BLEEDING EPISODES IN SEVERELY AFFECTED ADOLESCENT HAEMOPHILIACS AND THEIR MANAGEMENT WITH REPLACEMENT THERAPY

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by

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ORIGINAL WORK

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ABSTRACT

FACULTY OF MEDICINE

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BLEEDING EPISODES IN ADOLESCENTS WITH SEVERE HAEMOPHILIA A AND THEIR MANAGEMENT WITH REPLACEMENT THERAPY

by Anthony Aronstam

The consequence of undertreating haemophiliacs with Factor VIII is crippling deformity, but there are hazards associated with adequate therapy, which also strains human and financial resources. The work presented in this thesis attempts to rationalise the use of factor VIII.

A review of the literature covers aspects of the disease itself, of transfusion therapy, and of the hazards of treatment. A linking section describes the history of the Lord Mayor Treloar College and Hospital where the work was undertaken.

The work itself consists of retrospective observations and prospective studies made on severely affected adolescent haemophiliacs resident at the College between 1973 and 1979.

The first section is an analysis of 4935 bleeding episodes, and information is presented on patterns of bleeding and transfusion requirements. The role of prophylactic treatment is described in the second section. Two double-blind controlled trials of prophylaxis are reported,as well as an analysis of prophylactic treatment during 1976 and 1977.

The final section reports a double-blind controlled trial of the effect of three different dose regimes on the outcome of bleeds into the knee, ankle and elbow joints. The effect of past and continuing joint damage on outcome has also been studied.

The major conclusions are that patterns of bleeding alter during adolescence and transfusion requirements vary with the site of bleeding. Prophylaxis is effective but usage of factor VIII escalates steeply with more intensive treatment. Finally, the underlying condition of the joint affects the response to different dosage regimes.

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INTRODUCTION

Haemophilia is a disorder of haemostasis which is due to a sex-linked inherited deficiency of clotting factor VIII. A deficiency of clotting factor IX produces an identical clinical picture but will not be considered in this thesis, which is in large part concerned with the use of factor VIII-containing preparations for the treatment of bleeding episodes in patients with haemophilia A who do not have inhibitors to factor VIII.

The disease in its severe form is characterised by spontaneous bleeding mainly into joints and muscles, but also into other sites. The inevitable consequence of repeated bleeding into the joints and muscles is relentless progression to crippling deformity.

The advent of replacement therapy and the refinement of various factor VIII-containing materials has transformed the outlook. Adequate replacement therapy has greatly lessened the crippling deformities consequent upon severe and repeated bleeds into joints and muscles. Intensive physiotherapy to restore function is now possible due to cover with factor VIII preparations and corrective orthopaedic surgery can similarly be applied. It is thus conceivable that increasing availability of factor VIII concentrates and increasing use might eventually eliminate the crippling stigmata of this disease. Theoretically, the ultimate progression towards unlimited prophylaxis should eliminate bleeding entirely.

The increasing usage of factor VIII has, however, brought with it new problems. There is strong evidence that liver dysfunction is a consequence of intensive replacement therapy and increasing evidence that there are other harmful effects. There are also major problems concerned with the supply of factor VIII-containing materials and the limited resources available to the National Health Service

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in the United Kingdom make this a major consideration in planning therapeutic regimes.

The crippling consequences of under treatment and the long term side effects of adequate and over treatment make it important to rationalise the use of factor VIII.

This thesis will show how the results of clinical trials carried out and original observations made on haemophiliacs at the Lord Mayor Treloar College between 1973 and 1979 may contribute to this end.

The first part of this thesis is a review of the literature pertinent to the theme. This will consist of three main sections:-

a) THE DISEASE ITSELF: The history of the disease, its incidence, clinical features and the pathogenesis of haemophilic arthropathy will be reviewed.

b) REPLACEMENT THERAPY: The history of transfusion therapy and the development of concentrated preparations of factor VIII will be outlined. The relevance of the fate of transfused factor VIII, and of its half-life, to the rational use of factor VIII and to various therapeutic regimes will be discussed. Home therapy and prophylactic therapy are two growth points in current practice which have profound implications for the supply of and demand for factor VIII. Finally, the literature on other forms of treatment, both past and present will be reviewed.

c) THE HAZARDS OF TREATMENT: This section will review immediate problems including transfusion reactions and transfusion induced bleeding diatheses as well as long term problems such as the development of antibodies to factor VIII. A review of the literature on hepatitis in its many forms and the effect of

transfusions on the urogenital, cardiovascular, reticulo-endothelial and endocrine system will be presented.

