THE DIAGNOSIS AND MANAGEMENT OF HAEMOPHILIA AND CHRISTMAS DISEASE


From the Department of Haematology, Royal Infirmary and University of Manchester

The diagnosis of the clinically similar bleeding diseases Haemophilia and Christmas disease depends on the clinical history and the clinical picture, the family history and the special laboratory tests. With the technical methods now available, the diagnosis can be made positively in all cases. The clinical history can vary from a life of chronic or recurring invalidism since infancy to an affection so mild that only a tooth extraction or minor injuries cause trouble. Points that are diagnostically suggestive are: spontaneous haemarthroses, spontaneous bruising in childhood or bruises out of all proportion to trauma and bleeding for more than 48 hours after tooth extraction; less commonly spontaneous haematuria, melena and epistaxis may occur. Excessive bleeding after circumcision in infancy is frequently said to be the first haemorrhagic incident. The patients are nearly always males but females may have these diseases, although extremely rarely.

Family History

Owing to the sex-linked transmission of haemophilia and of Christmas disease by females who remain unaffected, one or more 'silent' generations are common and then the family history is lost or not observed. A typical family history is very valuable when obtained, but in our series of nearly 300 patients we only found it in about 60 per cent. of them. There is no doubt that new mutations explain some of the other 40 per cent.

Laboratory Diagnostic Tests

The whole blood clotting time is characteristically prolonged, often grossly, but in 32 per cent. of our cases the clotting time was normal.

The prothrombin consumption index is based on the fact that in these diseases little prothrombin is converted to thrombin and remains in the serum; whereas in the normal person no more than a trace of prothrombin remains in the serum after clotting. Normal values for this index are less than 40 per cent.; over 40 per cent., provided that the platelet count is normal, is diagnostic of haemophilia and of Christmas disease. But here again, in 28 per cent. of our cases, this test gave a normal result.

The thromboplatin generation test as originally described by Biggs and Douglas (1953) makes it possible to distinguish between deficiency of antihaemophilic globulin and Christmas factor. In order to confirm the presence of true haemophilia or Christmas disease the inhibitory action of the plasma must be demonstrated by the method of Nour-Eldin and Wilkinson (1958a, b, 1959) in addition to the deficiency in AHG or Christmas factor respectively. Wilkinson, Nour-Eldin and Israëls (1958) have demonstrated the absence of this blood-clotting inhibitor termed Bridge anticoagulant in three patients with von Willebrand's syndrome; this has since been verified in another three cases.

Christmas disease occurs with a frequency of about 15 per cent. of all patients having the clinical features seen in association with haemophilia.

Management

Most minor incidents can be dealt with in an out-patient clinic, but if any likelihood of transfusion arises, it is better to admit the patient, even if the danger seems to have passed. Minor operations and tooth extractions must not be attempted in an out-patient clinic or surgery.

Blood transfusion for the replacement of lost red cells and for giving the patient temporarily some antihaemophilic globulin or Christmas factor is an essential part of treatment. For red-cell replacement only, packed stored red cells can be used; for the supply of the antihaemophilic globulin factor, fresh blood—i.e. used within four hours of withdrawal—is essential. If the Christmas factor is required fresh blood is best in an emergency, but plasma from blood not more than five days old can also be used (Nour-Eldin and Wilkinson...
Human antihaemophilic globulin has been prepared in concentrated form by Kekwick and Wolf (1957) but only strictly limited quantities are available and it is valuable when the AHG concentration must be raised quickly. Animal antihaemophilic globulin (Bidwell, 1955) has been made from pig and ox blood, which contain much greater quantities than human blood and have been extensively tested and also found to be very valuable in emergency; their use, however, is limited somewhat by the rapid development of antibodies after the first course of treatment.

**Haematoma**

Subcutaneous bruises are common occurrences developing either spontaneously or as a result of minor traumata; apart from care in order to avoid further sources of injury in the latter case, these need no special treatment. Large haematoma involving the muscles and specially those reducing the haemoglobin concentration necessitate blood transfusions, and early treatment is often followed by extra-ordinarily rapid disappearance of the haematoma. As an example, the following case is described.

The patient (T.H.) was admitted on a Monday with an extensive bleeding into the lower third of the abdominal wall, the upper two-thirds of the left thigh and the whole of the gluteal regions, reducing his haemoglobin to 5.0 g. per cent. He was given 540 ml. of fresh blood and 250 ml. of packed cells. After five days, apart from yellow skin discolouration, there were hardly any signs of the haematoma. During this period no further fresh blood was administered; the haemoglobin level was raised by 500 ml. packed cells on the third day and 1,000 ml. stored blood on the fifth day. The patient was discharged on the eighth day with a haemoglobin level of 10.7 g.

**Haemarthrosis**

Table 1 shows the distribution of joints affected in a total of 247 patients. Figures 1 and 2 show some of the bone lesions met with.

