Discussed at meeting RPC HLC 15/1/74
Bragg, Hunter, Scott, Dickens, Dutton (RPC) (HLC)
Bungé + Scott.

# THE TREATMENT OF HAEMOPHILIA: OBJECTIVES & LIMITS

Haemophilia is caused by a lack (or reduction in plasma concentration) of an essential clotting factor called factor VIII. The condition is inherited as a sex-linked recessive character and the disease is thus manifested in males and passed from generation to generation through symptom-free females who carry the abnormal gene but in whom its affects are masked by the presence of the normal gene. The affected male bleeds excessively from injuries including the minor strains of everyday life which pass unnoticed by normal people. Without treatment past records show that patients died young, they led physically restricted lives and became crippled from bleeding into muscles and joints.

Modern treatment consists of the intravenous administration to the patient of material containing factor VIII to correct his coagulation abnormality.

## Therapeutic Materials

Before 1950 very little treatment was available. Blood Transfusion Centres did not separate whole blood into its components and the whole blood was not able to control most bleeding in haemophiliacs. In 1955 Bidwell developed a concentrate of clotting factor VIII from animal blood and this was used to protect patients having life endangering bleeding and patients who required surgical operations. From 1955 to 1965 there was a slow increase in production of whole human plasma by the transfusion service. Whole plasma is more effective than whole blood but was still unsuitable for the control of serious bleeding in haemophilic patients. In 1965 Pool and Shannon devised a simple method of separating factor VIII from plasma to make a product called cryoprecipitate in which factor VIII was concentrated. The product could be made without special apparatus in any blood bank and was effective in the control of all types of haemophilic bleeding. The production of cryoprecipitate promoted a major advance in treatment but the presentation of cryoprecipitate was not ideal. The dose activity was

never assured, the material was unstable and had to be stored in a deep freeze; the making up of a dose was time consuming and required care and skill. The conversion of cryoprecipitate to a freeze dried product of stable and known potency was the next obvious stage. This last stage has been achieved on a small scale in the United Kingdom by the Plasma Fractionation Laboratories in Edinburgh, Elstree and Oxford using plasma supplied by the transfusion services. Several commercial firms have been able to provide large amounts of freeze dried factor VIII using plasmaphoresis of paid blood donors enlisted in the United States and Europe, possibly elsewhere, as a source of plasma for fractionation.

## The Evolution of Haemophilia Therapy

Factor VIII is given intravenously in amounts needed to control each episode of bleeding. In the early days of treatment (1950 to 1960) factor VIII was given to control life endangering bleeding and the number of actual infusions were few. The work involved could easily be carried out by the staff of hospitals to which the patients were admitted. The introduction of cryoprecipitate introduced the possibility of treating all episodes of bleeding into muscles and joints and since 1965 patients have been encouraged to seek treatment early. The treatment of all episodes of bleeding however trivial has greatly increased the amount of work carried out by hospital departments at which the patients attend. Since 1954, when special centres to care for haemophilic patients were set up, the work of these centres has increased by a factor of 10 to 20 times In the early days the main work of the centres was to establish diagnosis and issue haemophilia medical cards to patients. Thus many centres were established under the direction of laboratory specialists. By 1967 it was apparent that the safe treatment of haemophiliacs would require a larger supply of concentrates than were then available and the personal involvement of physicians in the work of all haemophilia centres. In this year two steps were taken. An MRC working party was set up to consider the production of factor VIII and other concentrates and a Conference was held of the Directors of Centres for

the treatment of haemophilic patients. The working party and the Haemophilia Centre Directors worked together to produce two reports on the treatment of haemophilic patients based on observations made during the years 1969, 1970 and 1971. Both reports were finally published in 1974 though they were widely circulated in manuscript form for a year prior to publication.

The Haemophilia Centre Directors report was based on a system of annual data collection which is still continuing and which will finally give a true count of the number of patients in the country. These annual statistics give a record of the types of material used for treatment and an estimate of the proportion of patients suffering from complications of treatment.

In the six years nearly 2,500 different patients have been treated at the centres. This total must be less than the true number of patients since not all centres make returns and not all patients are treated at haemophilia centres. The MRC working party estimated that about 6 persons per 100,000 of the population suffer from haemophilia. This estimate is a little lower than those from 6 other European countries made in the last three years which average 7.3 per 100,000. There are thus probably at least 3,000 severely affected patients in the United Kingdom.

Each year a proportion of Haemophilia Centre Directors make reports on the treatment of about 1,000 patients with haemophilia and on average each patient now receives the amount of factor VIII concentrate derived from about 170 blood donations. If all of the patients in ~~the country~~ were treated similarly the factor VIII from 170 x 3,000 = 510,000 blood donations would be needed each year. This estimate agrees well with one made by the MRC working party of 500,000 blood donations annually as a minimum amount to be fractionated to provide factor VIII.

From figures available 71% of factor VIII is at present supplied as cryoprecipitate or whole plasma, 17%

is a dried preparation made from blood collected by the transfusion service in the United Kingdom and fractionated within the NHS. About 12% is supplied by commercial companies from paid donor blood collected overseas.

In the Haemophilia Centre Directors Survey it was shown that 1.4 to 2.4 percent of patients developed hepatitis each year from factor VIII infusions derived from blood collected and processed within the United Kingdom. Evidence suggests that the incidence of hepatitis will increase if a large proportion of the factor VIII used is made from commercial donor blood.