The second major section of this thesis is concerned with the original work done at the Treloar Haemophilia Centre between the years 1973 and 1979, and begins with an outline of the history of the Lord Mayor Treloar College, the Lord Mayor Treloar Hospital and the Treloar Haemophilia Centre. Original observations and experimental work will then be presented under the following headings:-

A) BLEEDING EPISODES AT THE COLLEGE BETWEEN 1973 and 1977

i) Patterns of Bleeding: Current dose regimes are based on clinical observations made many years ago. The generation of haemophiliacs now entering adolescence is much freer of crippling deformity than previous generations and there is an adolescent bulge in the haemophilic population. Adolescence itself is a time of increased activity associated with rapid changes in height and weight, all of which may predispose to new stresses and strains on joints and muscles. A study of the patterns of bleeding in a group of adolescent haemophiliacs has thus been undertaken in the hope that new information may point the way to new therapeutic approaches.

ii) Transfusion Requirements: Limitation of financial and human resources make a prediction of future transfusion requirements vital. A study of the overall transfusion needs of severely affected haemophiliacs has thus been designed to provide vital information for such predictions. Further, the extension of this study to transfusion requirements for bleeds into specific sites should help to identify bleeds which may need special measures such as higher initial dosage to prevent the evolution of a protracted and complicated bleeding episode, which may initiate chronic arthropathy or muscle contracture.

B) PROPHYLACTIC TREATMENT: This has been used by several workers but the regimes used have varied and reported results have conflicted. Two double-blind controlled trials of this form of therapy have been undertaken at the Lord Mayor Treloar College and are reported here. An analysis of the use of prophylaxis over a two year period following these trials is also reported.

C) EPISODIC TREATMENT: This is the cornerstone of current management. Little substantiated information is available about the influence of site and severity on response to different doses of factor VIII. The three commonest sites of bleeding are knee, ankle and elbow and a double-blind controlled trial of three dosage regimes has been carried out at the Treloar Haemophilia Centre and is reported in this thesis. The results have been further analysed in order to find the effect of past and present joint damage on the response to different dose regimes. The joint into which frequent bleeds occur is often a joint with hyperaemic synovium and a target joint is therefore often a joint with active inflammation. The end result is movement restriction and a restricted joint may be taken as evidence of previous damage to that joint. The effect of varying the dose level of factor VIII on joints which are targets, joints which are restricted, joints which are both target and restricted and joints which are neither have been studied and will be reported.

Finally, the results of original work done at this Centre will be summarised and recommendations concerning treatment regimes will be set out.

REVIEW OF THE LITERATURE

1. HAEMOPHILIA - THE DISEASE

DEFINITION AND HISTORY

Haemophilia may be defined as a lifelong, X-linked recessive bleeding disorder due to an isolated congenital and functional deficiency of factor VIII (Ingram 1976).

The disease is of ancient lineage and was first described in the Tractat Jebamoth of the Talmud in the second century A.D. (Bulloch and Fildes 1911). Three sons of three sisters died from bleeding following circumcision; the first son of the fourth sister was therefore excused (Ikkala 1960). Three centuries later, a tractat of the Babylonian Talmud (5th century) quotes the words of Rabbi Judah the Patriarch, redactor of the Mishnah, the second century compilation of Jewish law, which excuses a third male child from circumcision if two previous male siblings had died from bleeding following their circumcision (Rosner 1969). The disease was probably described in the eleventh century when the Moorish surgeon Alzaharavius observed that in certain villages there were men who when wounded suffered uncontrollable haemorrhage which caused death and in the twelfth century Maimonides applied the Rabbinic ruling to the sons of a woman who was twice married (Bulloch and Fildes 1911).

