Review Article

Haemophilia

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SUMMARY

The clinical and haematological features of haemophilia are reviewed and the historical aspects, pathogenesis and genetics are discussed. The problems associated with management, such as factor replacement, home therapy, physiotherapy, surgical intervention and the presence of inhibitors, are fully described. Finally, mention is made of the psychological problems of haemophiliacs and of the help given by the South African Haemophilia Foundation.

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Haemophilia is a congenital bleeding disorder which has been known for many hundreds of years. It afflicts predominantly males and is usually carried by asymptomatic females. The disorder encompasses classic haemophilia (haemophilia A) and Christmas disease (haemophilia B) and is caused by a deficiency of functional factor VIII or factor IX.

The currently accepted theory of blood coagulation shows that both factor VIII and factor IX are early reactants in the coagulation sequence (Fig. 1). The deficiency in the plasma protein may be either quantitative or qualitative. Bio-assay of factor VIII coagulant activity (VIIIc) in the plasma of patients reveals a quantitative deficiency. Immunological testing, however, shows the presence of normal quantities of a substance, antigenically similar to factor VIII, in the plasma of patients with haemophilia A (VIIIAgn).[1] A similar situation exists in Christmas disease, where there is deficient factor IX coagulant activity, yet normal amounts of a factor IX-related protein when tested immunologically. In haemophilia B Leyden there is an absence of factor IX activity on immunological testing[2] and it is remarkable that the levels of coagulant factor IX tend to rise with age in this rare genetic variant.[3]

DEFINITIONS

A unit of factor VIII or IX functional activity is defined as that activity present in 1 millilitre of normal blood. This ranges from 50% to 150% with a mean of ± 100%. A unit of cryoprecipitate is the amount of cold-precipitated factor VIII obtained from 500 ml of whole blood from a normal donor. A unit of fresh frozen plasma (FFP) is that amount obtained from 500 ml of whole blood from a normal donor.

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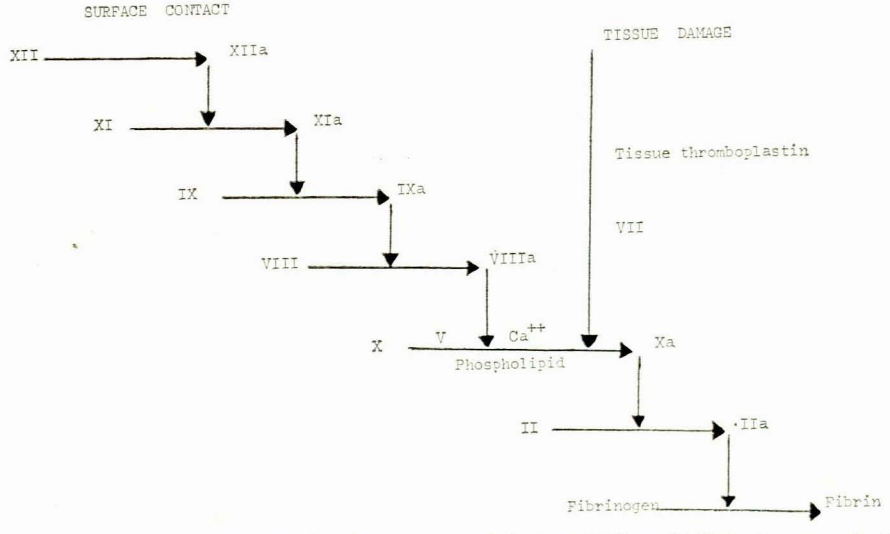

Fig. 1. Simplified scheme illustrating the importance of factors VIII and IX in the coagulation pathway.

THE HISTORY OF HAEMOPHILIA

This has recently been extensively reviewed by Ingram.[4] The earliest references to haemophilia are in the *Talmud*. The rabbi Simon ben Gamaliel forbade the circumcision of a boy because the sons of his mother's three elder sisters had died after circumcision. Maimonides, a 12th century Jewish physician, applied the rabbinic ruling to the sons of a woman who was twice married.

