for Factor IX, representing the true catabolic rate (Bowie *et al.*, 1967). From these considerations a large loading dose (e.g. 15–16 ml/kg fresh-frozen plasma) should be followed by two thirds of the dose (e.g. 10–11 ml/kg) at 12-hour intervals in haemophilia or 24-hour intervals in Christmas disease. The same is true when using cryoprecipitate or concentrates.

The degree of coagulation correction required depends upon the clinical situation (Strauss, 1972).

Closed soft tissue haemorrhages such as haemarthroses and small haematomata can be controlled by modest elevation of Factor VIII to 10–20 per cent or of Factor IX to 5–10 per cent. Cryoprecipitate is the product of choice in the case of haemophilia, but these levels can be achieved with fresh-frozen plasma in either haemophilia or Christmas disease.

Bleeding from a surface wound such as of tongue, lips or gums, where there is no restraining external pressure require somewhat higher levels, i.e. Factor VIII 20–40 per cent or Factor IX 10–20 per cent. These are difficult to maintain with plasma because of circulatory overload caused by both the volume and high protein content. Cryoprecipitate or concentrates are needed.

During and after surgery the level of Factor VIII must never be allowed to fall below the 30 per cent, nor the Factor IX below 15 per cent. To ensure this the peak levels need to be in the region of 60 and 30 per cent respectively, with 12-hourly doses in haemophilia and daily doses in Christmas disease. These levels are best obtained by the use of concentrates.

Treatment of intracranial haemorrhage in haemophilia requires even higher factor levels, close to 100 per cent throughout, and this can only be achieved by the use of concentrates (Davies *et al.*, 1966).

USE OF PLASMA, CRYOPRECIPITATE AND CONCENTRATES

The activity of all products can be expressed as units (one unit being the activity in 1 ml of normal pooled plasma). As stated above 1 unit/kg body wt raises the level 2 per cent in the case of Factor VIII, 0·5 to 1 per cent in the case of Factor IX. The clinical use of plasma components in the paediatric context has been reviewed by Buchholz (1974).

1. Fresh or fresh-frozen plasma. This should be thawed rapidly in a 37° C water bath immediately before use. At the time of use it contains an average of 0·7 units/ml (Rizza and Matthews, 1972).

A loading dose of 15–16 ml/kg will give a peak Factor VIII level of approximately 20 per cent. By giving further doses of 10–11 ml/kg at 12-hour intervals the level will usually be kept above 10 per cent. Each infusion must be given rapidly over $\frac{1}{2}$–$\frac{3}{4}$ hour. In Christmas disease the resulting Factor IX levels are about half of these figures. Due to slower *in vivo* decay, however, subsequent doses can be given daily rather than 12-hourly. In either disease the levels attained are adequate to control mild spontaneous bleeding or closed soft tissue haematomata including haemarthroses. Single dental extractions may also be covered but not multiple extractions or surgery. Circulatory overload is the limiting factor preventing further increase in dosage.

2. Cryoprecipitate. This method of concentrating most of the Factor VIII activity from 1 bag or bottle of plasma into 10–20 ml was first developed by Judith Pool (Pool and Shannon, 1965). Larger doses of Factor VIII can be given in smaller volumes obviating the problem of circulatory overload. In children the dose can be given by syringe and scalp vein set avoiding the need for setting up a transfusion. The small volume per bag allows rapid thawing in a 37° C water bath.

The average activity per bag has been given as 75 units in the UK (Rizza and Matthews, 1972), while in the US 100 units (Abildgaard, 1969) and 110 units (Strauss, 1972) have been quoted. In practice there is considerable variation from

one bag to another since the range of Factor VIII in healthy donors is 50 to 200 per cent of the mean. In children receiving only small numbers of bags per dose this variation can prove troublesome and it is a good practice to *double the calculated dose* to ensure adequate dosage (Dallman and Pool), 1968).

Taking the lower figure of 75 units per average bag a useful guide to therapy is

1 bag of cryo per 10 kg body wt raises the Factor VIII 15 per cent.

