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Developments and Problems in the Management of Hemophilia

By Peter Jones

TODAY the average, young, severely affected hemophiliac living in a developed country should be treating the majority of his bleeds himself and be approaching his nonhemophilic contemporaries in terms of both life expectancy and affluence. Meanwhile, the majority of the world's hemophiliacs (an estimated 24,000 in India alone*) exist with only a minimal, if any, form of therapy. There is no assurance—in any country—that the supply of quality blood products on which modern management is totally dependent will continue to match rising demand; there is still no safe long-term effective pharmacologic answer to chronic pain, and the management of antibodies (inhibitors) is based on a little conjecture and a lot of luck.

In 1963 Court, in his book on the care of children, wrote: "The combination of recurrent discomfort and disability for the child, limitation of activity, family anxiety and tiring, tedious and expensive hospital care makes haemophilia one of the most exacting illnesses in medicine."[9] Although the emphasis has shifted, along with management, from laboratory to consulting room and from hospital to the patient's home, this statement remains substantially true. It is the purpose of this paper to briefly explore some of the problems of management in the light of our clinical experience in Northern England.

CONGENITAL DEFICIENCY OF FACTOR VIII (HEMOPHILIA A) AND FACTOR IX (CHRISTMAS DISEASE, HEMOPHILIA B)

The clinical manifestations and X-linked inheritance of hemophilia A and B are identical, and the problems associated with their management have many features in common. In the United Kingdom, factor IX deficiency is five times less common than factor VIII deficiency,[55] and in both diseases the severity of the bleeding is related to the amount of deficient clotting factor present in the blood. Laboratory differentiation is essential for specific replacement therapy; cryoprecipitate and related lyophilized concentrates do not contain factor IX.

*Taking the incidence of *severe* hemophilia A as 1/25,000.[55]

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Diagnosis of Hemophilia A and the Hemophilia Carrier

When it is suspected that a boy may have or be born with hemophilia, arrangements should be made for the immediate counseling of the family. Above all, parents at such a time need the reassurance of familiar and established care, which cannot be provided by a succession of doctors, however expert, or by formal reviews of progress during which determined assaults on the child's veins do more to satisfy academic curiosity than to forward rapport. In my region this continuity may be provided by the family doctor but is more likely to be the responsibility of the Haemophilia Centre staff.

In the past there has been a time lag, often considerable, between the usual presentation of bruising or persistent oozing from cuts and diagnosis (Fig. 1). With improvements in organization this delay can be prevented, at least in those families with a previous history of hemophilia.

Using a computerized program of Hospital Activity Analysis and searches of hematology and inpatient records covering a population of 3.3 million persons we have recently established a register of people in Northern England with a proven or presumptive diagnosis of a hereditary bleeding disorder. Subsequent consultation with the families concerned has allowed the construction of further registers of obligatory and potential carriers.

Using the method described by Biggs and co-workers[4] for the two-stage assay of factor VIII coagulant activity (VIIIC)[16] and that of Laurell[33] for electroimmunoassay of factor VIII-related antigen (VIIIRAG), the technique for carrier detection originally described by Zimmerman et al.[68] is now offered to the families. In keeping with international agreement three individual tests are performed, with at least 2 wk between the collection of each sample. Families should be aware that although the accuracy of the method is as high as 74%,[54] or even 95%,[52] a girl cannot yet be told that she is definitely *not* a hemophilia carrier.

Detection of the carrier state of factor IX deficiency is even less certain, since only the plasma coagulant assay is available to identify levels suspiciously low compared with the normal population.

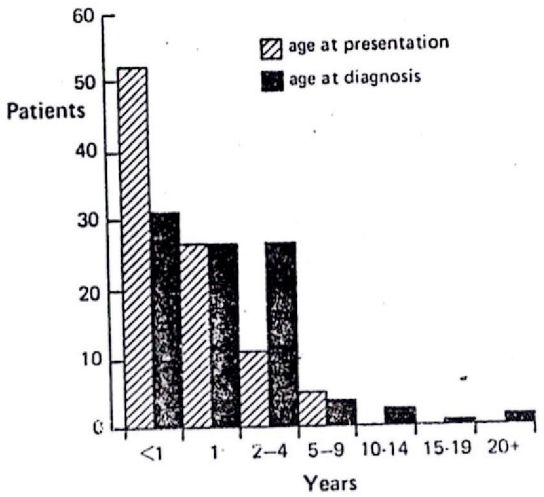


Fig. 1. Ages at presentation and diagnosis of severe hemophilia A and B. From the Newcastle hemophilia survey.