Spontaneous haemarthrosis, which is usually unaccompanied by surrounding articular haemorrhage, needs only support and rest, and we have found that a firm bandage, e.g. Domette, is the best type for this purpose. For the elbow a sling is advisable and usually adequate. We do not advocate the encasement of the joints in plaster, for apart from producing muscle wasting, it will not stop the swelling of the joint and it may cause the skin to be trapped 'between bone and stone.' Sedatives should be given to relieve the accompanying pain. Active movement must be

<table>
<thead>
<tr>
<th>Joints Aected</th>
<th>Spontaneous Lesions No. of Patients</th>
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<tbody>
<tr>
<td>Knee</td>
<td>140</td>
</tr>
<tr>
<td>Elbow</td>
<td>90</td>
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<tr>
<td>Ankle</td>
<td>51</td>
</tr>
<tr>
<td>Shoulder</td>
<td>10</td>
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<tr>
<td>Hip</td>
<td>15</td>
</tr>
<tr>
<td>Wrist</td>
<td>8</td>
</tr>
<tr>
<td>Interphalangeal</td>
<td>5</td>
</tr>
<tr>
<td>Great toe</td>
<td>1</td>
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started as soon as the pain is relieved. Physiotherapy is very helpful in restoring the movements of the joints and developing the weak muscles.

The traumatic haemarthrosis or that accompanied by bleeding in surrounding muscles necessitates more active treatment. Fresh blood transfusions are used to help to stop the bleeding and usually a daily volume of 540 ml. is required. A back splint for the lower limbs may be required, but this should be of the lightest weight and removed as soon as possible in order that physiotherapy treatment can be started.

Wounds

The following three principles underly the basic procedure adopted for dealing with these lesions:

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Fig. 2.—X-ray of left hip showing flattened head of femur simulating Perthe's disease. This is a rare finding in haemophilic joints.

Powdered thrombin is locally applied in its dry state to the wound on sterile petroleum-jelly gauze; ordinary gauze has two disadvantages, namely, absorption of the thrombin and adherence to any clot which may form.

Suturing must be avoided; a pressure bandage is all that is required, and this should be left undisturbed for at least five days so that any clot is not dislodged.

Prophylaxis against sepsis by suitable oral antibiotics is advisable; we usually use tetracycline.

Epistaxes are frequent symptoms. Having made sure that there is no local abnormality, a nasal pack is inserted after local application of thrombin. The pack, which is preferably left undisturbed for 48 hours is gradually removed by cutting off a few inches at a time. In a few cases, however, fresh blood transfusions will be needed in order to control the bleeding and to raise the haemoglobin level.

Nerve Palsies

Where these occur, the important point is to persist with treatment indefinitely, giving physiotherapy and muscle re-education for as long as may be required. In peripheral nerve palsies, fresh blood or antihaemophilic globulin transfusions are often required; in one case of bleeding into the cauda equina we were able to re-habilitate the patient by intensive AHG administration followed by a prolonged physiotherapy course.

Similarly several cases of median and ulnar nerve palsies have been successfully treated using fresh blood transfusions and local support.

Haematuria

Experience has shown that haematuria is the least troublesome form of bleeding, however alarming it may be for the patient and it rarely warrants any specific treatment. In most cases it clears up within two weeks or less causing no significant drop in the haemoglobin level. Nevertheless, it is advisable to make X-ray and other examinations to exclude the presence of a urinary stone or other possible lesions. Treatment consists of sedatives with belladonna.

Melaena

In contrast to haematuria, melaena is the most troublesome symptom and must be investigated and treated in hospital. Apart from bleeding from the mucous membrane, peptic ulceration sometimes may be a contributing factor. Although immediate transfusions of fresh blood or AHG fractions are usually required, the total amount required for controlling this haemorrhage varies even for the same patient on different occasions; this has varied between 1 to 20 litres (Nour-Eldin...
and Wilkinson, 1958b). During the treatment of these patients, a diet similar to that used in the treatment of gastric ulcer is advisable. If the main source of bleeding is thought to be in the stomach, thrombin by mouth is recommended, having proved of great value on many occasions, but a high concentration of this material is required, e.g. 1,000 units in a buffer solution every two hours together with alkalis to neutralize the gastric acidity. The use of gelatin in conjunction with thrombin seems to hamper the action of thrombin. The haemoglobin level should be kept in the region of 10 to 11 g. per cent.; it is our impression that higher levels sometimes seem to encourage further bleeding. Surgical measures are usually contra-indicated and every effort should be made to avoid them.

Retroperitoneal Haemorrhage

These abdominal haematoma are common and are often thought to be surgical emergencies which they are not. Rest, medical care, avoidance of surgery and the administration of daily transfusions of fresh blood or AHG are the main lines of treatment. Should it cause apparent intestinal obstruction, every effort must be made to maintain the nourishment of the patient by the I.V. route; aspiration of the stomach contents may only sometimes be required until the haematoma is absorbed and the obstruction is overcome; we have seen several cases of this kind and have so far successfully adopted this expectant treatment.