Twice this dose is therefore a little more effective than the standard fresh-frozen plasma dose of 15 ml/kg. Since there is no problem from the volume infused higher Factor VIII levels, in the 20–40 per cent range can be maintained allowing control of bleeding from external surfaces or after multiple dental extractions. The clinical use of cryoprecipitate in haemophilia has been well documented (Bennett *et al.*, 1967; Brown *et al.*, 1967; Prentice *et al.*, 1967). It is also highly effective in the correction of both the coagulation defect and the bleeding time in von Willebrand's disease (Bennett and Dormandy, 1966). It is of no value, however, in the treatment of Christmas disease. Factor IX, Factor XI (PTA) and most other coagulation factors remain in the supernatant 'exhausted' plasma during the separation of cryoprecipitate containing Factor VIII and fibrinogen.

Both plasma and cryoprecipitate have an advantage over human concentrates in carrying a low risk of transmitting serum hepatitis since each bag is prepared from a single donor rather than a pool.

3. Concentrates of Factors VIII and IX. Human concentrates are now commercially available of Factor VIII (e.g. Hemofil, Hyland Laboratories) and Factor IX (e.g. Konyne, Cutter Laboratories), similar concentrates also being available from many of the UK Blood Transfusion Centres. These have additional advantages over cryoprecipitate that their precise activity is known, that they can be stored at 4° C and can be carried by the patient when travelling, and that a concentrate is available for the treatment of Christmas disease as well as one for haemophilia. They are, of course, expensive (e.g. 10p per unit for Hemofil) and are not entirely free of the hepatitis hazard. Dosage is calculated in units as before, the Hemofil vials containing around 250 units in 10 ml or 800 units in 30 ml. 250 units given to a 10 kg child would raise the Factor VIII level from zero to 50 per cent providing no inhibitor was present. The Factor IX concentrates also contain Factors II (prothrombin), VII and X (Stuart-Prower) and are therefore of value in other clinical situations.

The particular use of concentrates is in the management of surgical operations in haemophilia and Christmas disease, where it is necessary to keep the level of Factor VIII continuously above 30 per cent or the Factor IX continuously above 15 per cent. Because of the short supply or high commercial price some units reserve concentrates for use in children or for adults who are allergic to plasma or cryoprecipitate (Rizza and Matthews, 1972), but the use of concentrates is increasing in the US.

Recent reports on the use of human concentrates include those of Mazza *et al.* (1970) and Johnson *et al.* (1971) for haemophilia and von Willebrand's disease, and of Hoag *et al.* (1969), Gilchrist *et al.* (1969) and Dike *et al.* (1972) for Christmas disease.

Bovine and porcine Factor VIII concentrates have the serious disadvantage that allergy develops within 10 to 20 days of their administration after which that particular species cannot be used again. Thrombocytopenia may also be induced. Animal Factor VIII is now largely reserved for life-threatening haemorrhage or major surgery in patients who have developed antibodies to human Factor VIII (Rizza and Matthews, 1972). Bovine and porcine Factor VIII are usually less susceptible than human Factor VIII to neutralization by these antibodies.

MANAGEMENT OF SPECIFIC PROBLEMS

On admission to hospital a notice should be placed on the patient's bed saying 'No intramuscular injections under any circumstances'. This includes premedication, for which oral atropine can be given.

1. Cuts and lacerations. Superficial cuts tend to stop bleeding in the normal time through drying if left undisturbed. If not this can be achieved by cleaning the wound and applying an absorbable dressing such as surgical or oxidized cellulose with or without the addition of topical thrombin.

Similar cuts in the mouth and tongue give more trouble since drying does not occur and the movements of speaking and eating prevent immobilization. Cotton wool pledgets soaked in topical thrombin often stop the bleeding. Otherwise a single dose of 15 units Factor VIII or IX per kg are needed. Corrigan (1972) has reported the efficacy of combining cryoprecipitate (2 bags/10 kg) with oral epsilon amino caproic acid (EACA) 200 mg/kg loading dose followed by 100 mg/kg 6-hourly. Continued cryoprecipitate infusions were obviated. EACA alone was ineffective.

More severe lacerations will inevitably need a similar dose of replacement therapy followed by normal wound hygiene. Local pressure should not be excessive or prolonged. The indications for suturing the wound are the same as in non-haemophilic individuals. In this case replacement therapy must be continued until the wound is healed. Sutures are of no value as an aid to haemostasis. Prevention of infection is doubly important in haemophilia. If blood loss is sufficient to cause anaemia this should be made good by the *slow* transfusion of packed cells in the intervals between the 12- or 24-hourly *rapid* infusions of replacement therapy.

