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INTRODUCTION

The term haemophilia, meaning "lover of blood", was coined comparatively recently in the long history of bleeding disorders, having been first used in the early 19th century. Then it defined a bleeding disorder which was transmitted by certain unaffected females to some of their sons. Now, as a result of the enormous increase in scientific knowledge developed in the interim, haemophilia can be defined more precisely as a coagulation disorder transmitted in a sex-linked recessive manner and primarily expressed in males, in which the level of factor VIII clotting (or biological) activity in the blood is reduced below normal because some of the precursor molecules, (named immunological factor VIII), are functionally abnormal and cannot be converted to clotting factor VIII. The clinical grade of severity of the disorder breeds true and correlates well with the amount of circulating clotting factor VIII, severely affected haemophiliacs having less than 1%, moderately affected between 1 and 5% and mildly affected between 5 and 50%. The normal range is 50 – 200%.

HAEMOPHILIA IN HISTORY

The first recorded references to haemophilia in man are probably to be found in Jewish writings of the 2nd Century A.D. where families are mentioned in which more than one male child died of excessive bleeding following ritual circumcision. The disorder also occurs in animals and probably first began in placental mammals through genetic mutation about 50 million years ago.

The severely affected patient bleeds 'spontaneously' in response to the 'microtrauma of living' and this grave gene deficiency was usually lethal in olden times before the reproductive age was reached. We therefore believe that the severe grade of the disorder was maintained in man by spontaneous genetic mutation and the mutation rate has been estimated at about 2×10^{-5} (W.H.O., 1972).

The history of haemophilia makes fascinating reading and the reader interested in a more detailed study of the subject is advised to read the excellent article by Ingram (1976). Apart from the methodic early clinical studies on the subject and the more recent scientific investigations recorded by Ingram, it is interesting to speculate on the role the disorder has played in European and Russian political history. Queen Victoria is thought to have acquired a carrier state at conception through genetic mutation, which was first recognised with the birth of her eighth child Leopold who was a severe haemophiliac. More significantly she produced at least two carrier daughters in her large family. One of these, Beatrice, transmitted the carrier status to her daughter Victoria Eugenie who married Alfonso XIII, King of Spain, and at least two of their five sons were severe haemophiliacs. Through Alix, whose daughter Alice married Tsar Nicholas II of Russia, was born in 1904 the severely affected haemophiliac, and only son, Alexis. The inability of doctors to prevent, or even alleviate, the repetitive painful joint bleedings associated with this disorder in the boy, may

have contributed to the evil influence that the monk Rasputin acquired over the unhappy Royal parents for the Tsarina had great faith in his healing powers. Isolated from everyday affairs by their preoccupation with their son's disability, the Royal parents may well have contributed to the tragic downfall and death of the family in the Bolshevik revolution. The drama of haemophilia is vividly portrayed in two novels by R.K. Massie ("Nicholas and Alexandra", 1968) and Dorothy Sayers ("Have his Carcase", 1932).

PRESENTATION AND NATURE

Classical haemophilia (factor VIII deficiency) has to be distinguished from von Willebrand's disease, and particularly from Christmas disease (factor IX deficiency) with both of which it shares some common clinical and laboratory features. The distinction, made as recently as 1952 in the case of Christmas disease, is important not least because modern clotting factor replacement therapy is reasonably specific for each disorder and the products used are not interchangeable.

The hallmark of a bleeding disorder is the persistence rather than the rate of blood loss. The typical haemophiliac is therefore a male in whom the clinical symptoms correlate well with the degree of his clotting factor deficiency. The severely affected patient, with less than 1% factor VIII, bleeds 'spontaneously', that is without apparent injury, the moderately affected in response to minor injury, but not spontaneously and the mildly affected in response to minor injury, but not spontaneously and the mildly affected only to moderate injury. More than 90% of bleedings in the severely affected patient occur into joints, and the knees, ankles and elbows are most frequently affected, though the reason why these particular joints should be involved is not known. The unpredictability of such bleedings in the severe haemophiliac with apparent normality in between episodes had a profound psychological effect on him in the days before modern factor replacement therapy became available to abort the bleeds in an early stage. Such joint bleeds, if untreated, produce intense pain and immobility and will eventually, when repeated sufficiently often, result in joint damage, permanent limitation of movement and finally crippling haemarthritic deformity. Less commonly occurring bleeds into muscles and tissue compartments can likewise, by their pressure effects, cause muscle necrosis or nerve damage and hence loss of function. Haemorrhage into a closed cavity such as the skull can cause brain damage and often death. Intracranial haemorrhage is now one of the commonest causes of death in this group of patients.