An American physician, John C. Otto (1803) is often credited with the first clinical description of haemophilia. He described a disease characterised by a bleeding tendency affecting only males but transmitted by females. However, Macfarlane (1938) states that the first record of undoubted haemophilia was published in 1793. A boy who died from haemorrhage after cutting his thumb had a brother and several uncles who had suffered a similar fate, while the females of the family were immune. The account appears in "Medicinische Ephemeriden" and though anonymous, is ascribed by other evidence to C.W. Consbruch (Bulloch and Fildes 1911). Nasse (1820) confirmed this pattern of inheritance and brought the disease to the notice of European Physicians. There is controversy over the first use of the

word haemophilia to describe this bleeding disorder. Birch (1937) credits the naming of the disease to Schonlein in 1839. Ikkala (1960) while acknowledging the claims for Schonlein, pointed out that the name appeared for the first time in the literature in the title of an academic dissertation by Schonlein's pupil Hopff (1828).

The defective coagulation of the blood that characterises this disease was suspected by Meckel (1816) and noted by Wardrop (1835) and Liston (1838) who observed that the shed blood of haemophiliacs clotted very slowly. Shortly afterwards Lane (1840) described the first successful transfusion of blood into a haemophiliac. In his paper he comments on the predisposition of bleeders to "gout" and relates an incident in the past history of his patient when he was treated for an "affliction of the knee joint" with leeches. The joint afflications of haemophiliacs were first ascribed to bleeding by Volkman (1868) but others such as Grandidier (1870) maintained that gout and rheumatism were the cause of the diseases of the joints in bleeders. These conflicting experiences were gathered together by Konig (1892) who definitely established the relationship between haemophilia and haemophilic arthropathy.

Wright (1893) using a method based on blowing blood out of capillary tubes first demonstrated lengthening of the coagulation time in a haemophiliac. The first step to defining this defect was taken by Addis (1911) who showed that a fraction of normal plasma added to haemophilic blood shortened the clotting time. He assumed that this fraction was prothrombin and it was twenty years before Govaerts and Gratia (1931) showed that the correcting fraction of the normal plasma was not absorbed by a Berkefeld filter or by tricalcium phosphate and therefore could not be prothrombin. This was confirmed when the prothrombin time was found to be normal in haemophilia (Quick 1935).

The view that haemophilic platelets were defective was taken by Minot and Lee (1916) and it was again twenty years before Patek and Stetson (1936) demonstrated that fresh plasma deprived of its platelet content was as efficacious as fresh whole blood in correcting the prolonged coagulation time of haemophiliacs. Patek and Taylor (1937) found that globulin fractions prepared by acid precipitates of diluted cell-free plasma at pH 5.5 contained all the antihaemophilic properties of the parent plasma. They called this fraction a globulin and later (Lewis et al 1946) antihaemophilic globulin or A.H.G.

The concept of the disease called haemophilia being a single condition was disturbed when Pavlovsky (1947) reported that the blood of some haemophiliacs would correct the clotting defect of the blood of others. In 1952 several groups of workers (Aggeler et al 1952, Biggs et al 1952, Schulman and Smith 1952) established that a disorder resembling haemophilia could be distinguished as due to a deficiency of another clotting factor. The new factor was ultimately designated factor IX and the A.H.G. deficient in classical haemophilia was called factor VIII (Wright 1962). The subsequent refinement of factor VIII to form potent concentrates for the treatment of bleeding in haemophilia A will be described in the section on transfusion.

Zimmerman, Ratnoff and Powell (1971) described immunological experiments which showed that although functional factor VIII was deficient in severe haemophilia A, there was still an antigen present which though functionally impaired was nevertheless related to factor VIII. The intensive research on the factor VIII molecule which has since taken place, is beyond the scope of this thesis.

INCIDENCE

The number of haemophiliacs living in the population depends on the birth rate, the life span and the mutation rate to the haemophilic gene. Lenthening life span will increase the number of haemophiliacs living and this will in turn result in an increase in the number of haemophiliac children born.

Biggs (1978a) has summarised estimates of the prevalence of haemophilia in various populations. In 1976 estimates were made in Greece, Italy, West Germany, France, Australia and Belgium of the prevalence of haemophiliacs per 100,000 of population. The mean of all the results gave a figure of 7.2 haemophiliacs per 100,000 of population, which compares with estimates in the United Kingdom of 6.0 per 100,000 by Biggs (1974) and 6.3 per 100,000 by Cash (1975).

