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Classic diseases revisited

Haemophilia

Summary

Although the nature of haemophilia has been understood for thousands of years, knowledge of its molecular genetics is recent. These X-linked bleeding disorders have diverse underlying DNA defects and, in 1992, DNA inversion within the X chromosome was found to explain half of the most serious cases of haemophilia A. The life-span and quality-of-life for patients with haemophilia had improved steadily throughout the early 1980s but the principal cause of death remained intracranial haemorrhage until the epidemic of HIV infection due to contaminated factor concentrates. Infection with hepatitis C virus is almost universal for patients treated with clotting factors before 1985. No curative treatment is available for hepatitis C at present. Knowledge of the transmission of viruses in concentrates has led to important developments in processing techniques to eliminate them. Recombinant technology has produced factor VIII and, more recently, factor IX concentrate which is likely to be very safe. Development of inhibitors to factor concentrates (especially factor VIII) remains one of the most serious complications of haemophilia. The variety of treatments available testifies to the lack of a single universally efficacious one. The use of prophylactic treatment has been conclusively demonstrated to result in a preservation of joint function in severely affected patients who might otherwise develop significant joint problems. The many facets of the care of patients with severe haemophilia, ranging from dental care to genetic counselling, can be advantageously co-ordinated in a haemophilia comprehensive care centre.

Keywords: haemophila, genetics, prophylaxis, recombinant factor replacement

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Haemophilia is an ancient disease. It neither selects nor spares any class or ethnic group. As early as the fifth century AD, haemophilia was referred to in the Babylonian Talmud.[1] A description of the disorder in the early 1800s by the American physician Otto,[2] accurately described the pattern of inheritance. In the late 1940s Pavlovsky[3] discovered that blood from one haemophilia sufferer could correct the defect in another. It was surmised that the bleeding was due to a lack of 'anti-haemophiliac factor' in the blood. The existence of two separate forms of haemophilia was not inferred until 1952 when one type of haemophilia was described lacking what we now know to be factor VIII and the other lacking 'plasma thromboplastin component', later called factor IX.[4] The more common of the two disorders, classical haemophilia or haemophilia A, has a prevalence of 1 in 10 000 and haemophilia B or Christmas disease has a prevalence of 1 in 50 000.

Genetics

Both haemophilia A and B are X-linked recessive disorders and therefore occur almost exclusively in males. The sons of haemophilia patients will be unaffected and all the daughters will be carriers. For carrier females with normal partners, half their sons will have haemophilia and half their daughters will be carriers.

The genes for both factors VIII and IX have been mapped to the distal end of the long arm of the X chromosome, bands Xq28 and Xq27.1, respectively. The genetic code itself has been sequenced for both genes. The factor VIII gene is very large, comprising 186kb of DNA with 9kb of exon (sequences of coding DNA). The coding base consists of 26 exons. Over 80 different mutations have been characterised[5] and they include deletions, insertions and point mutations. However, until recently, about 50% of severe haemophiliacs had no detectable mutations.[6,7] A novel form of mutation in which a very large sequence of DNA becomes inverted, has now been shown to account for almost all of these cases of severe haemophilia A.[6-9] Within the factor VIII gene there are two regions of coding DNA known as F8A and F8B. The former has two copies which extend outside the factor VIII gene towards the chromosomal telomere. This is the segment which is inverted (figure). The factor IX gene is 34kb in length and the essential genetic information is present in eight exons. Over 400 distinct mutations have been documented in haemophilia B,[10] most of which impair the synthesis, secretion or stability of factor IX. Interestingly, a significant number of both factor VIII and factor IX gene mutations occur at CG dinucleotides.[11] These mutations often involve arginine residues at critical positions, resulting either in changes at the molecules' functional sites or in inappropriate stop codons. About one-third of patients with haemophilia have new mutations.[12]

Using recent advances in genetics, it is possible to offer potential haemophilia carriers accurate diagnoses in the great majority of cases. This is particularly useful when assays of coagulation factors (phenotypic analysis) give uncertain results. Once the defect is known (or if there is an informative polymorphism of DNA to act as a marker), accurate and rapid antenatal diagnosis can be carried out from about nine weeks gestation using chorionic villous sampling.