Otto,[5] in 1803, gave a clear account of the disease and noted that the illness occurred only in males and appeared to be transferred by unaffected females. A very full review of the subject was given by Nasse[6] in 1820. The term 'haemophilia' appears to have been used first by Hopff in 1828 and again by Schönlein in 1839.[7]

In the Royal Houses of Europe, haemophilia occurred in Leopold, the eighth child of Queen Victoria. It is assumed that the mutation occurred in Queen Victoria's father, Edward, Duke of Kent, or perhaps in herself, since there was no previous indication of the disorder in the family. The best known royal haemophiliac was undoubtedly the Russian Prince Alexis, the son of Tsar Nicholas II and Tsarina Alexandra.

Of interest, too, is that haemophilia occurs in horses and in dogs. This indicates that the mutation rate must be relatively high, because haemophilic animals would probably not survive in the wild state.

INCIDENCE

The incidence of this relatively uncommon disease in its severe form is about 1 in 25 000 live births, but may be very much higher in certain communities such as Sweden, where the incidence has been recorded as 1 in 7 000.[8,9] Haemophilia A is 5 - 8 times more common than Christmas disease. Lurie and Jenkins[10] undertook a comprehensive survey of the incidence of haemophilia in South Africa, assimilating data from the Cape, Transvaal and Natal, and found that the incidence of haemophilia in White South Africans does not differ significantly from generally accepted figures. There was a suggestion that the incidence of haemophilia may be somewhat lower in the Black population, but in view of the geographical distribution, a spuriously low incidence may have been obtained. They felt that in the Coloured and Black population groups the lower number of less severely affected patients may have been due to under-reporting.

INHERITANCE

Both haemophilia A and haemophilia B are transmitted as sex-linked recessive conditions. When a haemophiliac marries a normal female, his daughters will be obligate carriers of the affliction and his sons will be unaffected. A carrier female who marries a normal male will produce sons with a 50% chance of being affected, and daughters with the same chance of being carriers of the gene (Fig. 2). Only if an affected male marries a carrier female may the daughter of such a union be a haemophiliac.

There is often a family history of 'bleeders' among male relatives, but some 25 - 30% of patients give no family history of the disease. This may be due to the relatively high rate of mutation of the gene or to the disorder being passed down several generations of females with no affected males in the family. The occurrence in a male in a later generation would appear to be due to a new mutation. True haemophilia may occur in females if the mother is a carrier of the gene and if the father is affected, but this is obviously extremely rare.[11,12] In addition, haemophilia A has been reported in XX/XO[13] and XX/XXX mosaicism[14] and haemophilia B in Turner's syndrome (XO),[15] the haemophilia gene residing on the X chromosome present. In other cases of severe female haemophilia with no evidence of chromosomal deviations, a mutation in the second X chromosome has been assumed to explain the occurrence of a homozygous female bleeder.[16,17] Recently 3 generations of women with apparent dominant inheritance of haemophilia A have been described.[18] In spite of low factor VIIIc levels in the range of 2 - 5%, their clinical course has been extremely mild.

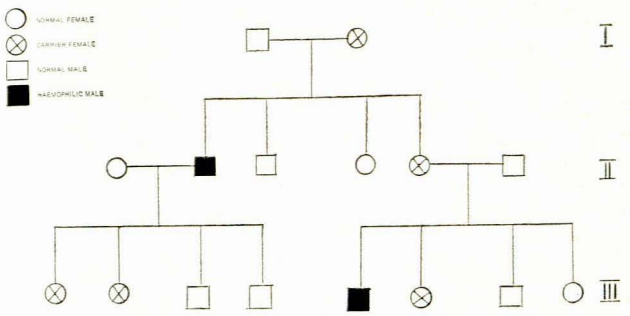

Fig. 2. Inheritance of haemophilia.

Carriers of the gene may themselves bleed more than normal, and if the factor VIIIc is low enough (less than 5%) these individuals may be severely affected and may experience spontaneous haemorrhages into muscles and joints in the same way as severely affected haemophiliacs.[19] Although carriers with levels over 30% are generally unaffected clinically, we have seen a patient who, in spite of a level of 34%, has had severe bleeding episodes.

The factor VIIIc level of a carrier is often below or at the lower limit of the normal range. In view of the overlap, the carrier state may be detected in approximately 25% of haemophilia carriers by functional factor VIII assays only.[1] Gomperts *et al.*,[20] using the ratio of functional factor VIII levels to factor VIII-related antigen (VIIIc/VIIIAgn), have confirmed earlier reports[1,21,22] that below a ratio of 0,65 the carrier status could be predicted within the 95% confidence limits.