Informed treatment of haemophilic patients has developed from the creation of relatively few special centres for their care but patients often have to travel long distances to attend a centre and if they are to come for every incident of bleeding they may have to travel once a week or more. Many Haemophilia Centre Directors encourage arrangements for patients to be treated in their homes. Home therapy gives patients greater freedom to live normal lives and may save much hospital expense. To supply this home therapy a freeze dried stable preparation of factor VIII is required. There is thus urgent need to replace the currently made cryoprecipitate by an NHS freeze dried concentrate. At present much home therapy is based on commercial factor VIII.

## The Social Consequences of Treating Haemophilic Patients

In the United Kingdom about 2 million blood donations are given annually by unpaid donors to the transfusion service. To provide the 500,000 donations, estimated as the minimum need for the haemophiliacs, one quarter of this blood should be separated into its components. Factor VIII is only one small

part of the blood and the other components including the red blood cells are valuable for other patients. The factor VIII for haemophilic patients could be thought of as a biproduct of the rational use of blood. It is wasteful to use whole blood to treat any patient who needs only a defined part derived from that blood.

For many years the treatment of haemophilic patients was limited by a shortage of supply of factor VIII. Now there is no shortage; the enterprise of the commercial companies has actually produced an excess of factor VIII at a price. Were all the factor VIII ~~needed by the~~ patients supplied by commercial companies the cost would be ~~about £5,000,000 annually~~. Moreover, it is not desirable that we should come to rely on the blood of other nations to supply reasonable needs of our own citizens. To make adequate amounts of factor VIII in suitable freeze dried form from United Kingdom donor blood will require money, good will and organisational energy but this provision is well within our capability and were all of the factor VIII derived from NHS blood it would be likely to be considerably less costly than foreign commercial factor VIII.

It is sometimes thought that the needs of haemophilic patients have been over-estimated by their medical advisors and that the patients should expect to lead "reasonably" restricted lives. It may be true that a quiet studious boy who hates organised sport requires less treatment than the noisy aggressive extrovert. But human nature does not come in prescribed packages. Moreover, the cost of maintaining a poorly treated patient can be as great as that required to maintain the patient in normal health.

The question as to whether or not we can afford to treat the haemophilic patients on a National scale has very little relevance to the individual doctor and patient conversing in a consulting room. Both doctor and patient know that adequate treatment is available. The doctor may well prefer to prescribe NHS factor VIII but when this is

not available has little option but to use one of the commercial preparations.

## The Limitation of the Number of Haemophilic Patients

In 1947 Haldane calculated that there were probably about 6.6 haemophiliacs born per 100,000 live births of either sex. The incidence of haemophilia at that time was about 2.2 per 100,000 of the adult population. Since 1947 the incidence of haemophilia in the United Kingdom and in several other European countries has increased to about 7 per 100,000, this increase is to be attributed almost entirely to the survival of patients who would have died young in previous decades. It is natural to hope that, having achieved a normal survival of affected persons, some attempt should be made to limit by genetic counselling the number of afflicted persons who are born. From the mode of inheritance it follows that all of the daughters of a haemophiliac will carry haemophilia and all of his sons will be normal. Thus were it possible to restrict the children of a haemophiliac to boys the disease should not crop up in his descendents. The sisters of a haemophiliac have a 1 in 2 chance of carrying the disease, were it possible to distinguish those females who are NOT carriers of haemophilia it could confidently be predicted that their children would be normal. Unfortunately this is not possible. Using modern laboratory tests it is possible positively to identify the carrier state in about 7 women out of 10 who may be carriers. This positive identification is not very helpful to the genetic councillor because a carrier of haemophilia has only a 1 in 4 change of having an affected son and for many women the chance seems a reasonable one to take. Moreover, about 40% of haemophilic children are born to families where there is no previous knowledge of the disease. In some cases the disease may have passed through several generations of females and all affected predecessors may be long since dead. In other cases the disease may arise anew by mutation, Haldane estimated the mutation rate to be 3.2 per 100,000 of the population per generation. In any event it is not practicable to screen the normal female population to discover the 6 per 100,000 females who may carry haemophilia.

Genetic counselling would be assisted by the near certain identification of normal women in known haemophilic families but the reduction in incidence of a sex-linked recessive disease with a high mutation rate is likely to take many centuries.

REFERENCES

Biggs, R. (1974) Jaundice and Antibodies directed against Factors VIII and IX in patients treated for haemophilia or Christmas disease in the United Kingdom. British Journal of Haematology 26, 313.

Biggs, R. Rizza, C.R.C., Blackburn, E.K., Cleghorn, T.E., Cumming, R., Delamore, I.W., Dormandy, K.M., Douglas, A.J., Grant, J., Hardisty, R.M., Ingram, C.I.G., Kerwick, R.A. Maycock, Wd'A and Wallace, J. (1974) Factor VIII concentrate made in the United Kingdom and the treatment of haemophilia based on studies made during 1969-72. British Journal of Haematology. 27, 391

Haldane, J.B.S. (1974) The mutation rate of the gene for haemophilia and its segregation ratios in males and females. Annals of Eugenics 13, 262.

Pool, J.G. and Shannon A.E. (1965) Production of high potency concentrates of anti-haemophilic globulin in a closed-bag system. New England Journal of Medicine 273, 1443.