The National Heart and Lung Institute (1973) has stated that 25% of haemophiliac births are due to mutation. If the mutation rate is constant, the proportion of mutations must necessarily fall as more haemophiliac children are born. Haldane (1947) calculated a mutation rate to the haemophiliac gene of 3.2×10^{-5} per generation. If correct today, this is likely to be a figure uninfluenced by the lengthening life span of haemophiliacs. Macfarlane, Biggs and Bidwell (1954) estimated there to be only 500 haemophiliacs in the United Kingdom while just twenty years later an M.R.C. Working Party (1974) suggested that there were about 3,000 haemophiliacs in the United Kingdom. Biggs and Spooner (1978) confirmed that 3,068 patients had been identified with haemophilia 'A' in 1974. Although these figures suggest that the basic data on which Haldane made his calculations may be erroneous, he took the incidence of haemophilia A to be 13.3×10^{-5} males which is very similar to modern estimates. The method used by Haldane assumes a population equilibrium and recent dramatic changes in the treatment of haemophilia have rendered this

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assumption of dubious validity (Merritt and Conneally 1976). There may, therefore, be a higher mutation rate to the haemophiliac gene than has been thought up to now.

The average life span of haemophiliacs in the United Kingdom has more than doubled in recent years to 42.3 years (Biggs 1977). This should lead to a doubling of the haemophiliac population. Further, Biggs points out that the leading of normal lives will result in the fathering of many more carriers and thus a second increment of increase in the haemophiliac population in two generations.

The mean prevalence of haemophilia in the West of Scotland is 1.2 per 10,000 of male population with a peak at age 19-23 of 2.03 per 10,000 of male population (Carter et al 1976). Taking into account the increased life span, the authors project a primary increase in the haemophiliac population of 81% which is very similar to Biggs' prediction. A peak incidence of haemophiliacs in the 10-19 age group was reported by Biggs (1977) and the bulge in the haemophiliac population at this age group will presumably move to later age groups with the lengthening life span. It is interesting that a similar population bulge was reported by Ahlberg (1967) at a time when Swedish care of haemophiliacs was amongst the most advanced in the developed world. An example of a country less developed at that time and with far less resources available was Singapore and Kwa , Chan and Chan (1967) report their haemophiliac population bulge in children under ten.

It is thus apparent that the haemophiliac population is likely to expand considerably over the next few generations. A further factor to consider is the proportion of the haemophiliac population that is severe. Those who plan resources must take into account the fact that the severest 20% of haemophiliacs use 80% of the resources (Carter 1976). Biggs and Spooner (1978) showed that 55.6% of known haemophiliacs in the United Kingdom had the severe form of

the disease with less than 2% of factor VIII. It is known that the severity of the disease remains constant within families (Macfarlane 1966). Assuming that the milder haemophiliac has always been able to produce children, then the increase in haemophiliac births is likely to be mainly of the severer forms. The implication is, therefore, that not only will the haemophiliac population increase, it will also have a relatively higher proportion of severe forms of the disease and the call upon blood resources will be even higher than currently predicted.

Finally, Merritt (1975) has pointed out that if current therapeutic regimes so normalised haemophiliac life that selection against the haemophiliac were reduced to zero, the frequency of haemophiliacs in the population would increase inexorably, not only because of the relaxed selection, but because of the continued addition of new mutants.

THE RELATIONSHIP OF FACTOR VIII LEVELS TO THE CLINICAL SEVERITY

The development of the thromboplastin generation test and its refinement for the assay of A.H.F. (Biggs and Douglas 1953, Biggs, Eveling and Richards 1955) provided a test that could specifically measure the coagulant activity associated with the antihaemophilic factor. The unit of factor VIII was defined as the activity in 1 mg. of a particular dried preparation of bovine A.H.G. which was equivalent to the activity in about 4 ml. of fresh average normal plasma. This unit was later redefined as the factor VIII activity in 1 ml. of average normal plasma obtained by adding 9 ml. of blood to 1 ml. of 3.8% sodium citrate (Biggs and Matthews 1966).