The expression of the gene within a single family tends to run true, in that severely affected haemophiliacs usually have severely affected relatives and those with a mild affliction produce mildly afflicted offspring.

THE CLINICAL PICTURE

The clinical picture is usually directly related to the level of functional factor VIII in the patient's plasma. Patients are classified as being severely, moderately severely, and mildly affected.

Severely Affected

Less than 1% of haemophiliacs are severely affected. These patients suffer spontaneous bleeding into joints and muscles, often with crippling deformity.

Moderately Severely Affected

Between 1% and 5% of haemophiliacs are moderately severely affected. These patients have less frequent haemarthroses and muscle haemorrhages than the first group. The low level of factor VIII affords some protection, but deformities are still frequent.

Mildly Affected

In 5 - 30% of haemophiliacs the disease is mild. Spontaneous bleeding and haemarthroses are uncommon in these patients, but they suffer excessive haemorrhage after trauma, tooth extractions and surgery. These patients are often unaware of their haemorrhagic tendency until they are subjected to major trauma or surgery.

Between the upper ranges of the mildly affected group and the lower limit of normal is a group of patients in whom the diagnosis is often missed, and in whom the only symptom is a tendency to excessive haemorrhage after major trauma.

Haemorrhages may commence early in life, for example, at the time of circumcision. If the child is not circumcised, easy bruising may be noted early, or the diagnosis may be delayed until about the age of 7 - 8 months, when the child becomes more mobile and more exposed to trauma.

Joint and Muscle Bleeding

The most common haemorrhagic manifestation of the severely affected haemophiliac is bleeding into joint cavities, especially the knees, elbows and ankles. These haemorrhages typically result from such trivial trauma that they are not noticed, or may arise spontaneously. The source of the bleeding is probably the synovial membrane. The blood fills and distorts the joint cavity and causes pain and muscular spasm, which increases the pressure on the joint. Repeated haemorrhages into the joints lead to thickening and increased vascularity of the synovium and damage to articular cartilage. Resorption of blood from the joint is often incomplete and the result is a chronically damaged and painful joint with thickened synovium. Decreased function resulting from the deformity often causes muscle wasting around the joints. The protective influence of the musculature around the joint is defective and recurrent trauma to the joint occurs easily. This is applicable particularly to the knee joint. A vicious cycle is set up and often leads to severe deformity after repeated bleeds. The final stage is one of ankylosis of the joint. The larger joints are more commonly affected than the smaller joints, and hinge joints are affected more often than ball-and-socket joints.

The clinical picture of acute haemarthrosis is that of a distended, warm, exquisitely painful joint with surrounding muscle spasm and loss of movement. The joint is usually held in a position of flexion, which decreases tension on the joint capsule.

Muscle Haematomas

Haemorrhages into muscle occur either spontaneously or after trauma. A large haemorrhage under tension within a fascial compartment may occasionally lead to occlusion of the arterial flow, producing a muscle infarct, necrosis, and a true Volkmann's ischaemic contracture. Damage to associated nerves may add to the peripheral deformity. The flexor group of forearm muscles is commonly affected in this manner.[23] A less well-recognized form of muscle necrosis may also occur. Deep haemorrhage may be painless and insidious, and may obstruct capillary circulation rather than main arterial inflow. This leads to patchy muscle fibre necrosis, round cell infiltration and irregular fibrous replacement of dead tissue, with ultimate shortening of the affected muscles. Associated joints which are otherwise normal may be pulled into a position of fixed deformity. The calf is particularly susceptible to this type of insult and fixed equinus deformity of the foot is commonly seen in haemophiliacs.[23] One of the muscle groups most affected by bleeding is the iliopsoas; with the production of pain, leucocytosis and fever, the differential diagnosis from appendicitis may be difficult.

Intra-abdominal Bleeding

Intra-abdominal bleeding may be retroperitoneal, intraperitoneal or within an organ. Retroperitoneal bleeding is not uncommon and, with intraperitoneal bleeding, may mimic surgical conditions. Haematemesis, melaena and haematuria are not uncommon, and may be severe and even life-threatening. The haemorrhage may originate anywhere in the gastro-intestinal or renal systems.

Intracranial Haemorrhage

Intracranial haemorrhage is extremely dangerous, tends to occur in younger patients in relation to trauma, and may be intracranial, subdural, or subarachnoid. It is the commonest cause of death in haemophiliacs, and any head trauma in haemophilic patients, no matter how trivial, requires close attention.