2. Soft tissue bleeding. This is the most common manifestation of severe haemophilia. Subcutaneous haematomata require one or more infusions of 15 units/kg, until symptoms subside. In certain areas such as the pharynx, floor of the mouth or neck it may be life-threatening. In restricted areas such as the limbs it may press on nerves or blood vessels leading to paralysis or contracture. Eye or ear may similarly be threatened. In unrestricted tissue spaces such as the back, thigh or abdominal wall the blood loss may be massive. In the psoas muscle or the retroperitoneal tissues an appendicitis or acute abdomen may be simulated. In all these more serious situations higher and more protracted doses of replacement therapy are needed, aiming to keep the Factor VIII level in the 30–40 per cent range for several days. Immobilization of the involved part in a functional position and physiotherapy after cessation of the bleeding are important adjuncts to the specific treatment (Abildgaard, 1969).

3. Haemarthrosis. Recurrent haemarthrosis is the single most crippling complication of severe haemophilia. Its prevention is the most important contribution to the patient's future life that the physician can make, since a previously affected joint is more prone to recurrent bleeds in future. Unfortunately there is evidence that full use has not been made of replacement therapy in the past (Ali *et al.*, 1967). The correct policy is to encourage parents and patients to attend hospital at the earliest sign of joint swelling so that an injection of replacement therapy can be given, usually without admission to hospital. This procedure will cut short many otherwise damaging periods of inactivity and hospitalization and subsequent atrophy or permanent joint disability (Ali *et al.*, 1967). A single high dose of 20 to 30 units/kg sufficient to raise the Factor VIII level to 40–50 per cent has practical advantages over a more protracted low dose course in hospital (Honig *et al.*, 1969). Cryoprecipitate 6 bags/10 kg or a Factor VIII concentrate should be given, since the volume of fresh-frozen plasma would be unacceptably large.

More severe haemarthroses, including those following trauma, require hospitalization, temporary immobilization of the joint in the position of maximum comfort and 2–3 days replacement therapy. In a minority of haemarthroses there may be benefit in aspiration under cover of full replacement therapy. Rizza and Matthews (1972) suggest the following criteria: A large, tense and very painful haemarthroses seen within 24 hours of onset in patients without circulating anticoagulants. After 24 hours the blood in the joint has probably clotted. The knee is the joint most frequently aspirated. A trial of replacement therapy (10–20 units/kg) with or without joint aspiration at the Children's Hospital, Cleveland, Ohio showed a reduction in average hospital stay from 4·9 days to 2·8 days in those aspirated (Wanken *et al.*, 1969).

The place of steroids in the management of haemarthroses has also been investigated. A double-blind trial using replacement therapy (25 units/kg) with or without prednisone (1 mg/lb b.wt./day × 1, followed by a half dose for 2 days) showed an increase in response rate from 34 to 89 per cent in the group given steroid (Kisker and Burke, 1970).

Physiotherapy becomes important within 1–2 days when the acute pain has resolved. The initial splint keeping the limb in the position of maximum comfort is removed and intermittent movements encouraged. If continued immobilization is necessary this should now be in a more functional position, accompanied by static muscle exercises. There is a special liability to quadriceps wasting in the case of the knee, which if allowed to occur will leave the joint unstable and liable to recurrence of haemarthroses. Static exercises are followed by straight leg raising and then gradual flexion exercises, prior to partial and finally full weight bearing. In severe haemarthroses replacement therapy can be given daily, just before the physiotherapist's visit, and during the first 2–3 days of weight bearing (Rizza and Matthews, 1972).

Advances in reconstructive elective operations in patients with chronic haemarthropathy are described in the monograph on 'Management of Musculoskeletal Problems in the Haemophilias' by Duthie *et al.* (1972).

4. Nosebleeds. This is less frequent in haemophilia than in von Willebrand's disease, but tends

to occur in individual patients. Loose packing with an absorbable dressing is often effective. If not, replacement therapy is indicated, followed by removal of the packing.

5. Haematuria. This is a common site of spontaneous bleeding in haemophilia and does not usually warrant detailed urological investigation. It may prove relatively refractory to normal replacement therapy. In such cases a trial of prednisone is justified, 2 mg/kg/day for 2 days, followed by 1 mg/kg for 2–3 days (Abildgaard *et al.*, 1965; Hartman, 1965). EACA should not be used because of the hazard of producing unlysable fibrin clots in the renal tract (Stark *et al.*, 1965).