Classification and clinical manifestations

Haemophilia is classified according to the baseline level of clotting factor. Severely affected patients have $<1\%$ of normal factor levels, moderate patients $1-4\%$, and mild $5-50\%$. Patients with severe haemophilia have frequent and often severe bleeds while those with mild disease may be little troubled by clinical manifestations. The complications usually associated with haemophilia are listed in box 1 and an illustrative case history is presented in box 2.

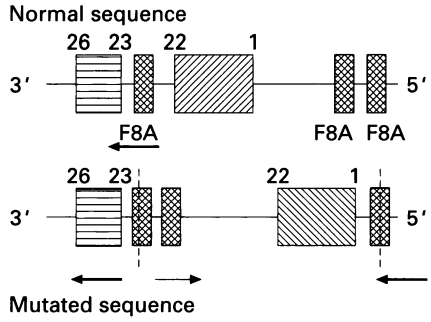

Figure 1 The normal factor VIII gene is shown in part, together with the extragenic copies of the F8A gene. In the mutated gene, the breakpoint at intron 22 and the large inverted sequence are depicted

Complications of haemophilia

Bleeding complications
- haemarthrosis - spontaneous/ frequent and disabling in severe haemophilia
- soft tissue haematomas
- intracranial haemorrhage
- excessive bleeding after surgery (including dental surgery)
- haematuria, epistaxis (less comon)
- haemophiliac arthropathy and joint deformity

Complications of treatment
- development of inhibitors
- thrombosis

Infective complications of treatment
- hepatitis C
- HIV
- hepatitis B

Psychosocial complications
- emotional problems of chronic disease (especially teenagers)
- problems with schooling and employment

Rare complications
- pseudotumours of bone

Box 1

Life-threatening complications

INTRACRANIAL HAEMORRHAGE

We know from the long established national Swedish register of causes of death, that before 1920 the median life expectancy of a child with severe haemophilia was about 11 years. Between 1921 and 1960 this figure gradually increased to 20–30 years. After the discovery of more specific and effective treatment for bleeding episodes, median life expectancy rose to over 56 years between 1961 and 1980. Data from the Swedish registry show intracranial bleeding was the single most common cause of death in this era and half the deaths were preceded by recorded trauma.[13] Bleeding elsewhere, if uncontrolled, may also present a threat to life in the haemophilia patient but death from uncontrolled mucosal or post-surgical bleeding should now be avoidable.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

The recognition of AIDS in patients with haemophilia in 1982[14] marked a reversal in the continuous improvement in life expectancy and quality of life experienced in previous years. AIDS has now overtaken fatal intracranial haemorrhage as the main cause of mortality in patients with severe haemophilia. The majority of severely affected patients with haemophila treated before 1986 have been infected with HIV, and many who were infected in the early 1980s have already died of AIDS-related illnesses. In the UK from 1985–92, 85% of deaths in seropositive patients were due to HIV infection.[15] There is, at present, no curative treatment and care is usually undertaken jointly by haemophilia and HIV specialists.

HEPATITIS

By 1972 it was recognised that clotting factor concentrate could transmit hepatitis.[16] Vaccination against hepatitis A and B is now universal practice and it is hepatitis C which currently causes most anxiety.[17] Before 1986 almost all patients given clotting factor concentrates were infected with this virus. The majority of infected patients develop some evidence of disease ranging from mild chronic active hepatititis to cirrhosis but so far few have developed hepatic failure and hepatocellular carcinoma. Most remain asymptomatic and may never develop any clinical problems. About 10% of patients may develop liver failure after 20 years or more of infection and co-infection with HIV may accelerate this process[18], as may alcohol abuse. Transmission of hepatitis C to sexual partners is an infrequent occurrence.

Medical treatment is of limited efficacy. Alpha-interferon is the only licensed agent but may help only 10–20% of patients to normalise liver function tests over a sustained period. Results are, if anything, less encouraging for those with haemophilia than for other groups[19]. The reasons for this are uncertain but may include associated HIV infection, infections with more than one strain of hepatitis C virus and the duration of infection which in all cases will be greater than 10 years and may be as much as 30 years. The difficulties of liver transplantation are compounded by re-infection of the new liver with hepatitis C after the transplant and most centres are reluctant to offer transplantation for patients infected with HIV who are already immunosuppressed.

DEVELOPMENT OF INHIBITORS

The development of inhibitory antibodies to factor VIII and factor IX poses a very difficult problem in the clinical management of haemophilia. Patients whose haemophilia is due to deletions (especially in haemophilia B) or nonsense mutations (and who therefore have no native protein) are more likely to form inhibitors to either factor VIII[5] or IX.