Pseudotumours

One of the most severe, but fortunately rare, problems in haemophilia is the development of haemophilic pseudotumours or cysts as a late complication of bleeding. After a haemorrhage into a fascial space or subperiosteally, the haematoma may grow as a result of breakdown of blood, with increased osmotic pressure drawing fluid into the cyst, or from repeated bleeding, or from both. These cysts are most common in the vicinity of the hip but may occur in any site. Their continued growth leads to local pressure effects, often with bony destruction. They may destroy joints and muscles, may perforate the abdominal wall, or may lead to perforation of hollow muscular organs, with fistula formation. They are difficult to treat and tend to recur after incomplete removal. Early treat-

ment of deep bleeding episodes has decreased the frequency of this complication.

MANAGEMENT OF THE ACUTE HAEMORRHAGE

This may be considered under two separate headings: (*i*) specific factor replacement therapy, and (*ii*) supportive treatment during the acute phase.

Specific Factor Replacement Therapy

This requires replacement of the factor lacking in the coagulation pathway by fresh blood, fresh frozen plasma, cryoprecipitate or factor concentrate. The earliest record of transfusion in the therapy of haemophilia was probably that of Lane,[24] who performed a direct transfusion of 340 ml of blood from a woman to an 11-year-old boy who had bled for 6 days after an operation for a squint. After the transfusion, the bleeding stopped and the boy recovered.

Fresh blood contains factor VIII but is unsuitable for therapy in haemophilia A because of the volume required to elevate the patient's factor VIII level and the time taken to infuse whole blood.

Fresh frozen plasma (FFP) is effective in managing bleeding of a minor degree. If fresh plasma is frozen and thawed, 20 - 30% of the original factor VIII content will be lost.[25] Factor VIII has a rapid turnover *in vivo* with a half-life of ± 12 hours. In the presence of bleeding and in fever and infections, the half-life of factor VIII may be shortened even further to 8 - 10 hours.[26,27] In the presence of severe haemophilia and/or severe haemorrhage, use should be made of cryoprecipitate or a concentrate of factor VIII, to avoid the danger of overhydration.

Cryoprecipitate. When FFP is thawed at 4°C a precipitate rich in factor VIII remains.[28] This precipitate may be dissolved at 37°C in a small volume (30 - 50 ml) and has been used extensively as a concentrated form of factor VIII for factor VIII replacement therapy. One unit of cryoprecipitate is that amount harvested from 500 ml of whole blood. The quantity of factor VIII in 1 unit of cryoprecipitate varies widely, but averages 80 - 100 units.

The decision whether to use FFP or cryoprecipitate depends on the availability of either product in a particular area. It does not matter which is utilized, provided that an adequate dose of factor VIII is infused to stop the haemorrhage. The choice then becomes one of availability and economics, both in finance and in donor material. FFP has the advantage that it is relatively inexpensive and widely available and has a more reliable activity. Its disadvantage is the volume infused. Cryoprecipitate has the advantage of small volume and therefore of ease and rapidity of infusion, but has the disadvantage of variable factor VIII activity. As a result, more donor material is utilized during its production and cryoprecipitate is therefore more expensive in terms of money and donors. FFP is used mainly in the Transvaal and cryoprecipitate in the Cape, OFS and Natal.

Concentrated preparations. Several types of concentrates are available in South Africa: (*i*) those produced by several blood transfusion services in strengths of 125 and 250 units of dried factor VIII and reconstituted with 50 ml of saline; (*ii*) commercial concentrates produced in the USA, such as Hemofil, which contain 700 - 800 units of factor VIII in 30 ml and which are derived from human factor VIII sources; and (*iii*) concentrates of bovine and porcine factor VIII.

Supportive Therapy

Supportive therapy is important in the treatment of acute haemorrhages. The symptom which requires most attention is pain. The presence of blood in the joint causes increased intra-articular pressure with capsular distension and resultant pain which may be so severe as to necessitate pethidine or morphine. Intramuscular injection should be avoided until factor VIII replacement therapy has been commenced, because extensive bruising may occur at the injection site. Pentazocine may also prove useful if the pain is not too severe. For mild analgesia either paracetamol, propoxyphene, or combinations of the two, may be used. These agents have very little effect on platelet function, whereas the adverse effects of aspirin on platelet function and gastric mucosae preclude the use of aspirin-containing compounds.