Although we were at first reluctant to test prepubertal girls for fear of arousing undue anxiety in childhood, subsequent discussions with families suggested that parents would prefer to know the likelihood of their daughter's carriership when she reaches the age of 8 or 9 yr. The subject can then be raised naturally over a period of time in much the same way as sex education occurs within a family.

The staff members of the Haemophilia Centre offer a counseling and contraceptive service to young hemophiliacs and carriers, who are encouraged to come and talk over the implications of the disorder with their partners before marriage. The possibilities of intrauterine sexing and termination of pregnancy are discussed. Pregnant carriers, whether obligatory or potential, are offered the services of the local maternity hospital for delivery; maternal VIIIC is assayed in the third trimester to ensure hemostatic levels at parturition. The infant's VIIIC and VIIIRAG are assayed in a fresh cord blood sample, a positive diagnosis always being checked within the first year.

It is less easy to recognize hemophilia B with certainty in cord blood except in severe cases, since factor IX may be temporarily quite low at birth together with the other vitamin K–dependent factors.

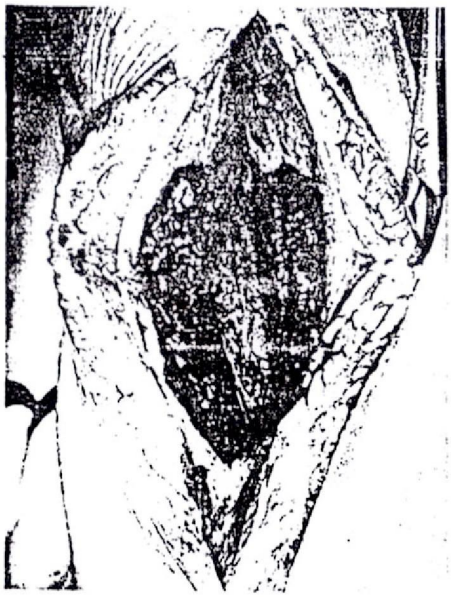
While feeling that cord blood diagnosis is necessary—parents can immediately know of a normal result, and identified hemophiliacs are ensured protection in the rare event of a bleed in infancy—the procedure does create the problem of when to tell parents, who are aware that a result is awaited, that their child has hemophilia. Our experience suggests that parents should be told before delivery that the cord blood results will not be available for some days, thus allowing them time to start to explore their baby peacefully before having to face a positive diagnosis. We do not believe that there is anything to be gained by divulging the results from a female infant; it is the author's opinion that parents should be told that it is not possible to prognosticate on carrier status at this age.

Except in emergency or when specific treatment is indicated, very young children presenting for diagnosis should not be subjected to venipuncture if this is likely to prove technically difficult; veins in the antecubital fossa or the hands or feet will appear in good time. Femoral or jugular vein punctures are strictly contraindicated. Severe hemophilia may often be inferred from the history and physical signs, and the infant may be provisionally registered until accurate diagnosis becomes possible, or until venipuncture is necessary for treatment; when this is the case rapid factor assay should of course precede specific blood product therapy.

PROBLEMS OF TREATMENT

Joint and Muscle Bleeds (Figs. 2–4)

With the advent of cryoprecipitate[47] and lyophilized factor VIII concentrates, hemophilia management has moved into the field of preventive medicine. The recognition that by the age of 7 yr most severely affected hemophiliacs can tell that they are bleeding internally well in advance of the appearance of physical signs provides the rationale for rapid outpatient transfusion and home therapy. Although full statistical proof of the efficacy of such treatment—which has



Fig, 2. Extensive hemorrhage resulting from an intramuscular injection into the lateral aspect of the thigh. Autopsy photograph of a 2-yr-old boy with severe hemophelia A who died from cerebral hemorrhage.

been challenged[32]—is unavailable (partly because of the comparative novelty of the procedures involved together with the natural chronicity of hemophilic arthropathy, and partly because of the rarity of severe hemophilia), it is apparent to the clinician that early treatment can abort the full-blown hemarthrosis, with its attendant pressure on capsule and ligaments, and acute pain, and allow an immediate return to muscular activity.