The strength of an inhibitor is measured by its ability to 'neutralise' factor VIII or IX activity in *in vitro* clotting assays and is expressed in Bethesda units. Inhibitors may be weak or potent, transient or persistent. They are thought to affect 10–20% of patients with haemophilia A[20] but rarely occur in haemophilia B. Close surveillance of patients receiving newer factor concentrates, both high-purity and recombinant, has detected more frequent inhibitor development in some studies and led to fears that inhibitor formation might be increased in patients using these concentrates. One prospective study has revealed little difference between patient groups[21] and sequential studies designed to detect the incidence of inhibitors in previously untreated patients have highlighted the importance of transient inhibitors and provided reassurance with regard to inhibitor development and recombinant factor VIII.[22] Differences in study design and frequency of assay may account for discrepant findings[13].

Although the transient nature of many inhibitors is reassuring, on one level it creates difficulties with regard to the evaluation of immune tolerance regimes

Illustrative case history

A man, now aged 35. Born with severe haemophilia A but no family history. Recurrent severe joint bleeds in elbow (target joint) and other joints. Commenced on home treatment. Severity of bleeding made prophylactic treatment desirable as already some degree of deformity was clinically demonstrable in the elbow and knee. Some bleeds required admission for bed rest and eight-hourly treatment. Insufficient amount of NHS factor VIII available to meet requirements of prophylaxis in the 1970s. Therefore, commenced on commercial concentrate.

Coped well socially, failed to manifest typical teenage 'refusal' of chronic disease. Highly intelligent with good progress academically. University education undertaken, leading to successful business career. Frequency of bleeding diminished in 1980s. No inhibitors. Excellent quality of life attained.

1978: hepatitis B

1986: confirmed HIV antibody positive

1991: confirmed hepatitis C antibody positive

Remained well despite 'transaminitis' working full time and receiving 'on demand' treatment. Took part in prospective study of interferon therapy for hepatitis C infection but withdrew because of side-effects. Bleeding episodes infrequent, no HIV-related illness

1995: episode of fulminant hepatic failure followed by good recovery with medical treatment.

Should he be offered a liver transplant?

Box 2

for the treatment of inhibitors. Immune tolerance induction involves the daily administration of clotting factor, often with immunomodulatory drugs. This approach has been shown to be most successful when administered as soon as inhibitors are detected. Inevitably this means some patients will be treated for a problem which would have resolved spontaneously. However, the potential seriousness of a high-titre inhibitor cannot be over-estimated. Treatment strategies vary and details are beyond the scope of this article, but outlines are given in box 3.

Treatment

The treatment options currently open to haemophiliacs are given in box 4.

BLOOD PRODUCTS

Treatment of haemophilia has evolved from 'the shadows towards the light'[31] over the past 25 years. Initially, fresh frozen plasma was the only product available for treatment of bleeding episodes and huge volumes were required. The discovery that the 'antihaemophilic globulin' was concentrated in cryoprecipitate[32] helped pave the way to the large scale production of crude lyophilised cryoprecipitate concentrates. With chromatographic purification, intermediate purity concentrates of factors VIII and IX became the mainstay of treatment of factor VIII deficiency through the 1970s and 80s and have been safe with respect to HIV and hepatitis C transmission, since effective donor selection and viral inactivation have been available.

There has been some concern that intermediate purity factor VIII concentrates are associated with immunosuppressive effects.[33] These effects have been attributed to the non-factor VIII plasma proteins in the concentrate and have contributed to the drive to use high-purity products. High-purity factor VIII concentrates have an increased concentration of factor VIII and are free from other plasma proteins, although albumin is added after processing to stabilise the product. They are recommended[34] for the treatment of patients infected with HIV and are increasingly being used for all patients in the developed world.

For patients with factor IX deficiency, intermediate purity factor IX is unacceptably thrombogenic, especially in the context of orthopaedic surgery. Thrombotic potential is probably due to contaminating activated coagulation factors. High-purity factor IX is now available and has replaced the intermediate purity product in the UK. Inhibitors of fibrinolysis should not be used in conjunction with factor IX therapy.