During an acute episode of joint bleeding, the affected joint should be immobilized in the position of maximum comfort, preferably by means of a well-fitting back-slab or Robert-Jones bandage, which is retained until pain has disappeared completely, usually after 24 - 48 hours. Thereafter the back-slab should be applied at night for a further week. During this time the physiotherapist should instruct the patient to perform static quadriceps exercises, followed by more extensive active exercises such as straight leg raising when adequate muscle tone has been regained. This is followed by active exercises against resistance, and partial weight-bearing before a return to full weight-bearing. A swimming pool for water-support exercises is very useful. It usually takes 5 - 7 days before partial or full weight-bearing is allowed.

In patients confined to bed after a major haemorrhage, routine bed exercises help to prevent haemorrhages into other joints. Before regular physiotherapy was started in these patients, Cole and Jones[29] frequently noted secondary haemarthroses, particularly in the elbows, shoulders and knees. The best time for physiotherapy is immediately after replacement therapy has been given.

In those patients with chronic arthropathy, considerable improvement in function may be obtained by graduated exercise to strengthen the muscles surrounding the joint. This should provide some protection against further bleeding, as well as improve the range of joint function.

Useful supportive drugs are epsilon-aminocaproic acid (Epsikapron) and tranexamic acid (Cyklokapron). These fibrinolytic inhibitors are particularly useful after tooth extraction but may also be used to stabilize the clot in patients with severe bleeding who require high factor VIII replacement. These agents are contraindicated in haematuria because of possible formation of clots resistant to lysis within the ureters, and consequent obstruction with retrograde hydronephrosis.

Aspiration of joints is seldom required, but may be of use in patients with very tense, painful, acute haemarthroses. Aspiration should be performed only by a competent operator, in a sterile theatre with full surgical technique and under adequate cover with factor VIII.

HOME THERAPY

The advent of home infusions has altered the therapy of haemophilia considerably. Home therapy, particularly with lyophilized factor VIII, is now available to all who have had the necessary instruction and who have adequate peripheral veins and proper storage facilities. The preparations most suitable at present are dried FFP, dried factor VIII concentrate (cryoprecipitate or intermediate potency agents) or Hemofil (Hyland Laboratories). Patients are trained to set up their own drips and when they have acquired the skills, they are supplied with dried factor VIII and the paraphernalia for intravenous infusions. A record should be kept of all haemorrhages and the amount of factor VIII used. Parents are trained to set up infusions for young patients. The family practitioner can also be of assistance to these patients.

The major advantage of home infusions is that there is minimal delay between the commencement of the haemorrhage and the institution of treatment. This in turn reduces pain, deformity, crippling and absence from work. A theoretical disadvantage is that the amount and cost of treatment may be increased. It has been found,[30] however, that home infusion leads to a relatively minor increase in the amount of factor VIII used and the increased risk of exposure to hepatitis virus is therefore only marginal. The practical advantages of home therapy far outweigh the disadvantages. Many patients have stated that bleeding in a joint is more effectively treated at home than by an inexperienced casualty officer, often after many hours of delay. In addition, it should be remembered patients are often aware of early haemorrhage long before there are physical signs of effusion.

Physiotherapy

The patient who treats himself haematologically can usually also give himself physiotherapy. However, this is not always diligently carried out by patients on home infusion programmes, and is one of the disadvantages of home infusions.[30] Active exercise is essential and the sport most suited to the haemophiliac is swimming. Other sports may be played, but contact sports should be avoided.

SURGICAL INTERFERENCE

With adequate replacement therapy, there is no operation that cannot be safely undertaken in a haemophiliac. For surgery the most potent dried concentrates are necessary and treatment needs to be continued until healing is complete. The surgery most often undertaken in the haemophilic patient is orthopaedic correction of deformity, usually of the knee or hip. Utilizing the concentrates available in South Africa, we have performed synovectomies, arthrodeses and total hip replacements.

On two occasions we have seen postoperative haemolytic anaemia due to naturally occurring iso-antibodies after the administration of large amounts of factor VIII. This has previously been documented, and a 50% fall in haemoglobin levels over 6 - 9 days may occur in these patients.[31-33] It is recommended that for intensive therapy of patients of groups A, B, and AB only type-specific cryoprecipitate be used, if available, and that the use of any other concentrates be restricted to a minimum by titrating dosage to AHF levels.[34] For symptomatic patients, washed group O erythrocytes of appropriate Rh specificity should be transfused.