It also seems reasonable to assume that the less the volume of blood entering a joint cavity, the less the influence on the synovium to hypertrophy in response to the breakdown products produced. In the case of muscle bleeds the effect of early treatment is visible, and crippling deformities due to contractures and atrophy are no longer prominent in a young hemophiliac on adequate therapy. It is because of the risk of such sequelae, and associated nerve palsies, that intramuscular injections are contraindicated in hemophilia even though replacement therapy may have been given.

Hemophilic arthropathy is subject to a relentless natural progression. Unfortunately, radiology provides only a crude measure of this damage, soft tissue changes being well advanced by the time evidence of destruction appears on the film (Fig. 4). Ultrasound and thermography appear to have no more to offer

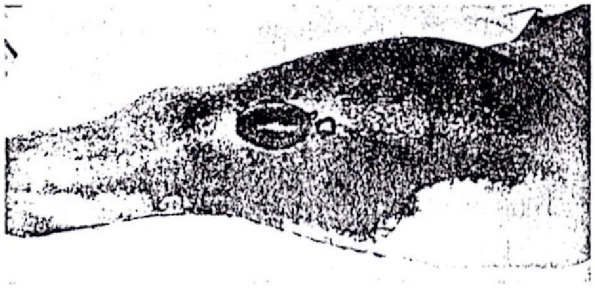


Fig. 3. Massive intramuscular hemorrhage into the thigh following impact with the corner of a table; a tension blister is present. Blood loss into the lesion was estimated at 3 liters in this 67-yr-old severely affected hemophilia B (factor IX deficient) patient.

Fig. 4. Villous hypertrophy of synovium removed from the elbow joint of a 22 year old severely affected hemophilia A patient following recurrent hemarthroses (specimen in saline, × 4 approx.)

than thorough and repeated clinical examination. Although requiring joint aspiration, indexes of biochemical or immunologic activity provide the most likely hope for future long-term evaluation of the hemophilic joint. The various radiologic and biochemical indexes in present use have been reviewed by Hilgartner.[22]

If the rationale for the rapid treatment of bleeds as a means of slowing (if not actually preventing) the onset of chronic arthropathy is accepted, it must also be accepted that such treatment should begin early in childhood. Arthrotomy evidence shows that erosion and pannus, in association with blood staining, may affect the articular cartilage of the knee within months of the first recorded joint bleed in even a mildly affected hemophilic adult.

Since the first hemarthroses of severe hemophilia begin in the preschool child, changes like these might be expected before the fifth year of life, and appropriate treatment should be made available to the parents. Our experience suggests that aggressive therapy between the first hemarthrosis and the muscular development of puberty, when the frequency of intraarticular bleeding starts to decline, provides a major key to the prevention of chronic arthropathy. It may be that when more statistical evidence is forthcoming there will be a case for regular factor VIII prophylaxis during these years.

Factor IX replacement therapy carries the same benefits as for factor VIII; but while factor IX is more stable in vitro, the response of a hemophilia B patient to treatment with it in terms of plasma levels is always lower than expected.[56] A factor IX concentrate must therefore be used to treat all but minor lesions (which may respond to fresh frozen plasma).

Pain

The control of pain for some hemophilic patients remains one of the more difficult problems in hemophilia management. As Dormandy[13] emphasized in response to a letter from a hemophiliac who suggested that a short active life on effective analgesia was preferable to a long life in pain,[20] the regular administration of powerful analgesics is not compatible with normal active life, long or short. With aspirin and the antirheumatic drugs excluded because of their actions on the gut or on platelet function,[44] and paracetamol (acetaminophen)

too mild to be effective except in children, the choice of analgesics is limited to drugs with substantial side effects and the risk of dependence.

The present practice is to recommend pentazocine (Fortral) 30 mg combined with promazine (Sparine) 25 mg for intermittent acute pain[20] and either dihydrocodeine (DF118) or pentazocine or dextropropoxyphene (Doloxene) for chronic pain.[45] Nitrazepam (Mogadon) is helpful when chronic pain is exacerbated by disturbances of sleep, and a regular prescription of diazepam (Valium) or chlorpromazine (Largactil) is sometimes necessary when concomitant anxiety is present. One of our patients with incapacitating pain due to muscle spasm showed an immediate response to baclofen (Lioresal); diazepam may act in the same way.

When chronic pain is a major complaint, depressive illness,[18] sometimes associated with psychosexual problems, should be considered.

In an attempt to control acute pain without resort to conventional drug therapy, we have tried a 1:1 oxygen–nitrous oxide gas mixture (Entonox) administered through a self-regulatory demand valve; although further evaluation of the technique in hemophilia is probably justified, we thought the effect too transitory to be of real benefit.