6. Gastrointestinal bleeding. Again this is a relatively rare occurrence in haemophilia. As well as 12-hourly replacement therapy until the bleeding has ceased packed red cells will need to be given between Factor VIII infusions so as to restore the haemoglobin level. If recurrent, a radiological search for a local gastric or intestinal lesion is indicated. The development of iron deficiency anaemia must be watched for, as in other patients with haemophilia, and treated with oral iron (e.g. Sytron) if present.

7. CNS bleeding. This should be suspected in any haemophiliac developing lethargy, headache or vomiting, especially if following a blow to the head. Replacement therapy should precede a diagnostic lumbar puncture. If angiography is needed massive replacement therapy should be given beforehand so as to raise the Factor VIII level to normal (Davies *et al.*, 1966). Although a rare site of haemorrhage in haemophilia subdural haemorrhage nevertheless constitutes one of the few causes of death in this disease that I have encountered in the paediatric age group. Management of one such problem is illustrated in Case 14.

Case 14. A boy of 4 (No. 188612) who was known to be a severe grade haemophiliac was transferred to the Royal Hospital for Sick Children for management by the paediatric neurologist. He had developed a persistent headache and was found to have neurological signs suggestive of an intraparietal lobe haemorrhage. There was no history of trauma. Only non-invasive investigative procedures were considered justified and arteriography was deferred. Ultrasonography showed displacement of the central fissure. The prime object of haematological management was to restore the coagulation system to normal 'round the clock' for a week, so as to allow spontaneous resolution of the haemorrhage if possible. His weight was 16 kg. It was therefore calculated that 16 units (1 unit per kg body wt.) should raise the Factor VIII level by approx. 2 per cent, therefore 800 units should be needed to raise it by 100 per cent. Because the available Factor VIII concentrate (Hemofil) contained 230 units per vial we chose to give him 690 units instead of 800 as a trial dose expected to raise the level by 86 per cent. In fact it was raised from less than 1 per cent to 78 per cent immediately after the dose. The level had fallen to 9 per cent 22 hours later, giving a calculated $T\frac{1}{2}$ of $6\frac{1}{2}$ hours. It was clear that twice-daily injections of Factor VIII would be needed to achieve a sustained level. Twelve hours after a dose of 460 units the level was 32 per cent and a further dose of 930 units (330 units per vial) pushed this up by 108 per cent to a level of 140 per cent (expected level 148 per cent). Twelve hours after this dose the level was 33 per cent (calc. $T\frac{1}{2} = 6$ hr). This was thought to be a reasonably satisfactory minimal haemostatic level. Subsequently it was found that good minimal levels could be maintained with smaller doses given 12-hourly, e.g. 46–55 per cent 12 hours after 620 units. The key point in dose control was to perform assays just before each 12-hourly dose, using the same venepuncture (21 butterfly needle). Piriton (10 mg) was always available while giving the concentrate but no reactions occurred. One possible complication of such a high-dose course as the above is an excessive rise in plasma fibrinogen level since this is a contaminant in such concentrates. In fact there was only a modest rise in fibrinogen level from 295 mg/100 ml before therapy to 463 mg/100 ml at the end of a week's therapy. By the end of the 7-day course the neurological signs had regressed, and the patient made an uneventful recovery.

8. Dental treatment. Prophylactic dental care should be instituted on a regular basis at an early age (Webster *et al.*, 1968). A régime of 4-monthly dental visits, topical fluoride application with a 1 mg daily fluoride supplement, restriction of between meal snacks and regular tooth brushing after meals reduced the rate of dental extraction from 9 per annum to zero in a group of 34 children (Steinle and Kisker, 1970). Extrusion of deciduous teeth often occurs without bleeding providing they are not forcibly loosened. Sometimes local pressure and topical thrombin are needed. A soft or liquid diet is given at such times. Dental fillings or restorations can usually be performed without replacement therapy or hospital admission. If local anaesthesia is required it should be by papillary infiltration. Mandibular or posterosuperior alveolar nerve block must not be used without prior replacement therapy because of the danger of bleeding into the neck and floor of the mouth.