Polytransfused patients are at risk of developing serum hepatitis, and this risk increases proportionately to the number of donors. Commercial factor VIII concentrates are prepared from pools of 2 000 - 6 000 litres of plasma obtained by plasmapheresis from paid donors.[35] Biggs,[36] in a study of 37 haemophilia centres in the period 1969 - 1971, found the incidence of hepatitis to be about 1,8%. More recently an outbreak of hepatitis associated with factor VIII concentrate was reported from Bournemouth.[37] Fifty per cent of patients who received commercial concentrate developed hepatitis (4 hepatitis B, 7 hepatitis non-B, 2 both types of hepatitis). The Australia antigen status of the patients should be determined at least annually by radio-immunoassay, but all blood, especially of severely affected patients, should be considered potentially infectious.

REPLACEMENT REQUIREMENTS

The patient's requirements are related to his baseline factor level, the nature of the bleeding, the type and potency of material used and its volume relative to the patient's plasma volume. It should be remembered that patients vary in their response to cryoprecipitate or dried factor VIII preparations.

The patient should not be overloaded with fluid or with plasma proteins. In patients receiving large amounts of cryoprecipitate we have observed plasma protein concentrations of 10 - 12 g/100 ml, with the consequent effects of increased osmotic pressure. This might have been obviated by the use of dried factor VIII in situations requiring prolonged and high-dose replacement therapy.

Minor bleeding requires that the factor VIII level be raised to 10 - 20% for 1 - 5 days; whereas major joint bleeding requires a level of 10 - 30% for 3 - 5 days. Severe haemorrhagic conditions such as head injuries, gastrointestinal haemorrhage or retroperitoneal haematoma, require elevation of factor VIII level to 30 - 50% for 7 - 14 days. Major surgical operations require a level of 50 - 70% at operation and 20 - 40% for 14 days, especially in operations such as total hip replacement with muscle cutting, raw bone surfaces and stripping of muscle from bone. Tooth extractions require elevation of factor VIII level to 20 - 40% at the time of operation, and then an antifibrinolytic agent such as epsilon-aminocaproic acid or tranexamic acid for 7 - 10 days. A useful formula for the determination of replacement therapy is:

$$\text{dose of factor VIII} = \frac{\text{Wt (kg)} \times \text{desired factor VIII rise (\%)}}{1{,}5}$$

As factor VIII has a half-life of approximately 12 hours, therapy may need to be given every 12 hours.

The principles of therapy in patients with factor IX deficiency are essentially the same. However, the response to infusion of factor IX is poorer than to that of factor VIII and therefore more factor IX may be required. This is reflected in the above formula by a decrease in the divider from 1,5 to 1,2. In view of the longer half-life of factor IX (about 20 hours), therapy need be given only once or twice per day. The commercial preparations of factor IX are less satisfactory than those of factor VIII and apart from the same danger of hepatitis, thrombotic[38] and anaphylactic reactions[39] and disseminated intravascular coagulation complications have been reported.[40,41] Home therapy may be conducted with these preparations or with FFP. The danger of thrombosis developing may be due to the presence of activated factor X in the concentrates. Such activated preparations should not be used except in special situations (see below).

INHIBITORS

Inhibitors are antibodies to factor VIII or IX, usually of the IgG class,[42,43] but occasionally IgM[44,45] or a combination of IgG and IgM.[46,47] They occur in 5 - 21% of the haemophilic population.[48-50] Rarely, inhibitors have also been described in non-haemophiliacs, especially in women during the postpartum period, in patients with auto-immune diseases and in the elderly. They rarely occur without underlying disease, and have been reported as reactions to drugs, especially penicillin.[51] We have not seen inhibitors to factor IX, but Nilsson and Hedner[52] quote an incidence of 10% in Sweden.

