

Historical Review

THE EARLY HISTORY OF HAEMOPHILIA TREATMENT: A PERSONAL PERSPECTIVE

This article is being written in an infirmary named after that most famous of haemophilia carriers, Queen Victoria. The history of the effect of the haemophilia gene on the royal families of Europe that descended from Victoria has recently been reviewed by Stevens (1999). In his paper, he gave some insight into what people with haemophilia had to endure in the days before effective treatment became available in the 1960s. For instance, in the year of my birth, Birch reported a study of 98 haemophilic patients and their affected relatives (Birch, 1937). Only six patients in the series had survived until their 40th birthday, 82 patients dying in childhood or early adolescence, often after trivial accidents or minor surgery. The changes in management since that time are graphically illustrated in the photographs.

The first photograph (Fig 1) shows a young man with severe haemophilia who presented as an infant with intracranial bleeding in the days before effective therapy. As an adult, he is profoundly handicapped not only from the sequelae of that bleed but also from his chronic haemophilic arthropathy. The second photograph (Fig 2) was taken in 1998 and shows a group of boys by the pool at La Charca, a purpose-built holiday facility for people with haemophilia in Murcia, Spain. The only youngster attending this summer camp who showed any sign of haemophilia was from Belarus; he had developed a chronic haemarthrosis of the knee because he did not have access to modern prophylactic treatment. The third picture (Fig 3) is a family photograph of one of the children, with his parents, who is taking part in a trial of second generation recombinant factor VIII. Both the quality of life he can look forward to and his life expectancy are normal.

DIAGNOSIS

Modern therapy is, of course, based on an accurate diagnosis and it is easy to forget that it is less than 50 years since it became possible to differentiate between the haemophilias. Factor VIII and factor IX deficiency were first differentiated in 1952 in the now legendary paper published in the Christmas edition of the British Medical Journal (Biggs *et al.*, 1952). This timing was entirely coincidental, the authors having named the new deficiency after Stephen Christmas, the first of the seven patients described. Their altruism was rewarded by correspondence from two disgruntled readers who, settling back to enjoy what they thought would be a jolly paper in keeping with

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the festive season, had found themselves thrust into an erudite description of the thromboplastin generation test. Dr Collins expressed disappointment that 'this festive title was merely a ferial eponym for an all-the-year-round-disease' and Dr Kemp was thankful that the second patient had not been called Easter. Rosemary Biggs retaliated by revealing that the disorder could have been called hypoco-thromboplastinaemia, hereditary orthothrombophobia or even Biggs–Dacie–Douglas–Macfarlane–Merskey–O'Brien–Pitney syndrome, but then no one would have read the paper.

Biggs's letter is interesting for another reason. In it, the author suggested for the first time that haemophilia A and haemophilia B might become the internationally accepted names and that a system of numbering for the factors should be worked out. This could only be attempted once the sequence of clotting factors had been ascertained, when it would 'forestall any suggestion ... that its possible precursor ... be known as Christmas Eve factor'. Behind the fun lay the enormous advance in both the diagnosis and the management of haemophilia and the beginnings of targeted component therapy, now realized in the development of pure recombinant factor VIII and IX concentrates.

FRESH-FROZEN PLASMA, CRYOPRECIPITATE AND THE FIRST HUMAN CONCENTRATES

Shortly after I qualified, the Newcastle Medical Journal carried an article on haemophilia by a physician working in the infirmary (Hall, 1965). The opening paragraph read 'The haemophilic (*sic*) presents a social problem of considerable magnitude often requiring a sheltered occupation and having to spend a lot of time in hospital, but so long as he does not bleed, he can, and frequently does, lead a normal life. Indeed, it is often his participation in such normal activities as motor car racing, playing cricket and shooting (admittedly with a 20 bore to reduce the kick) that lands him in hospital with abrasions and contusions of all degrees of severity. Add to this the spontaneous bleeding episodes which may occur into muscles, joints and from orifices plus the high incidence of dental caries (perhaps due to inadequate dental care and over-cosseting by anxious relatives) together with the risks of mundane conditions like piles and peptic ulcer, and the prompt and adequate control of bleeding can be seen to be of considerable importance to the haemophilic patient.'