The dose of factor VIII concentrate administered is based on the calculation that 1 international unit (IU) of factor VIII per kg of body weight will increase the plasma level by 0.02 IU/ml. A level of 0.5 IU/ml is considered necessary for treating most serious muscle or joint bleeds, but for major surgery or head injuries a level of 1 IU/ml (ie, 100% of normal levels) may be required. The half-life of factor VIII is eight hours and therefore 8–12 hourly dosing schedules are needed. For factor IX the half-life is longer (approximately 18

Treatment of patients with inhibitors to factor VIII or IX

Principle	*Method*	*Reference*
Acute treatments		
• swamp inhibitor	High dose factor concentrate (for low titre inhibitor)	23
• alternative species factor VIII	Porcine factor VIII	24
• bypass 'block' in clotting cascade	Infusion of prothrombin complex concentrates or activated prothrombin complex concentrates. Infusion of activated factor VII	25, 26, 27
Chronic treatments (may be commenced in acute situation in addition to above)		
• induce immune tolerance	Continuous factor VIII infusion and combination regimens	28
• immune suppression*	Cyclophosphamide	
• removal of inhibitor	Plasma exchange/pheresis, protein A column immunoadsorbtion	29, 30

*Usually used in conjunction with other modalities of therapy, most notably in the Malmo regime[28]

Box 3

Haemophilia: treatment options

- factor replacement: intermediate purity, high purity factor VIII; high purity factor IX; recombinant factor VIII; (recombinant factor IX); porcine factor VIII; activated prothrombin complex concentrates; factor VIIa (plasma derived or recombinant)
- release of endogenous stores: desmopressin (for mild haemophilia A only)
- clot stabilisation: tranexamic acid, epsilon amino-caproic acid (useful adjunctive therapy in mild haemophilia)
- topical applications: topical thrombin (of limited use in gingival/mucosal bleeding)

Box 4

hours *in vivo*) and once-daily treatment is sufficient except for the most serious bleeds. For factor IX, 1 IU/kg body weight will increase the plasma level by 0.01 IU/ml.

Measurement of peak and trough levels should be carried out to guide treatment and an inhibitor screen should be performed before planned surgery. In some situations, such as replacement therapy for surgery, the use of continuous infusion of factor VIII is advantageous as lower doses are required and troughs are avoided.[35]

NON-BLOOD PRODUCT HAEMOSTATIC TREATMENT

The hormone desmopressin is capable of raising the plasma level of factor VIII, two- or three-fold.[36] It is thought to work by releasing stores of factor VIII from the endothelium; therefore, tachyphylaxis occurs after several doses until reaccumulation of stores can take place. It is only useful in patients with measurable factor VIII (ie, mild to moderate haemophilia) and is usually given by slow intravenous infusion at a dose of 0.3 μg/kg. Not all patients respond predictably and factor VIII levels are checked post-infusion to ensure that a satisfactory response has occurred. It is now available (on a named patient basis) for subcutaneous injection and this route greatly enhances its acceptability in small children. Because of the associated side-effects of fluid retention and hypertension, the use of desmopressin is not recommended in patients under two or over 60 years of age. It should not be used in patients with known ischaemic heart disease or those who have sustained a severe bleed or injury. Administration of desmopressin is associated with activation of fibrinolysis and, in general, the concomitant use of a fibrinolytic inhibitor, such as tranexamic acid or epsilon amino-caproic acid is recommended. Fibrinolytic inhibitors can also be usefully administered in conjunction with factor VIII but anti-fibrinolytic therapy is contra-indicated in the presence of haematuria and is not used with factor IX concentrate.

ADMINISTRATION OF TREATMENT

Treatment can be administered 'on-demand' or prophylactically. Currently the majority of haemophilia treatment is administered on-demand and this can be done either in the hospital or the home/community setting. For severe haemophilia, home treatment is now established as safe and effective and, in general, is acceptable to this well-motivated group of patients and families.[37] For patients with moderate or mild haemophilia, on demand treatment in hospital is most appropriate. It should be remembered that even mild haemophilia may result in bleeding severe enough to necessitate vigorous treatment and hospital admission. Patients and families are encouraged always to contact the haemophilia centre for advice.