Infusions of factor VIII usually produce a marked anamnestic rise in the antibody level after 3 - 4 days and it may take 4 - 8 months before it falls to pre-infusion levels. For practical purposes all patients with inhibitors are severely affected haemophiliacs and in only a few cases have inhibitors been reported in mild haemophilia.[53] In view of the antibody nature of the inhibitor, corticosteroids and immunosuppressive agents have been used to suppress the antibody level with variable success. Corticosteroids have not proved to be of much value and the immunosuppressive agent with the best results is cyclophosphamide. This agent has been most effective in inhibitors occurring in the postpartum period or associated with underlying diseases. Complete eradication of the inhibitor has occurred in only 6 patients with haemophilia A, who have subsequently received factor VIII without antibody reappearance.[53-55] In a larger number of patients the anamnestic response has been blunted or even prevented,[56-58] but in the majority of cases immunosuppressive therapy has been a complete failure.[56,59,60] Patients with non-haemophilic inhibitors have been reported to have spontaneous remissions, especially in postpartum cases and those associated with auto-immune diseases. In patients with no underlying disease, inhibitors respond to therapy less frequently and spontaneous remission is uncommon.[61]

Recently, prothrombin complex concentrates have been used in patients with inhibitors, with good results. Abildgaard *et al.*[62,63] have recently reported the use of the factor IX concentrate Konyne to treat 64 bleeding episodes in 5 haemophilic patients with factor VIII inhibitors. Prompt control of bleeding was observed in each instance with factor IX doses of 15 - 100 U/kg and no complications were encountered. Both Auto-factor IX and Proplex have been reported as being equally effective.[64] There does not appear to be a relationship between these concentrates and inhibitor level, and no increase in dosage is required for high levels. The exact mechanism of action is not fully known, but it would appear that a high content of activated factors IX and X is necessary to bypass the need for factor VIII in the coagulation process. Thrombotic[38] and anaphylactic reactions[39] and disseminated intravascular coagulation have been reported with the use of these concentrates, especially in the presence of liver disease.[40,41]

Porcine and bovine factor VIII are also available for the therapy of patients with inhibitors. They are effective in the short term only, since there is some cross-reactivity, and antibodies to these animal factor VIII preparations build up rapidly. Their use may be life-saving.

VON WILLEBRAND'S DISEASE

In 1926 von Willebrand described a family with a bleeding diathesis in whom the affected members had a prolonged bleeding time, normal coagulation time and normal platelet count and morphology. In addition, the disorder is now known to be associated with low factor VIII levels and a prolonged and progressive rise of factor VIII after infusion of plasma or factor VIII. It is inherited as an autosomal dominant gene with variable penetrance and expression[65] and affects females slightly more commonly than males.

More severely affected patients present early in life with a tendency to prolonged bleeding from superficial cuts and scratches and with bleeding from nose, mouth and gums. Haemarthroses occur in up to 50% of severely affected patients. Gastro-intestinal bleeding is not uncommon and difficulty is often encountered in determining this source.

Patients with mild von Willebrand's disease have only mild spontaneous bleeding, mainly nose-bleeding, gingival bleeding, bruises and menorrhagia.

The diagnosis is usually not difficult. There is a low factor VIII level, prolonged bleeding time, failure of platelets to aggregate with ristocetin, and a prolonged rise of factor VIII after infusion not only of normal plasma and antihaemophilic globulin, but also of haemophilic plasma. On the other hand, transfusion of von Willebrand's plasma into haemophiliacs does not raise their level of factor VIII.

Principles of therapy are the same as in haemophiliac patients. Less factor VIII is required because of the endogenous manufacture of factor VIII after transfusion.

PSYCHOLOGICAL ASPECTS

The haemophilic child usually grows up in a very protected environment. He is often cloistered by parents with guilt feelings, and reacts either by denial of his illness or by overdependence. Many children and parents do not wish to discuss the illness and regard it as some-

thing of a stigma. However, very many families and patients adjust well to their difficulties, and schooling takes its normal course, but patients may not participate in contact sports. In severely affected patients the attitude of the school is important and a visit to the teacher by the family practitioner may assist understanding of the problems that may arise. Generally, home infusion has drastically reduced the days lost from school because of haemorrhages and some patients maintain a supply of dried factor VIII at school. Patients are soon accepted by their peers, but may initially have to endure questioning and even teasing. Subsequent career opportunities are dependent upon school education. Problems in earning a livelihood often result from unsatisfactory school education.

The South African Haemophilia Foundation aims to improve understanding of haemophilia among doctors and laymen, supports research into the condition and assists haemophiliacs. All patients and their families are urged to participate actively in the Foundation.

Finally, we feel that no couple of whom the woman is a potential haemophilia carrier should deny themselves the right to a family. Even if a child is affected, modern treatment may prevent crippling deformity, and the haemophilic patient may have a full and rewarding life.

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