Extraction of permanent teeth requires admission to hospital for 5–7 days. In the past our policy was to give 12-hourly fresh-frozen plasma (15 ml/kg) or cryoprecipitate (2 bags/10 kg) for 3–4 days, commencing immediately before extraction. Following the demonstration by Tavenner (1968) and confirmation by Walsh *et al.* (1971), Corrigan (1972) and Forbes *et al.* (1972) that antifibrinolytic agents EACA or AMCA (tranexamic acid) reduced the need for continuing replacement

therapy in both haemophilia and Christmas disease we have changed to this policy. A single preoperative dose of cryoprecipitate is given to raise the Factor VIII level to around 50 per cent (say 4 bags/10 kg). This is followed by an IV dose of EACA 0·1 g/kg and 6-hourly oral EACA postoperatively in the same dose for 7–10 days. Alternatively tranexamic acid (AMCA, Cyclokapron) can be given orally at a dose of 0·5 to 1·0 g 8-hourly for 5 days. The incidence of nausea may be lower after tranexamic acid (Tavenner, 1972). Before commencing either of these antifibrinolytic drugs it is a good practice to formally exclude haematuria by examining the urine for RBCs. It is also my practice to check the haemoglobin level and cross-match one unit of whole blood before extraction, and to give an antiseptic mouth wash such as 0·1 per cent pure Hibitane in the days following extraction.

9. Surgery in haemophilia. In all major surgery the essential principle is to keep the Factor VIII level consistently above 30–40 per cent until healing is complete (Biggs, 1957; Britten and Salzman, 1966). Haemostasis is normal at this level. For this purpose each dose should be aimed to give peak levels of 60–80 per cent. Half these levels are needed in Factor IX deficiency. Concentrates are the preferred source for replacement therapy. If at all possible a test dose should be given to the patient a day before operation aiming to bring the level to 60–80 per cent, with confirmation by assay. This allows a more accurate assessment of the individual patient's requirement than can be made on the basis of weight alone. It is also advisable to exclude the presence of circulating inhibitor since very much higher doses would then be required, perhaps using animal Factor VIII.

Eight-hourly infusions should be given on the day of operation and for the first 3–4 days, with 12-hourly infusions for the next 8–10 days until the wound is healed (Rizza and Matthews, 1972). It is wise to have 4–6 units of blood cross-matched and available before starting the operation and to provide close haematological monitoring throughout the postoperative period. Elective surgery in haemophiliacs should only be performed in hospitals capable of providing accurate assays at frequent intervals (Abildgaard, 1969).

In serious accidents the same situation applies as in major surgery and high initial Factor VIII doses are needed. Management of elective surgery in Christmas disease is illustrated by Case 15.

Case 15. A boy of 8 with mild Christmas disease (No. 38663) required elective surgery for an inguinal hernia. A concentrate of Factor XI prepared by the Blood Transfusion Service was used, which contained 280 units per vial. Six such vials were given (1,680 units) as a test dose. This raised the Factor XI level from 10 to 90 per cent, which was 80 per cent of the expected rise. Just prior to operation several days later he was given a similar dose of 6 vials. There was no problem with haemostasis during the operation. Subsequently it was found that a 24-hourly dose of only 4 vials was sufficient to maintain a minimal level of 32–40 per cent, i.e. just prior to the next dose. The course was continued for 11 days and healing was uneventful.

10. Injections and immunization. Intramuscular injections are prohibited in haemophilia or Christmas disease. Drugs can be given orally or IV where appropriate. This must be remembered in the context of premedication for surgical anaesthesia. Routine childhood immunizations can be given by deep subcutaneous injection with pressure on the site for several minutes.

11. Home transfusion and prophylactic treatment. Rabiner and Telfer (1970) have reported on a programme of home transfusion in a group of selected severe haemophiliacs with previous frequent haemorrhagic episodes. A responsible member of the family was trained in the administration of Factor VIII concentrate, stored at home, after consultation with the centre by telephone. Their preliminary experience has shown a reduction in the number of school or work days lost, an increased consumption of Factor VIII and no instances of anaphylaxis. The patients are clearly spared time-consuming and psychologically undesirable frequent visits to hospital and the Factor VIII will in most instances be given with less delay. This could well be of importance in haemarthroses. Lazerson (1973) analysed utilization in such a programme and found that there was an overall increase in 14 out of 17 patients, but that this increase was not likely to exceed 5 units/kg/per year. Rizza and Matthews (1972) comment favourably upon a similar pilot study in this country. It is reserved for those with very frequent haemorrhage (e.g. at least once every 2 weeks) and is unsuitable for patients with inhibitors. Le Quesne *et al.* (1974) in the UK and Levine (1974) in the US have similarly come to the conclusion that home treatment is highly efficacious in reducing the morbidity of haemophilia and improving the quality of life. No increase in utilization occurred except in patients previously undertreated.