People with haemophilia were not very popular in those days, 'bloody nuisances' as I recalled in the recent *Wellcome Witnesses to Twentieth Century Medicine* series (Tansey &



Fig 1. Untreated haemophilia is often a lethal disorder. Survivors are frequently crippled in childhood.

Christie, 1999, p. 35), but the art of securing haemostasis was popular and it attracted a band of dedicated workers who, in the space of a few years, transformed the lives of affected families. At the time of Hall's article, treatment with Russell's Viper Venom, adrenaline and Tuamine nasal drops were advocated, as well as plasma. The last was preferably

'exercise plasma' because it was known that it contained larger quantities of anti-haemophilic globulin (AHG) than plasma collected at rest. Although it took an hour to infuse one dose of animal or human AHG and reactions were common, Hall wrote that the treatment 'explodes the myth that major operations in haemophiliacs are always dangerous. However, one important point which must never be forgotten is that every haemophilic patient when in hospital should have a notice hung over the bed stating "NO ASPIRIN, NO INJECTIONS, NO EXERCISE".' 'Tell that to the children' I thought, as we struggled to keep them in bed long enough for their haemarthroses to abate.

Hall's reference to exercise plasma acknowledged the results of several workers intent on collecting source material that was likely to yield high levels of clotting factor. Hardisty and Ingram (1965) emphasized the loss when anticoagulants such as ethylene diamine tetra-acetic acid (EDTA) or oxalate were used, and recommended acid-citrate-dextrose in plastic packs. It was suggested that certain donors, including older men, people with blood groups A or B rather than O, those who had just exercised and volunteers given predonation stimulation should be used. The stimulants included adrenaline, vasopressin, desmopressin and, somewhat later, the exposure of male donors to *Playboy* magazine (Ingram, 1961; Rizza, 1961; Cash *et al.*, 1974).

Freeze drying produced an even greater loss in activity, measured at between 50% and 75% by Hardisty and Ingram (1965). As a consequence, they predicted that it would be impossible ever to obtain enough source material 'to allow for the optimal treatment of all haemophilic emergencies, much less for routine prophylactic replacement therapy'. They quoted Kekwick and Wolf (1957), who had calculated that 2% of the total annual donations given in Great Britain annually would be needed for haemophilia treatment with fresh plasma alone, and Macfarlane *et al.* (1954), who said that half a million permanent donors would be required. The authors concluded that human AHG would have to be limited to the treatment of acute bleeds and surgery, plasma being used for everything else. These



Fig 2. A group of haemophilic boys at a Spanish holiday camp in 1998.



Fig 3. Home therapy, prophylaxis and the safety of recombinant therapeutic products help to ensure a near normal quality of life for families with haemophilic children.

early predictions have, of course, largely been borne out in reality, and are referred to again later. In 1973, after the failure of government to implement the available technology and stimulate the blood transfusion services to concentrate on component therapy, the first commercial blood products were imported into the UK.

It was R. G. Macfarlane who, in his elegant comparison of vertebrate haemostasis to household plumbing, paved the way for this rapid progress in the treatment of the inherited bleeding disorders. Although it may have been debatable then as to whether the treatment of a patient or the services of a plumber were more expensive, today there can be no contest, at least in economically rich countries. Before the development of concentrated clotting factors, principally by the Oxford team and especially by Ethel Bidwell, we relied on whole blood or fresh-frozen plasma (FFP). Indeed, when the first concentrates became available, they were in such short supply that the entire stock for the UK could be used for the surgical management of a single patient.

It is possible to treat life-threatening episodes of bleeding in patients with severe haemophilia using only fresh whole blood. A child with haemophilia A survived a spinal haematoma in this way in Newcastle in the 1960s, well before the days of component therapy, and the treatment is described in both of the standard textbooks of the time.