In the long run the best answer to chronic pain often lies in orthopedic surgery, with, for instance, replacement of a grossly damaged hip joint or arthrodesis of the knee; the best prophylaxis remains early factor VIII or IX replacement therapy.

Factor VIII Antibodies (Inhibitors)

Seven percent of hemophiliacs in the United Kingdom develop antibodies to transfused factor VIII,[7] presenting the clinician with the dual problem of when and how to treat their bleeding episodes. Left untreated, the great majority of closed bleeds resolve with rest and time, but the long-term outcome, as in the case of the older generation of patients who had no recourse to therapy, is likely to be severe crippling. When antibodies appear in early childhood—a patient 8 mo of age has been described by Dormandy and Sultan[15] and one of our patients is of age 2 yr—the problem is particularly distressing. Thankfully there is no proven relationship between the volume of replacement therapy and the development of antibodies.

Unfortunately the evidence on which to base practical conclusions on the best way to treat the antibody patient is confusing; multicenter clinical trials are urgently needed. For routine management the choice lies among "masterly therapeutic inactivity," disregarding the antibody and treating bleeds conventionally with factor VIII replacement transfusions, treating all significant bleeds with a prothrombin complex preparation,[2] and attempting to suppress the antibody using immunosuppressive drugs.[15] In the event of life-threatening hemorrhage the choice is between high-dose human or animal factor VIII, with or without immunosuppression, and prothrombin complex preparations containing factors II, IX, and X,[42] with or without "activation." In these circumstances exchange transfusion or plasmapheresis has also been recommended.[19,57,62]

So much depends on the age and quality of active life enjoyed by the individ-

ual patient, and on the frequency and severity of bleeding, that it is difficult to draw conclusions between these approaches and to offer generally applicable guidelines on management. The policy in Newcastle rests on the work of Dormandy and Sultan,[15] Rizza and Biggs,[53] and Allain and Roberts.[3]

First, it seems imperative to identify antibody formation early if immunosuppression is to be effective. Dormandy and Sultan, in an enquiry conducted on behalf of the World Federation of Hemophilia,[15] studied reports on 56 patients treated with immunosuppressive therapy. Although they concluded that the chances of successfully preventing the reappearance of antibody were small (7 cases), the authors emphasized that these chances rose if immunosuppression was given during or soon after the primary immune response. Cyclophosphamide was the most frequently used drug in this enquiry, but no one regimen stood out as being more successful than another,[15] and the concomitant use of steroids remained uncertain (Dormandy KM: Personal communication).

The two most important conclusions from the work of Rizza and Biggs[53] are, first, that if urgent treatment is to be given (and particularly if surgery is required) action must be decisive and immediate, and, second, that there are a few patients who do not show the usual rise in antibodies after treatment. This latter group have been referred to as "low responders" by Allain and Roberts,[3] who recommended that they be treated along conventional lines although with high-dose factor VIII injections.

Although most antibodies are discovered when a bleed fails to respond to previously effective therapy, or in the course of the *mandatory* preoperative check, present evidence suggests that all severe hemophiliacs should be regularly screened, both by direct testing and by measured response to an injection of factor VIII. Those patients in whom an antibody is found (and who do not respond to immunosuppressive therapy) should be assessed to see if they are likely to benefit from conventional therapy. Our experience is that clinical response to low-dose factor VIII transfusion is often good no matter what the laboratory findings, providing that the dose is given early in a bleeding episode. With the exception of those patients known invariably to respond with high-level antibody production, we have therefore adopted a liberal approach to the treatment of hemarthroses in antibody patients, treating them with low-dose factor VIII injections (10–20 units/kg body weight).

For treatment of life-threatening hemorrhage, either human or animal factor VIII concentrates are used at a dosage of 10,000 units/12 hr,[56] together with antifibrinolytic therapy, provided that this is not contraindicated by renal pathology. If this regime fails, a prothrombin complex is used with comprehensive monitoring for evidence of disseminated intravascular coagulation.[43]

Before specific treatment of a serious hemorrhage is given the site must, as far as is practicable, be immobilized so that a formed clot is not disturbed by movement. The center staff should work closely with the nursing staff involved to ensure that concern about turning the patient regularly to avoid bedsores and the routine proffering of bedpans are not allowed to interfere with this instruction. Meticulous attention to the fluid balance is necessary when a large volume of blood has been lost internally. Two of our antibody patients rapidly became profoundly dehydrated following retroperitoneal hemorrhage, one suf-

fering acute tubular necrosis before his eventual recovery. For these reasons it is probably best to nurse these patients in an intensive therapy unit, but again close consultation between staff members is required, since the usual invasive monitoring techniques are contraindicated, and it is very important to conserve peripheral veins for future intravenous therapy.