Classical haemophilia is the commonest of the single clotting factor disorders in Great Britain and has an approximate incidence of 6 per 100,000 in the population. About half of these patients are severely affected and the remainder are about equally distributed in the moderately and mildly affected grades. Whilst there is reason to believe that even some severely affected haemophiliacs have not yet been diagnosed and recorded, there is even stronger evidence that more of the moderately and mildly affected patients have escaped the net. These latter groups do not manifest their disability so obviously as the severely affected patients, particularly as the accepted blood loss due to trauma in normal males varies widely.

Christmas disease (factor IX deficiency) is about one fifth as common in the population as haemophilia.

MANAGEMENT

The factor VIII molecule is unstable in solution; it and factor V, only rarely congenitally deficient, are known as the 'labile' clotting factors. It has a half-life at blood heat *in vitro* and *in vivo* of 8 – 12 hours, whereas that of factor IX is 18 – 24 hours. It is ofen not appreciated that primary normal wound healing which, depending on the size of the wound, the presence or absence of infection and the nutritional state of the patient, may take up to 14 days to complete requires adequate levels of factor VIII and the other clotting factors in the blood throughout. Failure to meet these needs will result in immediate or delayed wound bleeding according to the time in the healing process that it occurs. The quantity of factors needed is roughly proportional to the size of the wound. Less explicable is the fact that 'spontaneous' injury needs less clotting factors for healing than does overt trauma of apparently similar degree. The mildly affected haemophiliac

who has some endogenous production of factor VIII can therefore cope unaided with mild trauma as can the moderately affected patient with minimal trauma, but the severely affected haemophiliac will often bleed abnormally in response to the occult trauma 'of being'. The principle of treatment of injury in these patients is to raise the deficient clotting factor to a safe blood level by exogenous means and to so maintain it until healing has been achieved.

In the 'spontaneous' joint bleed this may mean obtaining a 'once only' peak of 20% whereas for more severe trauma, for example operative surgery, a pre-operative level of at least 60% will usually be required, and thereafter the trough level must not fall below 20% until late in healing. To achieve this goal repetitive infusions of factor VIII as often as six-hourly may be necessary for much of the healing period. The greater the threat of re-bleeding, for example in intracranial injury, the longer is it wise to sustain a haemostatic level of the clotting factor in the blood. Meticulous surgical haemostasis together with wound rest by splintage etc. minimises factor VIII requirements and is always advocated in the management of injury in haemophilia.

The improved management of severe haemophilia is the result of four main factors: (i) precise diagnosis, (ii) early treatment of bleeding episodes, (iii) a better understanding of factory VIII requirements as discussed above and (iv) the availability of stable, concentrated preparations of clotting factor VIII. Clearly it is impossible to raise and maintain the factor VIII level of a severe haemophiliac from less than 1% to at least 60% with whole blood or even plasma without causing circulatory overload and heart failure. The availability of such concentrated factor VIII products has therefore revolutionised the management of haemophilia.

The History of Replacement Therapy

The history of blood transfusion in man is much shorter than that of haemophilia. It began in the 17th century, initially with the use of animal as well as human blood, and usually in either case with disastrous results to the patient. It was mainly due to the discovery, first by Landsteiner of the ABO blood groups, and then by Weiner of the Rhesus (Rh) groups, in the last fifty years that blood transfusion has become safe and practicable.

The management of bleeding battle casualties in World War II soon brought an appreciation of the urgent need for early restoration of the intravascular deficit by an isosmotic, colloid containing fluid even without red cells, at least until the loss of these became very severe. The separation of plasma from whole blood by centrifugation followed by the preparation of a dried, and hence stable, product met this need. Such a product was also easy to reconstitute and administer in forward battle areas, and did not require the skilled technical compatibility matching which is always desirable, and often essential, when whole blood is used. By this time Macfarlane in Oxford and other workers elsewhere, had also realised that only intravenous factor replacement therapy would satisfactorily and safely control bleeding in the haemophiliac.