Closely related to this 'early warning' treatment of haemophilia are the recent explorations into prophylaxis for selected severely affected patients with frequent haemorrhagic episodes. Trials of the

prophylactic administration of antifibrinolytic drugs have produced conflicting evidence. Gordon *et al.* (1965) in Glasgow used EACA 3·3 g q.d.s. for six weeks and found a lower, but not statistically significant, incidence of haemorrhagic episodes compared to a placebo group of patients. Bennett *et al.* (1973) gave tranexamic acid, a more powerful drug, 2 g/day and found minimal effect with no change in incapacity from the disease or in amount of replacement therapy needed. They review the previous trials, and the hypothesis that antifibrinolytic drugs are useful for prophylaxis clearly remains unproven at present. There is no question of any elevation of coagulation factors during antifibrinolytic drugs, but perhaps a 'shift in the balance' between coagulation and fibrinolysis.

Prophylactic administration of Factor VIII or IX in severely affected patients has met with greater success. Clearly this is reserved for patients with quite exceptionally severe and frequent haemorrhages. Kasper *et al.* (1970) reported their experience in two such adults. Bleeding episodes were reduced to a half by 250 units/day and to a quarter by 500 units/day. When 2,000 units per week were used there was complete freedom from bleeding for the first 48 hours, but a recurrence by mid-week. Hirschman *et al.* (1970) investigated the effect of cryoprecipitate (6 to 12 bags) upon the incidence of spontaneous haemarthroses in 2 adults with severe haemophilia and two 12-year-old twins with the usual combination of haemophilia plus von Willebrand's disease. Haemarthroses continued to occur but less often. A haemophilic pseudotumour of the iliac crest that had been steadily getting larger showed distinct regression in one of the adults.

The rationale for intermittent prophylactic replacement therapy is that spontaneous haemorrhage is only seen in patients with Factor VIII levels below 1–2 per cent and infusions of concentrates at 36 to 48-hour intervals can keep the concentration above this level for most of the time (Fig. 18.10). Strauss (1972) found that 20 units/kg of Factor VIII every 48 hours kept the level above 1 per cent. In Christmas disease the longer half-life of Factor IX allowed effective prophylaxis from 10 units/kg twice-weekly.

12. Treatment of pain in haemophilia. The lack of effective drugs to control the recurrent episodes of pain suffered by those with established haemophilic arthropathy has been graphically described in a letter to the *Lancet* by an affected patient (Harvey, 1973) and a leading article in the same issue (*Lancet*, 1973B). Since aspirin is prohibited

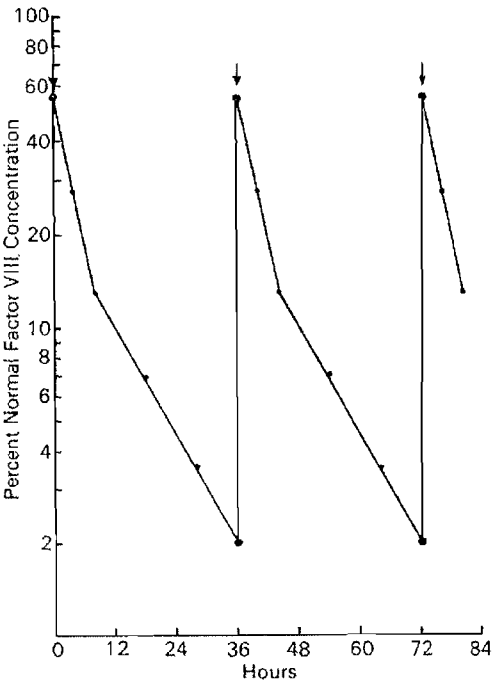


Fig. 18.10 Factor VIII levels in a patient receiving cryoprecipitate derived from 2–4 l of whole blood every 36 h (arrows). ●, measured values; ●, values based on diffusion and decay rates that are uniform in uncomplicated cases of haemophilia. (Reproduced from *Blood* (1970), **35**, 189, by permission of the authors Hirschman *et al.*).