Side Effects of Factor VIII Blood Product Transfusion

Hepatitis. The introduction of commercial factor VIII lyophilized concentrates into the United Kingdom in 1973 was followed by at least three separate outbreaks of hepatitis among hemophilic recipients, both hepatitis B and non-B varieties being implicated.[10] The outbreaks were associated with batches derived from paid donor plasma pools of up to 6000 liters tested for HB_s antigen by countermigration electrophoresis. More sensitive testing using radioimmunoassay (RIA) of one of these batches, and of a further 13 batches from two manufacturers, revealed HB_s antigen positivity in 8 of the 14. Dane and Cameron noted that since the amount of antigen detected in the positive batches was near the detection limits of their test, even more sensitive testing might have increased this rate.[11]

Since these outbreaks, one of which involved 15 hemophiliacs (seven HB_s antigen positive) in Newcastle, the incidence of new cases of hepatitis has rapidly declined. The reasons for this decline are probably the increased sensitivity (RIA) in testing of individual donations by the manufacturers, who screen out positive donors, and the development of an increased resistance to infection in the hemophilic population. While we disagree with the suggestion of Craske et al. that commercial concentrates be reserved for the treatment of life-threatening bleeds and to cover major surgery[10]—there is still insufficient material from voluntary donation programs to meet everyday requirements, and improved screening of paid donors has resulted in a fall in incidence of HB_s antigen–positive plasmapheresis subjects[40] to 1.8/1000—it is our practice to restrict young children and mildly affected hemophiliacs to cryoprecipitate therapy.

More worrying than these visible outbreaks of infection, which were expected because of the large donor pools needed for source material, are the possible long-term effects of frequent transfusion therapy with lyophilized concentrates. Several viruses may be involved in posttransfusion hepatitis,[64] among them cytomegalovirus,[61] and probably other as yet unidentified hepatitis viruses.[41,48] Whether or not repeated exposure to these or other agents will result in a rising incidence of chronic liver disease remains to be seen, but the hemophilic population at risk should be regularly screened for evidence of subclinical abnormality.

Kasper, reporting from the United States, where lyophilized concentrates have been in general use for longer than in the United Kingdom, found 12 of 203 patients without overt hepatitis to have an enlarged liver or spleen or both and 80 of 203 to have some disturbance of hepatic function (raised serum bilirubin, 5; mild SGOT elevation, 32; moderate SGOT elevation, 43).[43] At the Tenth Congress of the World Federation of Hemophilia similar reports were received from Greece,[67] Italy,[41] New York,[23] Paris,[63] and Pittsburgh.[21]

Another (but related) problem concerns the management of the known HB_s antigen carrier. Local arrangements will of course vary, but in general HB_s antigen–positive hemophiliacs should be treated as outpatients and subjected to surgery and invasive investigation only when absolutely necessary. When hospital admission is advisable patients with open wounds or overt bleeding should be barrier nursed, and investigations should be kept to a minimum. A most important aspect of management is to ensure that everyone concerned, including the laboratory technician, is aware of the diagnosis. Dentistry is of necessity restricted because of the contraindication to the use of air-driven equipment, but most large centers now have facilities for routine conservation and extractions.

Other side effects. Although transitory allergic reactions (mild urticaria and rigors) are commonly experienced with cryoprecipitate therapy, they are easily controlled with antihistamines. It is our practice to give chlorpheniramine (Piriton) 5–10 mg intravenously with each dose of cryoprecipitate.

Also associated with plasma and cryoprecipitate therapy is acute allergic pulmonary edema, which, if not recognized and energetically treated, may be lethal.[31] We have had experience of four cases, one in a girl with von Willebrand disease, all of whom rapidly responded to intravenous hydrocortisone and furosemide (Lasix). The key to the condition is provided by a chest radiograph showing multiple fluffy opacities in a patient presenting with chest, back, or abdominal pain, dyspnea, and cyanosis in the absence of evidence of circulatory overload.