The knowledge gained during the War years in the preparation, handling and use of plasma stimulated further exploration of this product for its more specific component fractions. This had two main objects, namely (i) to produce more specific products of high potency which would make possible sustained, intensive replacement therapy in patients, and (ii) to make more economic use of blood which, in Great Britain, is obtained from voluntary donors who have to be allowed a minimum period of four months to make good the deficit produced by the giving of one whole blood donation.

Factor VIII requirements at that stage, because of the instability of the molecule *in vitro*, were best met by using fresh plasma (within no more than four hours of blood donation) which was inconvenient. However, the factor VIII activity in such plasma could be preserved for at least three months either by immediately deep freezing it to not less than -20° C or by freeze drying it.

Unfortunately neither of these measures solved the problem of the unacceptable volume it was necessary to transfuse to achieve and maintain an adequate haemostatic level of factor VIII in a severe haemophiliac for other than trivial bleeds.

The next logical sequence was plasma fractionation. After the pioneer work in this field of Cohn et al (1946), crude concentrates of human

and animal products were produced in various European and American centres in the early 1950's and used with increasing success in the management of the more serious and major bleeding episodes in haemophiliacs whether they were spontaneous or traumatic, accidental or elective in origin. The species specificity of the highly potent concentrates obtained from the pig and the cow limited their use in man because of the sensitisation and thence severe reactions they eventually induced in the recipient, but they fulfilled an important interim role where large dosage of factor VIII was needed until the human product could be adequately refined. This latter achievement dates from a chance observation made in America by Judith Pool and her colleagues (1965). She noticed that when human plasma was deep frozen at -20°C and then slowly thawed, the large plasma protein molecules, factor VIII (m. wt about 2×10^6) and to a lesser degree fibrinogen (factor I, m. wt 560,000), would at 4°C remain for a time as a sludge or cryoprecipitate whilst the other plasma proteins went into solution. By careful removal of most of the liquid supernatant the sludge could be harvested and then stored stable deep frozen at not less than -20°C in the little remaining plasma until required for use. It could then be dissolved as required in the retained plasma by controlled thawing at blood heat (37°C) and injected intravenously at once. Comparatively high doses of factor VIII could thus be obtained in an acceptably small plasma volume by pooling as many of these cryoprecipitate donations as were necessary.

The theoretical and practical disadvantages of such cryoprecipitate were (i) the time consuming skill needed in preparation of each individual pack, (ii) the variability of factor VIII levels in the normal donors and the manipulative loss in preparation, (iii) the need for controlled temperature thawing (37°C) to avoid factor VIII loss immediately prior to use and (iv) the need to enter several packs with its attendant infection risk to obtain a sufficient dose of factor VIII for therapeutic use.

On the other hand despite the technical, organisational and economic difficulties of harvesting large quantities of whole blood, separating and deep freezing the plasma immediately, storing and transporting it deep frozen to a central large scale fractionation unit, and the technical difficulties of large scale fractionation without loss of potency of the components, cryoprecipitate has been an important interim advance in the treatment of haemophilia and it still remains so today. Nevertheless, at various centres in Britain (Oxford, Elstree, Edinburgh) large scale plasma fractionation is a reality and the quality and quantity of the products available, not least of factor VIII, are increasing and in some cases (e.g. factor IX) do meet all the present day requirements. The freeze dried factor VIII so produced has many advantages over the stalwart cryoprecipitate. First, it is produced from a large, pooled, plasma batch and equal aliquots of the finished product are freeze dried in individual vials; thus the dose is constant in each vial from any batch. Secondly, by standard random sampling the vials can be checked for potency and sterility and duly labelled with this information. Thirdly, the product is stable for a considerable time if kept at 4°C, and it can be reconstituted in a small volume of sterile water immediately prior to use to give a known factor VIII dose which usually has a potency of at least twenty times that of an equal volume of fresh plasma.

The present aim is to produce dried products of ever greater potency with acceptable recovery loss in manufacture and in such quantities that they will meet *all* needs of haemophiliacs for factor VIII.