and chronic administration of phenacetin may cause renal papillary necrosis, only a limited range of drugs including dihydrocodein (DF 118) and pentazocine (Fortral) are left. Pentazocine may give rise to physical dependence as well as causing somnolence and sometimes hallucinations. Stronger drugs such as pethidine are excluded on grounds of liability to addiction. Paracetamol (Panadol, Acetaminophen) is probably the safest analgesic in spite of the theoretical possibility of renal damage, being a metabolite of phenacetin, and of hepatotoxicity after massive overdose. In subsequent correspondence on this subject Dormandy (1973) recommended IV pentazocine plus promazine for severe pain due to acute haemarthroses or muscle haematoma; and 'ringing the changes' between dihydrocodein (DF 118), dextropropoxyphene (Doloxene) and oral pentazocine (Fortral) for constant and severe pain of established arthropathy. She makes a strong plea against the use of addictive drugs in this chronic disease.

13. Treatment of patients who have developed inhibitors. It is well recognized that inhibitors to Factor VIII develop in 10–20 per cent of severe haemophiliacs, i.e. those with Factor VIII levels below 1 per cent at diagnosis. Similar inhibitors to Factor IX can develop in severe Christmas disease. These are IgG antibodies which result from the immunizing effect of transfusions in patients for whom normal Factor VIII or IX are foreign proteins. Their presence should be suspected in any patient failing to respond to adequate doses of replacement therapy, especially if assay or other coagulation tests fail to show the expected rise in factor level. The theoretic considerations concerned with susceptibility to such immunization by replacement therapy in a number of genetically determined diseases, including various coagulation factor deficiencies, have recently been discussed by Boyer *et al.* (1973).

It is not possible to predict which patients will develop inhibitors. Strauss (1972) has pointed out that immunization, if it is going to occur at all, will have shown itself by the time the patient has received 100 days or so of replacement therapy. There is no direct relation between amount or type of replacement therapy. Most patients are not destined to develop inhibitors, and justified infusions should not be withheld for fear of inducing this complication.

A recent survey of all Haemophilia Centres in the UK has shown the incidence of antibodies to be 6·15 per cent among haemophilia of all grades and 2·36 per cent among all patients with Christmas disease. In the age group up to 10 years 13 out of 318 with haemophilia (4·1 per cent) and 1 out of 34 with Christmas disease had antibodies. Even in the age group below 5 years they were present in 3 out of 91 haemophilic children.

Once an inhibitor has appeared it is important to restrict the use of replacement therapy to the absolute minimum, reserving it for haematomas threatening to compress nerves or blood vessels, for large haemarthroses and, of course, for unavoidable surgery. When red cell transfusions are needed the packed cells can be washed free of plasma. There is a tendency for the antibodies to diminish over a period of years, but they rapidly reappear within a week of giving further Factor VIII.

If it is essential to give replacement therapy massive doses may be needed using human concentrates, or even animal concentrates in dire emergency. The management of such patients has recently been described by Rizza and Biggs (1973), using a newly developed quantitative *in vitro* measurement of the antibody level, based upon the earlier methods of Biggs and Bidwell (1959). Patients with less than 5 units/ml of antibody by this test show some response to treatment with Factor VIII in terms of postinfusion rise, accompanied by a good clinical response. Unfortunately the activity of the antibody tends to rise rapidly over a few days making continued treatment difficult. It is in those failing to respond that use of bovine or porcine Factor VIII becomes justifiable (Rizza and Matthews, 1972), since they are less susceptible than human Factor VIII to these antibodies. Recently the use of activated prothrombin complex concentrate has been described in such patients with good clinical response and without serious side effects (Kurczynski and Penner, 1974). At present their use is *sub judice*.

Other methods that have been suggested are attempts to suppress the antibodies by a combination of Factor VIII and cyclophosphamide (Green, 1971). Good results have been obtained in two children given 300 mg/m^2 of cyclophosphamide IV followed by concentrates and oral cyclophosphamide 3 mg/kg for 2–3 days (Lusher and Evans, 1971). The expected rise in antibody level after Factor VIII infusion was suppressed. Other heroic measures include exchange transfusion or plasmapheresis to reduce the antibody level (Abildgaard, 1969). It is clear that patients with antibodies should only be treated in experienced centres with more than usual facilities. The problems of management of such a patient are illustrated in Case 16.