The range of this activity in the normal population was found to be from 50-200% of average normal (100%). In 1958 115 patients with haemophilia were surveyed and the factor VIII levels were related clearly to the clinical course of the disease (Biggs and Macfarlane 1958). In particular, it was shown that a factor VIII level of more than 5% was always associated with the milder forms of the disease.

Building on these and other observations, the Oxford group developed the concept of four grades of haemophilia based upon factor VIII levels. Those with a level of 25-50% showed a tendency to bleed only after major injury. With a level of 5-25% severe bleeding occurred after surgical operations or minor injury. A level of 1-5% was associated with severe bleeding after minor injury and occasional spontaneous bleeding episodes. The severest form of haemophilia with spontaneous bleeding into muscles and joints and possible crippling was found with levels of factor VIII of 0% (Duthie et al 1972). These observations were supported by other workers. Ahlberg (1965) showed that chronic joint changes were rare in patients with more than 2-3% of factor VIII. Aggeler et al (1961) thought that

those with more than 8% of factor VIII rarely had unprovoked haemorrhages and Nilsson, Blomback and Ramgren (1961) maintained that all patients with the severe form of haemophilia had less than 1% of factor VIII.

Current therapeutic regimes are based on these observations but there appear to be other factors which should be taken into account as a wide spectrum of bleeding frequency occurs in haemophiliacs with no demonstrable factor VIII (Rainsford and Hall 1973).

SITES OF BLEEDING

Bleeding into joints and muscles accounts for 80-90% of all haemophiliac bleeds (Rizza and Spooner 1977) and joint bleeding had occurred in 196 out of 210 haemophiliacs surveyed by Ali et al (1967). Several authors are agreed that the knee joint is the commonest site into which bleeding occurs (Gilbert 1977, Arnold and Hilgartner 1977, Zimbler, McVerry and Levine 1976, Stuart et al 1976, Kwa, Chan and Chan 1967 and Abildgaard 1969). Admissions to orthopaedic centres implying severer bleeding episodes have also been for knee joint bleeds more commonly than for bleeds into other sites (Trueta 1966, Duthie et al 1972 and Ackroyd and Dinley 1976). Milder bleeding episodes treated at home also occurred more commonly into the knee than into other sites (Rizza and Spooner 1977).

Many authors have maintained that the elbow joint is the second commonest site of bleeding (Gilbert and Glass 1977, Arnold and Hilgartner 1977, Rizza and Spooner 1977), and consequently the second most frequent cause for the admission of haemophiliacs to orthopaedic centres (Trueta 1966, Duthie et al 1972, Ackroyd and Dinley 1976). Other workers, however, have found the ankle to be the second commonest site of bleeding. Abildgaard(1969) reviewed 107 episodes of bleeding in haemophiliac boys and found the ankle to be second in frequency to the knee. Kwa, Chan and Chan (1967) in a small study of bleeds in haemophiliacs aged mainly under 10 reported similar findings. These two surveys suggest that ankle bleeds are commoner than elbow bleeds in young haemophiliacs. The work of Stuart et al (1966) lends weight to this. In a prospective study they showed that ankle bleeds were more frequent than elbow bleeds in the under 12 age group. The positions were reversed for older patients. The effect of age is more fully discussed in the next section.

All the above authors agree that the knee, elbow and ankle are the three commonest site into which bleeding occurs, but there is less information about bleeds into other sites. Gilbert (1977) and Rizza and Spooner (1977) put shoulder bleeds 4th and hips 5th in bleeding frequency while Arnold and Hilgartner (1977) have observed the reverse. The number of bleeds into the less frequent sites of bleeding, where reported, are too small for conclusions to be drawn.

Haemophilia is present at birth and factor VIII estimations carried out on cord blood in haemophiliac boys show the reduced level of the clotting factor (Duthie et al 1972).

THE EARLIEST MANIFESTATIONS:

Providing the child is not exposed to haemostatic challenges such as circumcision, trauma and injections, the first manifestations of haemophilia may not occur until the child is three to four months old when he begins to crawl about and explore the world (Duthie et al 1972). These authors mention excessive bruising over bony prominences and prolonged bleeding from the tongue or lips following minor trauma as the earliest manifestations of bleeding. In the series of Favre-Gilly (1957) haemorrhage was rare before the age of two.