However, the mainstay of treatment until the introduction of cryoprecipitate in 1965 remained FFP. This worked well for relatively minor bleeds, including haemarthroses, in those with haemophilia A, but was difficult to administer in therapeutic doses to those with haemophilia B. The difficulty was one of clotting factor recovery. Whereas factor VIII emerged practically unscathed after transfusion, factor IX activity mysteriously disappeared and it took around one-third more FFP to raise the clotting activity to equivalent levels. Consequently, although it was not unusual to have to deal with incipient heart failure in haemophilia A, it was routine in haemophilia B. Hardisty and Ingram (1965) observed that the average adult male could take up to 1 l of plasma twice a day for 4–8 d and children should be given smaller quantities in proportion to their blood volume. 'These amounts are usually sufficient to cover minor surgical operations and tooth extraction, and are more than adequate for the treatment of spontaneous bleeding'. Thankfully, frusemide had just been introduced into clinical practice and it was routinely prescribed to reduce the problems of circulatory overload. Frequency of micturition was thereby added to the list of miseries that had to be endured by haemophilic patients.

While the means of treatment were being developed, most patients suffered at home with occasional forays into the hospital. My first patient with severe haemophilia had been in hospital 27 times and had seen 17 different doctors before he was 5 years old. His parents were desperately trying to bring him and his siblings up in a dilapidated terraced house in the slum area of the city. The only treatment available was FFP. Aspirin was used for pain. The boy had no schooling, no security and no hope. With the help of a social worker, the city authorities and a school teacher, we began to put together the jigsaw of haemophilia management that was later known as comprehensive care. It involved working with the family in order to look at every aspect of his health and development, and to effect change for the better wherever that was possible. The results were startling. The boy thrived and was later to bring up a family of his own. This first patient, and others like him, taught us more about haemophilia than any amount of academic knowledge available at the time. So, by the time cryoprecipitate was introduced in the mid-1960s, we already had the background of care needed to prescribe outpatient treatment for the majority of bleeds. When the freeze-dried concentrates became readily available in the UK in 1973, home therapy was a natural progression.

In a series of treatments for a major bleed, the patient would inevitably receive plasma from several donors. In a discussion on the use of pooled plasma, Bidwell noted two arguments from those opposed to such pooling. First, there was concern that inappropriate clotting, initiated during the collection or processing of a single donation, might result in instability of factor VIII in the pool. Second, there was the increased risk of transmitting serum hepatitis. Bidwell calculated that a patient 'undergoing treatment for, say, dental extraction will need over 10 days the plasma from 40–60 donors'. She recommended that pools should be from no more than 10 donors, with careful bookkeeping to

ensure that the risk of exposure to more than one pool was minimal (Bidwell & Dike, 1966). In clinical practice, this proved to be impracticable, but her observations are, of course, especially pertinent in the hindsight of what was to follow 20 years later in the haemophilic population.

There were other difficulties. The worst of these, from the patient's point of view, was 'the drip'. Several packs of FFP were slowly administered through a rubber giving set attached to a rigid needle which was invariably large and often blunt. The procedure meant hospital admission. It also meant loss of school or work, both for the patient and, in some cases, for the parent or partner accompanying him. Not surprisingly, many bleeds were treated conservatively at home or simply shrugged off and treated with analgesia, commonly aspirin. From the doctor's viewpoint, the worst side-effect of FFP (and, later, cryoprecipitate) was acute allergic pulmonary oedema. Two or three times a year, a patient would suddenly become ill with laboured respiration, a cough, wheezing, pallor and cyanosis, and a paradoxically low pulse rate. The chest radiograph revealed fluffy opacities in both lungs and the whole syndrome cleared magically with intravenous hydrocortisone and frusemide. Untreated, the condition was lethal.

Shortly after the first description of Christmas disease, the first edition of *Human Blood Coagulation and Its Disorders* was published (Biggs & Macfarlane, 1953). It, and two later editions, provided an 'in-house' description of the way in which patients were treated in Oxford. To those of us working with people with haemophilia and related disorders, the Oxford expertise and the ready welcome given to those with problems (especially if they took a bit of solving!) cannot be overemphasized. Rapid transfer by air was a novelty in those days and there is a story, no doubt apocryphal, that a helicopter summoned to deliver a patient to Oxford had to stop on the A1 to refill with petrol. The accompanying laboratory technician availed himself of the opportunity to buy fish and chips at the service station during the stop. The patient survived both the journey and his subsequent surgery.