ORGANIZATION OF MANAGEMENT

The Hemophilia Center

There can be little doubt that the management of hemophilia should, where practicable, be conducted from a center staffed by clinicians and paramedical workers with experience in treating the bleeding diatheses. The advent of home therapy strengthens rather than diminishes this need, partly because of the expense of the therapeutic materials required in a home-based program and partly because progress in terms of reduction of morbidity can be measured only by careful follow-up conducted by workers with expertise in the various disciplines involved.

The first hemophilia centers in the United Kingdom were set up by the Medical Research Council Haemophilia Committee in 1955. Changes in the number, structure, and functions of these centers continue to reflect changes in therapy; there are now over 50 hospitals listed by the Department of Health and Social Security as providers of some degree of specialized service for hemophiliacs.

In an attempt to solve the paradox of ensuring fast treatment near the patient's own home while at the same time providing the costly backup facilities required for major surgery and the management of complications, these hospitals are grouped, each major geographical region being served by a reference center. Hemophiliacs have direct access to their local centers for both emergency treatment and more comprehensive supervision but may at times be

referred to the reference center for certain specialized measures including complex surgery.

In addition to providing—like other centers—a comprehensive laboratory service for diagnosis and monitoring, 24-hr clinical cover, and advisory services in preventive medicine and dentistry, social medicine (including education and employment), and genetic counseling, the reference centers have the responsibility for the coordination of home therapy or prophylactic programs and for supervising the allocation of therapeutic materials in close cooperation with the National Blood Transfusion Service. Some of the reference centers are also recognized as World Federation of Hemophilia Training Centers and all work closely with the British Haemophilia Society.

Figure 5 shows the organizational structure of the Newcastle Reference Centre, with links to both statutory and voluntary bodies concerned with the life of the hemophiliac in the community, to its associated hemophilia centers and district general hospitals (on which a minority of patients still rely for convenient emergency treatment), and to the Regional Transfusion Service. Although all the members of the Reference Centre team have experience in hemophilia care, only a minority (doctor, nursing sister, technical staff, and secretary) work full time with hemostatic disorders.

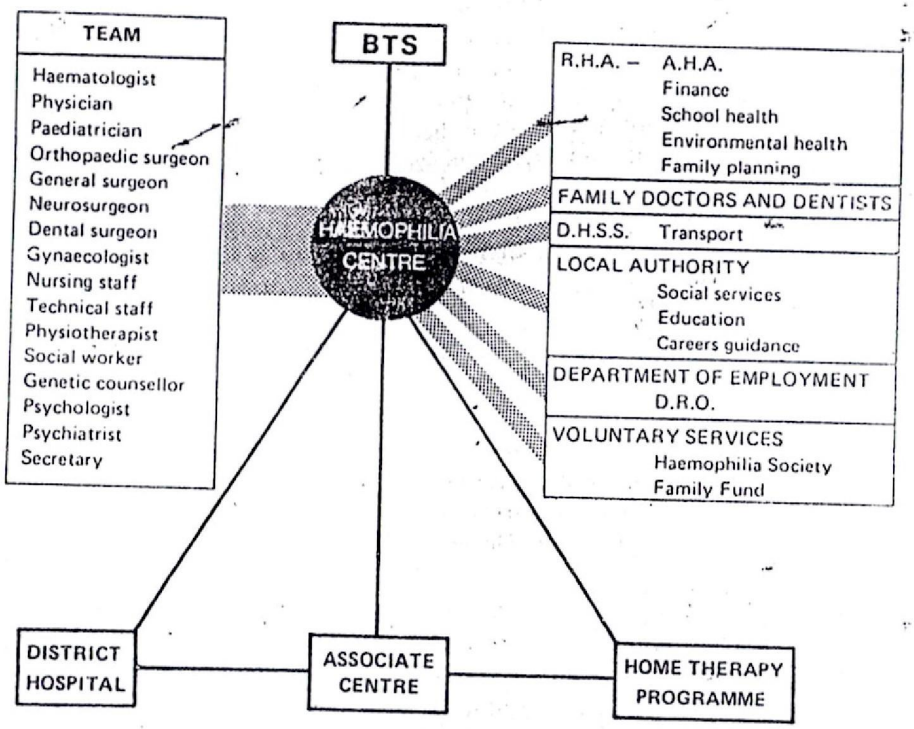


Fig. 5. Organization of hemophilia management. AHA, Area Health Authority; DHSS, Department of Health and Social Security; DRO, Disablement Resettlement Officer (employment); RHA, Regional Health Authority. Note: The Family Fund (in Great Britain) is a government-sponsored trust that provides help in some cases not covered by the official UK Social Security organization.