Management today

How has the management of haemophilia changed and kept pace with the blood product development? First, it has become more aggressive; that is treatment of spontaneous bleeding, commonly into joints, is given earlier and is more effective so that bleeding is arrested before distention and pain occur, and temporary disability, permanent damage and deformity are minimised or prevented. This results in less time lost from school, work or leisure activities. Secondly, major surgery, whether for disorders that may beset us all, such as the complications of peptic ulcer or extensive dental caries, or for those peculiar to the haemophiliac, such as joint deformities from past haemarthroses, has been made much safer and can now be undertaken electively and not only as a desperate life-saving

measure. For these aims to achieve fruition other associated developments have been necessary. Haemophilia Centres have been established and developed in major hospitals so that precise diagnoses can be made and patients counselled, advised and instructed. At these Centres specialised out-patient treatment is available on a 24-hour basis and the haemophiliac can report direct to the Centre using the Ambulance Service or his own 'car for the disabled' to get there. Joint bleeds etc. can thus be treated at a very early stage and the haemophiliac, if sufficiently competent, can be taught self-injection of the factor VIII made available at the Centre 'on demand'. When he is fully trained, and when adequate dried factor VIII supplies are available, he can change to the Home Treatment programme. He will then be issued with a limited supply of dried factor VIII with which he can treat joint bleeds – the bugbear of the severe haemophiliac's life – at home and thus save time and trouble and gain independence. Since 95% of all factor VIII used by a severe haemophiliac is for such bleeds, the advantages of home therapy are obvious. For bleeds other than into joints, out-patient management at the Centre, or occasionally in the Ward, is still advisable and the haemophiliac must not attempt such treatment at home.

The future

Whilst present progress has revolutionised the life of the severe haemophiliac, given him self-confidence and a much greater degree of independence, it has not cured him. At present we know of no means of achieving this. Perhaps as supplies of factor VIII improve still further, we will be able to offer him prophylaxis, but the short factor half-life would probably necessitate twice daily self-infusion of factor VIII rather like an insulin-dependent diabetic though using the intravenous route. However, about 10% of haemophiliacs develop a neutralising 'antibody' to factor VIII which is not dose related, and at present is causally not understood. In some it persists in the plasma indefinitely and in others it wanes if not provoked by further therapy, but in all it constitutes a bar to replacement therapy, either totally or save in urgent circumstances. Management of these patients is at present not very satisfactory even though blood products with 'factor VIII bypassing activity' have some beneficial use. We can, however, hope for a radically different approach to the problem of haemophilia. It is possible even now to sex the foetus *in utero* accurately in early pregnancy, and where the mother is a known or potential carrier of the disorder this may be advisable; however, the procedure is associated with a small abortion loss. Hopefully in the near future it will be possible to measure the factor VIII level in the foetus accurately and thus offer therapeutic abortion of an affected male foetus if desired.

The investigation of suspected female carriers of haemophilia is becoming more specific, based upon the dissociation of the levels of clotting and immunological factor VIII in the blood of those positive for the trait, but it is not yet wholly reliable. An entirely new approach to the management of haemophilia depends upon using an exogenous stimulus to induce a temporary increase in endogenous production of factor VIII. Deamino-D-arginine vasopressin (DDAVP) given intravenously or as snuff is used for this purpose but is effective only in the moderately or mildly affected patient (Mannucci et al, 1975). And so the search for better products, more effective and simpler treatment, prophylactic rather than therapeutic, goes on. Selective abortion as a preventative measure is never likely to overcome the perpetuation of the disorder through spontaneous genetic mutation and hence the goal must ultimately be to find a cure. This still seems to be a long way off, but progress towards it accelerates.

The Haemophilia Society

What have haemophiliacs done to help themselves? In the early 1940's in Britain they formed their own Haemophilia Society and this is now linked with other similar societies elsewhere in the world in the World Federation of Haemophilia. Through their Society, and as a minority group in the population, they have helped to dispel fear and ignorance of the disease and this has improved their opportunities for better medical care, schooling, employment and leisure. The Society has, through organised meetings and its literature, helped parents of newly diagnosed haemophiliacs and the effected children themselves, to adjust and adapt to the disability and to lead a fuller, more balanced life. It has provided funds for research and has agitated

and helped to make Governments understand the needs of all handicapped people, and of those with haemophilia in particular.

And so whilst haemophilia and its problems are so much better understood and managed than in those far off days of the Rabbinic references to exsanguination of ritual circumcision, there is still much to be done and the contributions made in this field in the future, as in the past, will add to as much as they derive from, the advances made in medicine in their widest sense. ●●

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