PROPHYLAXIS

The obvious efficacy of treatment and the convenience of use of factor concentrates has encouraged the concept of prophylactic treatment. Patients with severe haemophilia experience bleeding episodes 30 times a year or more. The potential for irreversible joint damage is graphically demonstrated in some older patients who have survived life-threatening bleeds but whose degree of permanent joint deformity is testimony to the need for primary prevention of joint bleeding. This has only been possible since the manufacture of stable factor concentrates in sufficient amounts was achieved in the 1970s, although Sweden was one of the first countries to institute a comprehensive programme of prophylaxis beginning as early as 1958.[38] The aim of prophylaxis is to convert severe haemophilia to mild/moderate disease by administering sufficient factor VIII, on a three times a week basis (or factor IX twice a week) to keep trough levels of factors above 1%. Reporting on the results of prophylaxis in a population of 60 severe haemophiliacs, the Malmo group noted older patients had minimal joint deformity.[38] For younger patients (<17 years) the majority had no detectable joint damage and all 60 patients had good quality of life. It is clear that joint disease is preventable even in severe haemophilia. The Swedish group commence prophylaxis between the ages of one and two years,[38] necessitating the insertion of indwelling venous access with all its attendant problems.

VIRUSES AND CONCENTRATES

It had been recognised since 1972 that hepatitis B and non-A, non-B hepatitis could be transmitted by clotting factor concentrates[16]. With the recognition that concentrate transmitted HIV infection to haemophilia patients, efforts to produce virally inactivated concentrates were intensified.[31] These have culminated in the production of a generation of products which are safe and free from lipid-coated viruses. Some products have undergone double viral

inactivation steps – for example, dry heating or ultrafiltration may be combined with a chemical inactivation step such as the use of solvent detergent processes or sodium thiocyanate[31]. Thanks to these measures there have been no cases of seroconversion from HIV, hepatitis B or C recorded in the UK since 1986. Despite this significant achievement, caution is warranted because documented transmission of hepatitis A and parvovirus B19 have occurred in Europe[39,40] and this indicates that non-lipid coated viruses can escape inactivation procedures.

RECOMBINANT FACTOR VIII (rVIII)

Factor VIII derived by recombinant technology is now available in the UK and should carry no viral risk. Manufacturers, however, add small amounts of human albumin in order to stabilise their products. A concentrate free of all human protein is now undergoing clinical trials, as is a recombinant factor IX concentrate.

The administration of care

THE COMPREHENSIVE CARE CENTRE (CCC) CONCEPT

Although *treatment* of haemophilia may be seen in the narrow context of administration of haemostatic medications as outlined above, *care* of the haemophilia patient is a much broader issue. The Department of Health recently recognised this by publishing a Health Service Guidelines document.[41] This firmly establishes the concept of a comparatively small number of specialised units, able to provide the facilities to deal with the broad range of problems and complications which can occur in patients with haemophilia. The protocol requires the establishment of a co-ordinated network of collaboration with specialists in rheumatology, orthopaedics, HIV and hepatitis, dentistry, social work, physiotherapy and occupational health. Special arrangements must be in place to ensure that children receive both expert haemophilia and paediatric care, usually through joint clinics. CCC's must operate a 24-hour service for patients (and staff in other centres) for advice and treatment.

Establishing and co-ordinating community and prophylactic care is usually the responsibility of the CCC but other hospitals may become involved as haemophilia centres. These centres may also offer a wide range of services but usually rely on a CCC for some aspects of specialist care such as diagnosis and the counselling of carriers and patients with regard to genetics and antenatal diagnosis. The effect of these arrangements has been to limit and regulate the 'market' in healthcare (created by the new National Health Service reforms) for the benefit of the haemophilia community.

COMMUNITY CARE

With the growth of home treatment and prophylactic treatment programmes, patients with haemophilia and their families are spending less time in hospital, both as out- and in-patients. This welcome development is not new[42] but has become more widespread. It has meant that some aspects of care and follow-up normally attended to in hospital are now carried out in the community by a co-ordinator[42] (usually a haemophilia nurse specialist) who organises aspects such as home treatment, prophylaxis and vaccination programmes. The haemophilia nurse specialist may undertake the continuing education of patients and their families and may also visit schools and community groups when required. The expansion in the role and responsibility[43] of the haemophilia nurse specialist is a necessary and welcome development in the improvement of services for patients with haemophilia.

The future

Attention must remain focused on blood product safety to protect the current cohort of children. It is important that we can reassure their parents that they will not suffer from transmissible disease and the use of factor VIII derived by recombinant technology is likely to replace biologically derived factor VIII in this age group and in previously untreated patients.

Prophylaxis will be more widely used as viral safety is ensured and cost effectiveness becomes evident. We should aspire to raising the median survival of patients with haemophilia to approach that of the general population and simultaneously to improve their quality of life and freedom from disabilty.