Follow-up and Records

In the past, when the hemophiliac was an intermittent visitor to a casualty department or an acute medical ward, more attention was likely to be paid to the treatment of his hemorrhage and to his earliest possible discharge than to his general physical, psychological, and social health. Conversely, it was difficult for the family doctor to take an active interest in these aspects of his patient's life because of the need for frequent hospitalization for transfusion.

With increasing awareness of the possible "subclinical" effects of hemophilia (among them chronic liver disease secondary to multiple transfusions, renal damage and hypertension secondary to recurrent hematuria or analgesic nephropathy, and abnormalities of cerebral function secondary to occult intracranial hemorrhage) and the knowledge that increasing longevity will be accompanied by the disorders associated with aging (the degenerative diseases, malignancy, and prostatic hypertrophy), it is clear that regular follow-up is essential. Although it could be argued, particularly with the advent of home therapy, that this should take place in the context of family practice, it is probably better for general follow-up to be the responsibility of the hemophilia center. Here it can be combined with regular assessment of bleeding episodes and therapy and of musculoskeletal performance, and the results from a number of patients more easily be combined to provide a true picture of the incidence of abnormality.

The routine in Newcastle is to try to see each severely affected child once every six months and moderately and mildly affected children and severely affected adults at least once a year. The follow-up procedure includes reviews of the hemostatic and general history, a social review covering environment, education, or employment, and, when appropriate, enquiry into family planning. A general physical examination is performed and includes urinalysis and measurement of height, weight, and blood pressure. The team physiotherapist measures joint range and muscle power and assesses movement and gait. The hematologic and biochemical profile, when this has not already been performed in association with the home therapy program, includes a full blood count, serum iron and transferrin estimations, blood urea, liver function tests, screening for hepatitis-associated antigen and antibody, factor level, and factor antibody. Radiology of joints subjected to bleeds in the past year and an annual chest radiograph in adults are performed. Patients without recourse to regular private dental checks are assessed. When necessary immediate referral to the team specialists in other disciplines, including orthopedic surgery, is possible.

As far as possible the follow-up clinics are kept as informal as possible, and every opportunity is given for a family to discuss their problems in private.

As these clinics evolved and the Centre staff tried to assimilate the constant flow of data from them and from diagnostic clinics, the wards, and the home therapy program, it became obvious that the usual hospital medical record system was not designed for hemophiliacs, some of whom had managed to accumulate several pounds of paper in records over the years.

With the help of a number of organizations, including the World Federation of Hemophilia and the staff of international hemophilia centers, we are at

present attempting to design a workable record keeping system for hemophilia.[28] As a secondary objective (more difficult, but important if worthwhile results are to be achieved) this system is being designed to allow for the long-term comparison of data from individual treatment programs. In the context of the concern about the future supply of blood products for hemophilia such comparative data may prove to be invaluable.

Treatment in the Developing Countries

Whatever the problems experienced with the management of hemophilia in richer nations, they seem insignificant in comparison with the conditions experienced by medical personnel in some of the developing countries. Very little can be achieved without access to an efficient blood transfusion service; the organization of such a service should be the primary objective, the blood resource of the country concerned being used for its own population.

The costs involved in the preparation of cryoprecipitate[8] are small compared with the costs involved in large-scale fractionation; unless a mutually advantageous program in association with one of the expert companies involved with fractionation can be funded, capital should be put towards the production of cryoprecipitate and its storage rather than towards the import of more refined products. If necessary cryoprecipitate may be prepared in a local blood bank using plastic bags,[47] the final supernatant being used either for the treatment of minor lesions in hemophilia B patients or as factor VIII–deficient fresh plasma.

Although it has disadvantages, cryoprecipitate is still the material of choice for hospital-based programs in many centers and is used extensively for both surgical coverage and outpatient treatment in Newcastle.