A further mark of the respect with which the authors and

their team are held is reflected in the list of contributors to the augmented 1972 volume, now entitled *Human Blood Coagulation, Haemostasis and Thrombosis* (Biggs, 1972). As well as the Oxford members (with a very young Charlie Rizza), they included Born, Douglas, Hardisty, McNichol, Merskey and Nossel.

In 1965, Judy Pool and her colleague A. E. Shannon discovered cryoprecipitate, soon reduced in clinical terminology to 'cryo' (Pool & Shannon, 1965). Their discovery was due in part to serendipity. Intent on finding a way to separate the clotting factors from plasma, they tested individual fractions of the liquid after cooling. What they nearly did not do was to test the 'gunge' left at the bottom of the container after centrifugation. That it was the gunge that was rich in factor VIII and fibrinogen is now history. Cryo revolutionized both the immediate treatment of patients and the process of fractionation, and cryo paste soon became the start material for the production of factor VIII concentrate.

Cryo remains the only treatment available in some countries. Its advantages are that, in comparison with FFP, the factor VIII content is present in a relatively small volume, that it is relatively easy to prepare and that it is made from local whole blood or plasma donations in a closed system. The major disadvantages are that the factor VIII content of each pack is unknown and that several packs must be pooled in order to make up an adequate dose (Fig 4). In addition, we now know that because it cannot be treated to eliminate pathogens there is a high risk of viral transmission (Evatt *et al*, 1999).

In addition to the advent of cryo, a further advance made a big difference to the management of open bleeding in the 1970s, especially that after dental extraction. Antifibrinolytic therapy, first with epsilon-aminocaproic acid (EACA; Epsikapron) (Walsh *et al*, 1971) and later with tranexamic acid (Cyklokapron), prevented early clot breakdown, and thus the need to continue treatment with clotting factor replacement. Previously, cryo and EACA patients undergoing dental extraction were admitted to hospital and treated for up to 10 d. Although sockets were protected with

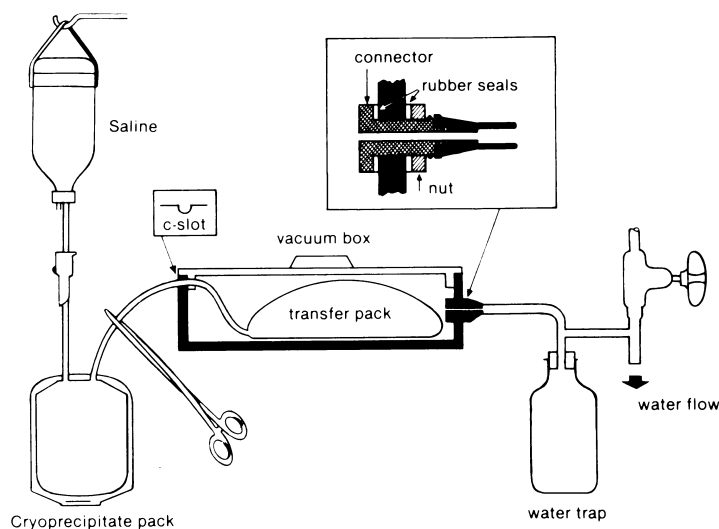


Fig 4. A pooling device for cryoprecipitate, designed for use on the ward by the author in 1966. Cryoprecipitate from several packs was sucked into a transfer pack before administration to the patient. It was important to wash each pack out with a small volume of saline to recover as much factor VIII activity as possible after defrosting at room temperature.

preformed splints, often packed with AHG, it was not unusual to have to cope with breakthrough bleeding by applying digital pressure until the haemorrhage had stopped. This job was sometimes handed to the first person to walk past the bed, but was more usually performed by the excellent nursing staff willing to sit with a patient throughout the night. It is worth noting how important patient contact such as this was; patients with chronic disorders such as haemophilia who are reliant on hospitals need to be assured of a continuity of care from staff they know and trust. Hence, the importance of a dedicated centre and ease of access to specified wards when in-patient treatment is necessary.