It is likely to be some years before gene therapy becomes a reality since there are many problems still to solve. The ability to create a low resting level of factor VIII or IX by the introduction of functional cells whose survival and activity can be ensured over a period of months or years, would transform the care of haemophilia even if a genetic cure is a more distant goal.

1 Katznelson JL. Haemophilia, with special reference to the Talmud. *Heb Med J* 1956: **I;** 165.
2 Otto JC. An account of haemorrhagic disposition existing in certain families. *Med Repos* 1803; **6:** 1–4.
3 Pavlovsky A. Contribution to the pathogenesis of haemophilia. *Blood* 1947; **2:** 185.
4 Aggeler PM, White SG, Glendenning MB. Plasma thromboplastin component (PTC) deficiency: a new disease resembling haemophilia. *Proc Soc Exp Biol Med* 1952; **79:** 692.
5 Tuddenham EGD, Cooper DN, Gitschier J, *et al.* Haemophilia A: database of nucleotide substitutions, deletions, insertions and rearrangements of the factor VIII gene. *Nucleic Acid Res* 1991; **19:** 4821–33.
6 Naylor JA, Green PM, Rizza CR, Giannelli F. Factor VIII gene explains all cases of haemophilia A. *Lancet* 1992: **340;** 1066–7.
7 Naylor J, Brinke A, Hassock S, Green PM, Giannelli F. Characteristic mRNA abnormality found in half the patients with severe haemophilia A is due to large DNA inversions. *Hum Mol Genet* 1993; **2:** 1773–8.
8 Goodeve A, Preston FE, Peake IR. Factor VIII gene rearrangements in patients with severe haemophilia A. *Lancet* 1994; **343:** 329–30.
9 Lakich D, Kazazian Jr HH, Antonarakis SE, Gitschier J. Inversions disrupting the factor VIII gene are a common cause of severe haemophilia A. *Nature Genet* 1993; **5:** 236–41.
10 Giannelli F, Green PM, High KA, *et al.* Haemophilia B: Database of point mutations and short additions and deletions-third edition. *Nucleic Acid Res* 1992; **20** (suppl): 2027–63.
11 Youssoufian H, Kazazian Jr HH, Philips DG, *et al.* Recurrent mutations in haemophilia A give evidence of CpG mutation hot-spots. *Nature* 1986; **324:** 380–2.
12 Gitschier J, Kogan S, Diamond C, Levinson B: Genetic basis of haemophilia A. *Thromb Haemost* 1991; **66:** 37–9.
13 Hoyer LW. Haemophilia A. *N Engl J Med* 1994; **330:** 38–47.
14 Lederman MM. Ratnoff OD, Scillian JJ, Jones PK, Schacter B. Impaired cell-mediated immunity in patients with classic haemophilia. *N Engl J Med* 1983; **308:** 79–83.
15 Darby SC, Ewart DW, Giangrande PLF, Dolin PJ, Spooner RJD, Rizza CR. Mortality before and after HIV infection in the complete UK population of haemophiliacs. *Nature* 1995; **377:** 79–82.
16 Kasper CK, Kipnis SA. Hepatitis and clotting-factor concentrates. *JAMA* 1972; **221:** 510.
17 Lee CA. Hepatitis C and haemophilia. (editorial) *BMJ* 1995; **310:** 1619–20.
18 Telfer P, Sabin C, Devereux H, Scott F, Dusheiko G, Lee C. The progression of HCV-associated liver disease in a cohort of haemophilic patients. *Br J Haematol* 1994; **87:** 555–61.
19 Telfer P, Devereux H, Colvin B, Hayden S, Dusheiko G, Lee C. Alpha interferon for hepatitis C virus infection in haemophilic patients. *Haemophilia* 1995; **1:** 54–8.
20 Sultan Y. Prevalence of inhibitors in a population of 3435 haemophilia patients in France: French Haemophilia Study group. *Thromb Haemost* 1992; **67:** 600–2.
21 Ehrenforth S, Kreuz W, Scharrer I, *et al.* Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. *Lancet* 1992; **339:** 594–8.
22 Lusher JM, Arkin S, Abildgaard CF, Schwartz RS and the Kogenate Previously Untreated Patient Study Group. Recombinant factor VIII for the treatment of previously untreated patients with haemophilia. *N Engl J Med* 1993; **328:** 453–9.
23 Kasper CK. Treatment of factor VIII inhibitors. *Prog Hemost Thromb* 1989; **9:** 57–86.