Case 16. A boy of 5 (No. 186744) known to be a haemophiliac with a circulating inhibitor was admitted with a haematoma extending from the thigh to the ankle following a kick from another child. His weight was 18·8 kg. A dose of 6 bags of cryoprecipitate was given (which would normally raise the Factor VIII level to approx. 40 per cent). Pre- and postinfusion assays showed zero levels. Human Factor VIII concentrate (Hemofil) was therefore obtained and 6 vials (230 units each) were given (equivalent to 18–24 bags of Cryo). This caused a rise from zero to 15 per cent Factor VIII in the patient followed by disappearance of pain, diminution in the circumference of the thigh and return of full movement within 24 hours. One further dose of 6 vials of Factor VIII concentrate was given 24 hr after the first, giving a rise from zero to 13 per cent. There were no adverse side effects. No further replacement therapy was necessary, and was deliberately avoided so as not to stimulate a rise in inhibitor titre unnecessarily.

From the degree of rise in Factor VIII level, and assuming a plasma volume of 45 ml/kg, it was calculated that the level of inhibitor was approximately 1½ units/ml of the patient's plasma.

antifibrinogen antibodies may develop in some patients following replacement therapy, reducing the survival of infused fibrinogen.

A similar type of defect with prolonged thrombin time and apparently low fibrinogen when determined by thrombin clottability can occur due to *dysfibrinogenaemia* (von Felten *et al.*, 1966; Blombäck *et al.*, 1968). Structurally abnormal fibrinogen is synthesized that is still detectable by immunological assay although not reacting normally to thrombin. There is a mild to moderate haemorrhagic state. Inheritance is autosomal dominant, unusual among the coagulation disorders. Such cases could easily be confused with hereditary afibrinogenaemia.

Factor XIII (fibrin stabilizing factor) is an enzyme present in normal plasma which catalyses the formation of gamma-glutamyl-epsilon-lysine bridges between fibrin units rendering a firmer, more closely knit cross-linked form of fibrin which becomes insoluble in 5 M urea or 1 per cent monochloacetic acid in the process (Lorand *et al.*, 1968). Pure fibrinogen clotted by pure thrombin gives a loose form of fibrin still soluble in these reagents (Laki and Lorand, 1948).

Duckert *et al.* (1960) described a 7-year-old boy with a deficiency of this factor who showed a delayed haemorrhage from the umbilical stump, occurring during the second week of life. This was followed by a persisting history of increased bleeding usually starting 2–3 days after injury. This was accompanied by delayed healing and excessive retracted scar tissue. These manifestations fit in well with the concept of structurally impaired fibrin formation. Subsequent case reports have emphasized the characteristic sign of umbilical haemorrhage at the time of separation of the cord, the delayed nature of the bleeding, from several hours to 4 days after trauma, and have also shown a high incidence of intracranial haemorrhage in these children (Hanna, 1970). Haemarthrosis is uncommon and does not cause crippling. Gastrointestinal bleeding can occur. Habitual abortions can occur due to Factor XIII deficiency, but can be corrected by regular prophylactic plasma transfusions (Fisher *et al.*, 1966). A recent study of 4 patients in 2 Pakistani families with this deficiency supports the probable autosomal recessive pattern of inheritance (Aziz and Siddiqui, 1972).

All usual coagulation tests of the intrinsic and extrinsic coagulation pathways give normal results in this deficiency. Only if the test in which 0.2 ml of the patient's plasma is recalcified and clotted at 37° C with 0·2 ml of $M/_{40}CaCl_2$ and then incubated with 3–5 ml of 5M urea is performed will it be detected. In Factor XIII deficiency the clots will dissolve in 1–2 hours, whereas normal clots remain undissolved after 24 to 48 hours' incubation at RT. Correction experiments show that addition of 0·6 to 1·2 per cent of normal plasma to the mixture are sufficient to render the clots insoluble (Aziz and Siddigui, 1972). Transfusion of all blood products will likewise correct the haemostatic defect. Amris and Hilden (1968) have described the advantages of using cryoprecipitate for this purpose. Two 14-year-old patients were treated with 2 to 4 units at 3 to 4 week intervals. It is suggested that this may be justifiable in children because of the danger of intracranial haemorrhage (Hanna, 1970).

The clinical disorders due to Factor XIII deficiency have been reviewed by Duckert and Beck (1968).

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