ANIMAL AHG

The spur to the early attempts to produce clotting factor replacements for human therapy was the prediction that there would never be enough material available from human blood. This prediction remains as true today as it did then, at least in a global sense. Despite advances in blood and plasma collection and processing, the great majority of those with severe haemophilia in the world receive no treatment. The reasons for this are straightforward. They are not diagnosed accurately, there is no organization of care, there are insufficient resources available for even rudimentary treatment and available blood transfusion resources are often inadequate and unsafe. In addition, haemophilia is rare and its problems pale into insignificance in comparison with other non-communicable diseases, including malignancy and cardiovascular disease, and the infectious diseases.

So, in the 1950s, Bidwell explored the possibility of using the virtually unlimited supplies of animal blood as the source material for clotting factor concentrates and has recently described how she set about extracting AHG from ox and pig blood obtained from the local abattoir (Tansey & Christie, 1999, pp. 13–16). The resulting products were infused into patients and the results were described by Macfarlane *et al* (1954). They showed that the available clotting activity was far more potent than that found in human AHG, that the *in vivo* recovery was excellent and that the products worked well clinically. Unfortunately, this efficacy was relatively short lived, intolerance being found after several days of treatment. Factor responses fell away and, if wound healing was not sufficiently advanced, secondary haemorrhage occurred.

Apart from this intolerance, there were few side-effects. These included a transient thrombocytopenia, usually with the bovine product, but this was generally regarded as being of little clinical importance in the days when animal AHG was known to stop bleeding and was often the only material available. Some patients also experienced allergic reactions. These observations, together with the antigenicity and an early observation that the predicted response did not occur after a second dose, led to the advice that no one should be exposed more than once to either product. In practice, this was not always feasible and, in my experience, patients were treated, under laboratory control, with repeat doses after

several months. Any allergic problems were covered by intravenous hydrocortisone and chlorpheniramine. After a refractory period, responses usually returned to normal and haemostasis could again be assured for 7–10 d.

Under the circumstances, these animal products were therefore life-saving. In particular, they provided cover for surgery, often to alleviate peptic ulcer in the days before H₂-receptor antagonists. Porcine AHG, which was less likely to cause thrombocytopenia, was given first and was usually effective for at least a week. Bovine AHG was then substituted and used until the danger of secondary haemorrhage was over and wound healing was advanced. If efficacy was lost at any time, human material was prescribed. Experience with these scarce resources taught us that, whether treating major bleeds or covering surgery, it was essential to raise the relevant clotting factor level high enough both to prevent bleeding and to sustain that prevention from the start. Attempts to conserve material, to stretch things out for as long as possible, were met with failure. Stable clots did not form and wounds broke down and became infected. What should have been over in 10 d became a long-term problem that, by the time it was resolved, utilized far more resources than if the patient had been treated properly in the first place. This lesson is still relevant today. In richer countries, haemophilia treatment may still be seen as a low-volume, high-cost speciality in which corners may be cut to divert finances elsewhere, an argument used within recent years to question the use of both prophylaxis and the prescription of recombinant materials. In poorer countries, the temptation to conserve stocks is obvious. In both cases, inadequate dosage is a false economy.

DESMOPRESSIN

1-Deamino-8-D-arginine vasopressin (DDAVP; Desmopressin), first described by Zaoral *et al* (1967), is a synthetic analogue of the posterior pituitary hormone vasopressin. Vasopressin, or antidiuretic hormone, promotes water reabsorption in the kidneys and stimulates the contraction of smooth muscle. Lack of the hormone results in diabetes insipidus. When given in pharmacological doses, it causes vascular constriction, with pallor, and contraction of the smooth muscle of the gut, with abdominal cramps. The effect on the vasculature means that the drug is contraindicated in people with vascular disease. Although desmopressin has less pressor activity and is therefore better tolerated than vasopressin, it should be used with caution in young children and the elderly and in patients with cardiovascular disease. When repeated doses are indicated, careful attention must be paid to fluid balance and the possibility of hyponatraemia. I have seen one case of water intoxication leading to coma in a young girl with von Willebrand's disease who was dripped after intravenous desmopressin and surgery by staff who thought that she would become dehydrated without extra fluid. She made a full recovery, but once is enough!