When supplies are scarce it is false economy to underestimate the dosage required for a hemorrhage. In general, the earlier a bleed is treated the less blood product is needed, but this first dose must be effective. Figure 6 shows the result of undertreating a tongue bite with fresh frozen plasma; several days of intermittent therapy were required for a lesion that would nowadays respond to one injection of pooled cryoprecipitate containing sufficient factor VIII. Details of factor VIII dosage have been given by Rizza.[56]

In open bleeds the use of an antifibrinolytic drug such as ε-aminocaproic acid (EACA) (Epsikapron) or tranexamic acid (Cyklokapron) is recommended to prevent the breakdown of formed clot once factor VIII has been given. The usefulness of EACA in the control of bleeding following dental extractions and in the consequent reduction in replacement therapy required has been proved in an Oxford-based trial;[66] in our experience a similar effect is seen in other types of overt hemorrhage.

HOME THERAPY

It is perhaps because the concept of a hemophiliac treating himself at home is such a logical extension of therapeutic progress that comparatively little has been written about the subject in the medical literature. What has been written has mainly concerned method, blood product supply, and results in terms of savings in education, employment, and time spent in hospital.[1,5,12,17,29,34–38,46,

Fig. 6. Result of late and inadequate replacement therapy. Friable clot and granulation tissue extend from a tongue bite in a 10-yr-old severe hemophilia A patient without factor VIII antibodies.

[49-51,56,58-60,65] Levine has presented the first evidence that home therapy may slow the progression of chronic arthropathy.[39]

The home therapy program in Newcastle started relatively late, in 1973, when commercially prepared lyophilized factor VIII concentrates were first licensed for use in the United Kingdom. Prior to this some UK patients had been treating themselves in programs organized mainly from the Royal Free Hospital, using mostly cryoprecipitate,[36] and from Oxford, using lyophilized concentrate prepared by Bidwell at the Lister Institute.[56] At other centers, notably Edinburgh, geographic proximity of the patients and a welcoming room providing for self-transfusion combined to provide a fast and efficient treatment service. Meanwhile, in the United States and continental Europe home therapy had become established, with programs ranging from the meticulous care of small groups of children in Stanford[34] to the growing computerized organization of the Brackmanns working from Bonn.

Principally because of financial restrictions involved with a shortage of lyophilized concentrate produced from voluntary donations within the National Health Service,[6,14,24,25] the Newcastle program started cautiously and was confined to schoolchildren and to adults in permanent employment. Other selection criteria were as follows:

(1) Patients selected for home therapy should either bleed frequently enough to justify the training and expense involved or be geographically isolated from a suitable hospital or doctor.

(2) In general, they should be over 5 yr of age, have suitable veins, and have a relative or friend capable of understanding and performing the technical procedures required and of reacting sensibly in an emergency.

(3) They should live in a reasonable environment, have immediate access to a telephone, and possess a reliable refrigerator for the storage of concentrate.

(4) They should agree to keep accurate records of all bleeding episodes and treatments and attend regularly for follow-up.

Fifty-five patients are at present on the program, using a mean number of 18,796 factor VIII units per patient per annum.[27] Details of the procedure in home therapy have been given by Lazerson,[34] Levine and Britten,[38] Jones,[26] LeQuesne et al.,[36] and Rizza.[56]

Problems

Home therapy, whether it is based on self infusion at the first evidence of a bleed—so-called crisis or on-demand therapy—or on prophylaxis, provides neither doctor nor patient with a panacea. As the program progresses frequent contact between young well-adjusted hemophiliacs and their families and the center staff is lost, hospital management becoming increasingly devoted to patients or families with major physical, social, or psychological problems. This change in emphasis, while accepted by the core team in the center, may not be appreciated by staff members concerned with general hospital medicine. Frequent explanation and ongoing support are needed from the center to convince junior doctors and nurses that not all hemophiliacs have high-level antibodies, or problems with analgesia or alcohol, or difficult relatives.

For those hemophiliacs and their families to whom frequent visits to the center for treatment have become an established way of life, the first months of home therapy, however welcomed for its convenience and opportunities, may result in feelings of intense loneliness. In order to alleviate this and help with other problems of adjustment, the family should be visited at home by the nurse responsible for the day-to-day running of the home therapy program and, if possible, by the center social worker. In our limited experience it takes at least a year for the average family to adjust to home therapy, and often much longer for a child or adolescent boy to inject himself regularly rather than let a parent do it for him.

Another effect we have noted, in a minority of patients, is an increased desire for analgesic drugs. This seems to be unrelated to pain, but may be related to the removal of the comparatively easy access to analgesia when presenting with an acute bleeding episode in hospital. It follows that while continuing to encourage independence the center staff should maintain very close contact with hemophiliacs started on home therapy for some time, and that this contact should include the patient's family doctor.

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