Bleeding in the Floor of the Mouth

This is always a frightening manifestation and very early administration of fresh blood seems to be the key to avoid extension of this dangerous form and site of haematoma. For these patients equipment for tracheotomy and oxygen administration should be available for instant use. On two occasions we have been obliged to resort to tracheotomy. In one patient, who was seen in this department 48 hours after injury, the haematoma was too extensive to regress after fresh blood transfusions, the patient's breathing became very embarrassed and a tracheal tube could not be passed. Seeing that the patient's condition was deteriorating, tracheotomy was carried out as an emergency after AHG administration, and the child recovered rapidly and completely within 17 days with no subsequent disability.

Teeth

The extraction of teeth offers no troubles or anxieties now. The procedure followed in this department has been described in detail in a recent article (McIntyre, Nour-Eldin, Israels and Wilkinson, 1959), but the main points to be noted from this are as follows:

(a) The number of teeth needing removal is not any obstacle at all for carrying out the required extractions at one sitting.

(b) Local anaesthesia can be used in most cases and is preferable to general anaesthesia.

(c) Haemostasis is partly controlled by an individually moulded local acrylic splint, and local haemostatic substances, e.g. thrombin or snake venom, are no longer required.

(d) A fresh blood transfusion is given immediately before the dental operation usually followed by a daily transfusion for at least three subsequent days. Post-operative bleeding may be most severe on the fifth and sixth post-operative days in adults and on the third and fourth days in children, but subsequently ceases quite quickly.

(e) Antihaemophilic globulin is ordinarily not required for this purpose. In fact, not more than 540 ml. fresh blood is required in one day. This, however, may be supplemented with stored blood or packed red cells in order to raise the haemoglobin level should it have fallen too low.

(f) Since the loss of AHG on storage is unpredictable even at -25°C., freshly collected frozen plasma is not recommended as a prophylactic or therapeutic measure in teeth extraction or for that matter for any other bleeding manifestations.

Major Surgical Operations

It is extremely dangerous to embark on any such major operations without having corrected the blood-clotting defect. Recent work (Macfarlane et al., 1957; Nour-Eldin and Wilkinson, 1958b), has indicated that extra-ordinary amounts of AHG are necessary in order to achieve a reasonable improvement in the blood clotting defect which would allow operative manipulations to be carried out safely. This is a formidable task since AHG has a rapid turn over (Langdell et al., 1955; Nour-Eldin, 1958) and the maintenance of a good haemostasis is usually required for a long post-operative period in order to allow perfect healing. The amount of AHG required will depend on the level of Bridge anticoagulant (Nour-Eldin, Wilkinson, 1958b), but in any case will run into the equivalent of many litres of average normal plasma. The simple method, for estimating the fundamental changes in the blood-clotting defects, described by Nour-Eldin and Wilkinson (1958b) has now been tested in five operations carried out on four haemophilic patients and has provided a useful indicator to the expected amount of bleeding occurring during the operations. It has also shown that proper control before and during the operative procedure is most essential for the attainment of good results; post-operative attempts to stop the resulting haemorrhage are apt to be
futile if proper correction has not been obtained pre-operatively.

**Parenteral Injections**

Even more than in normal children haemophilics will need immunization against poliomyelitis, diphtheria, whooping cough and smallpox. This is a great worry to both the parents and the practitioner. Many of the haemophilic patients, however, have been successfully immunized for these diseases; provided that digital pressure is maintained on the site of injection for three to five minutes after the withdrawal of the needle, and no harmful complications should arise; on only two occasions did a small haematoma develop which, however, subsided without any special treatment. Immunization against smallpox is preferably induced by the prick method rather than the scratch technique.

**Social**

It is rather difficult to deal with all the social aspects of this disease and the problems presented by these patients in an article of this size but a few points deserve special mentioning.

Since 1951, 50 patients have sought the advice of our Almoner, the problems involved have been concerned with schooling (16), occupation (21), re-housing (8), transport (4), and convalescence (1). As regards schooling, each case has to be studied and considered on its merits. But we have always encouraged the parents and the patient to try ordinary schools, provided that the school teachers and medical officers are informed and are willing to co-operate. In some cases, however, there is a loss of education due to frequent absences. This can be overcome by additional home-teaching for 1 to 2 hours a day, and this course is much to be preferred to reference to special schools which, in our opinion, are not suitable for children with haemophilia and Christmas disease. They have no special provisions for treating these conditions; furthermore, mixing with patients who are severely crippled or mentally deficient may have severe psychological repercussions.

Our thanks are due to the Department of Medical Illustration for help in the production of figs. 1 and 2.
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