In retrospect, it was concern over the possible harmful effects of desmopressin, coupled with the view (later

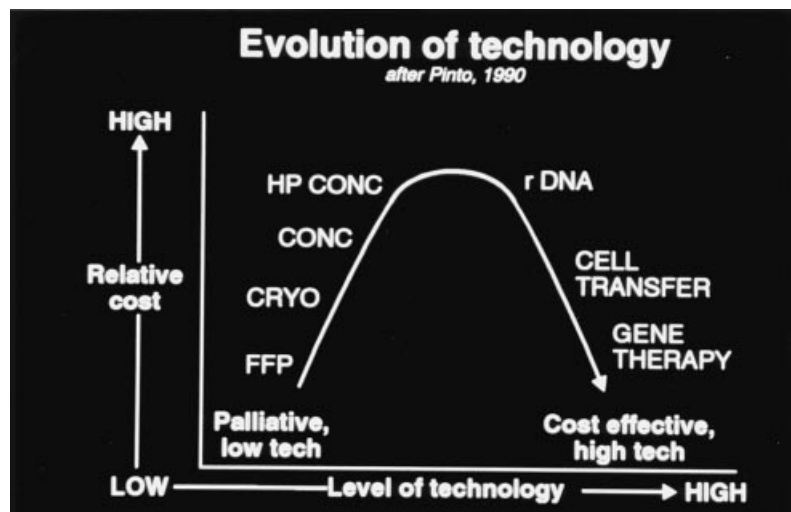


Fig 5. As pharmaceutical developments reduce morbidity and their application becomes widespread, the overall costs of managing haemophilia should fall (adapted from Pinto, 1990). FFP, fresh frozen plasma; CRYO, cryoprecipitate; CONC, concentrate; HP CONC, high purity concentrate.

disproved) that only a limited number of doses could be given before a refractory period without haemostatic response occurred, that delayed its introduction into general medical practice as an alternative to blood products in some patients. Although desmopressin was licensed for its haemostatic properties in the UK in January 1978, it was not until March 1984 that licensing was completed in the USA. This meant that the major impact of the drug in mildly affected patients with haemophilia A or von Willebrand's disease post-dated the hepatitis C and acquired immunodeficiency syndrome epidemics linked with those products.

THE FUTURE

What of the future? Eight years have passed since the National Heart, Lung and Blood Institute, together with the United States National Haemophilia Foundation, sponsored a workshop on gene therapy in Washington, DC. Haemophilia was then one of several diseases approved by the National Institutes of Health (NIH) as a priority disorder for at least partial control by gene augmentation. With this technique, in which a normal gene is inserted alongside the dysfunctional gene, a precise feat of 'cut and paste' gene replacement is avoided. In addition, it is necessary only to raise the relevant factor level into the moderate/mild range to overcome the spontaneous bleeding of severe haemophilia.

At the time of the workshop, hopes were high for the rapid development of the techniques involved. Although those hopes were, in retrospect, premature, the latest results from animal experiments and the start of the first clinical trials in humans suggest that success may now be near.

When gene therapy (or the transfer of normal factor-producing cells) does become both practicable and safe, it should be of immense benefit to the 80% or so of people with haemophilia who presently have no recourse to treatment, most of them in developing countries. Although likely to be expensive initially, the relative cost of managing the disorder should eventually fall sufficiently to bring this hope to

fruition (Fig 5). Or, perhaps, echoing those early attempts to use animals in Oxford, the mainstay of treatment for the majority of people will be with clotting factors produced by transgenic engineering.

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