24 Brettler DB, Forsberg AD, Levine PH, *et al.* The use of porcine factor VIII concentrate (Hyate C) in the treatment of patients with inhibitor antibodies to factor VIII: a multicentre US experience. *Arch Intern Med* 1989; **149:** 1381–5.
25 Lusher JM, Shapiro SS, Palascak JE, *et al.* Efficacy of prothrombin complex concentrates in haemophiliacs with antibodies to factor VIII: a multicentre therapeutic trial. *N Engl J Med* 1980; **303:** 421–5.
26 Sjamsoedin LJM, Heijnen L, Mauser-Bunschoten EP, *et al.* The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with haemophilia A and antibodies to factor VIII: a double blind clinical trial. *N Engl J Med* 1981; **305:** 717–21.
27 Hedner U, Glazer S, Pigel K *et al.* Successful use of recombinant factor VIIa in a patient with severe haemophilia A during synovectomy. *Lancet* 1988: **2:** 1193.
28 Nilsson IM, Berntorp E, Zettervall O. Induction of immune tolerance in patients with haemophilia and antibodies to factor VIII by combined treatment with intravenous IgG, cyclophosphamide and factor VIII. *N Eng J Med* 1988; **318:** 947–50.
29 Slocombe GW, Newland AC, Colvin MP, Colvin BT. The role of intensive plasma exchange in the prevention and managment of haemorrhage in patients with inhibitors to factor VIII. *Br J Haematol* 1981; **47:** 577–85.
30 Nilsson IM, Jonsson S, Sundqvist S-B, Ahlberg A, Bergentz S-E. A procedure for removing high titre antibodies by extracorporeal protein-A-Sepharose adsorption in haemophilia: substitution therapy and surgery in a patient with haemophilia B and antibodies. *Blood* 1981; **58:** 38–44.
31 Mannucci PM. Modern treatment of haemophilia: from the shadows towards the light. *Thromb Haemost* 1993: **70;** 17–23.
32 Pool JG, Hershgold EJ, Pappenhagen AR. High-potency antihaemophilic factor concentrate prepared from cryoglobulin precipitate. *Nature* 1964; **203:** 312.
33 Cuthbert RJG, Ludlam CA, Steel CM, Beatson D, Peutherer JF. Immunological studies in HIV seronegative haemophiliacs: relationship to blood product therapy. *Br J Haematol* 1992; **80:** 364–9.
34 UK Regional Haemophilia Centre Directors Committee. Recommendations on choice of therapeutic products for the treatment of patients with haemophilia A, haemophilia B and von Willebrand's disease. *Blood Coagul Fibrinolysis* 1992; **3:** 205–14.
35 Martinowitz U, Schulman S, Gitel S, Horozowski H, Heim M, Varon D. Adjusted dose continuous infusion of factor VIII in patients with haemophilia A. *Br J Haematol* 1992; **82:** 729–34.
36 Mannucci PM, Ruggeri ZM, Pareti FI, Capitanio A. 1-Deamino-8-d-arginine vasopressin: a new pharmacological approach to the managment of haemophilia and von Willebrand's diseases. *Lancet* 1977; **i:** 869–72.
37 Jones P. Haemophilia home therapy. *Haemostasis* 1992; **22:** 247–50.
38 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years experience of prophylactic treatment in severe haemophilia A and B. *J Int Med* 1992; **232:** 25–32.
39 Mannucci PM. Outbreak of hepatitis A among Italian patients with haemophilia. *Lancet* 1992; **339:** 819.
40 Santagostino E, Mannucci PM, Gringeri A, Azzi A, Morfini M. Eliminating parvovirus B19 from blood products. *Lancet* 1994, **343:** 798.
41 NHS Management Executive *Provision of haemophilia treatment and care. NHS Health Service Guidelines*, 1993; 20.
42 Colvin BT, Aston C, Davis G, Jenkins GC, Dormandy KM. Regional co-ordinator for haemophilia in domiciliary practice. *BMJ* 1977; **2:** 814–5.
43 Cahill MR, Woosey CP, Hayden SM, MacClean M, Colvin BT. Implementation of a nurse practitioner policy for the requisition and administration of drugs in a haemophilia comprehensive care centre. *Haemophilia* 1995; **1:** 172–4.