HAEMARTHROSES:

Duthie et al (1972) state that haemarthroses begin to occur from the age of twelve to eighteen months when the child starts to walk and run. Gilbert (1977) states that recurrent haemarthroses are rarely seen before the age of five. This view is apparently contradicted by the observations of Ali et al (1967) who found that one quarter of boys under five had deformed joints. Many of Ali's cases were those who had not received plasma therapy and it is likely that Gilbert's cases were treated enthusiastically and early, thus preventing the recurrent haemarthroses consequent upon the inflammatory reaction of the synovium to the persistent accumulation of blood (vide infra) in untreated bleeds. Arnold and Hilgartner (1977) are less specific and state that repeated bleeds into joints begin in 'early childhood'.

ARTHROPATHY:

Birch (1937) described a depressing picture of painful deformity in early childhood. Ali (1967) described cases of early joint damage and Arnold and Hilgartner (1977) state

that before modern treatment all severe haemophiliacs had arthropathy by early adolescence. Ahlberg (1965) used factor VIII concentrates early which was possibly the reason that he was able to state that chronic joint changes were not common before ten years. After this age he found that the degree and frequency of joint changes increased successively with age. However, a later report by Forbes and Davidson (1973) stated that 80% of haemophiliacs had abnormal knee joints by the age of ten. The degree of disability did not appear to increase in severity after the age of fifteen to twenty.

FREQUENCY AND SEVERITY OF BLEEDS:

Gilbert (1977) noted that bleeding frequency began to increase at seven to eight and began to decline by the third decade postulating that this might be due to either a change in lifestyle or fibrosis of the synovium. Stuart et al (1966) found that the severity of bleeds as measured by time off school was greatest in adolescence but the frequency of bleeding was greatest in the under twelves. The bleeding frequency declined with advancing age. Both Ahlberg (1965) and Ramgren (1962) have stated that the severity of the disease increases until around twenty-one and then declines.

THE ACUTE HAEMARTHROSIS - A CLINICAL DESCRIPTION

"Among the symptoms of haemophilia probably no symptom is of such importance as that which causes bleedings in the synovial sac" (Konig 1892). Eighty-two years later the haemarthrosis still shadowed haemophiliac life. Wintrobe (1974) in his classic reference book stated that "haemarthrosis is the most common, the most painful and the most physically, economically and psychologically debilitating manifestation of the hereditary coagulation disorders".

SYMPTOMS

Premonitory symptoms:

An abnormal sensation described as pricking, warmth, slight stiffness or weakness in the joint is said by some haemophiliacs to herald the onset of a haemarthrosis (Duthie et al 1972). Davidson (1949) singles out stiffness as the first symptom. Boone (1976) agrees that there is an initial feeling of discomfort or slight stiffness in the affected joint. Dietrich (1976a) appears to encompass all the foregoing symptoms when he states that a "funny" feeling in the joint is a premonitory symptom of joint bleeding. Wintrobe (1974) however, takes the view that pain is the earliest symptom of a haemarthrosis while Donaldson and Kisker (1974) taking the middle road state that the onset of bleeding into a joint is heralded by pain or stiffness or both.

Pain:

Whatever their views on the early symptoms all authors are agreed that pain rapidly becomes the major symptom of the haemarthrosis as it progresses. Duthie et al (1972) believe that this is due to rapid mechanical distension of the pain-sensitive joint capsule and cite the relief of pain which follows the aspiration of only a few ml. of blood as supporting evidence. Davidson (1949) describes the evolution of pain from that present on

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movement of the joint to severe pain even at rest considerably exaggerated by motion. Ingram (1974) describes the usual symptoms as painful limitation of movement, progressing to continued pain at rest. Severe pain as a major symptom is also mentioned by Abildgaard (1969) and excruciating pain by Wintrobe (1974).

PHYSICAL SIGNS

Swelling:

Visible and palpable swelling is described as the first objective sign of bleeding into the joint by Duthie et al (1972) who maintain that a definite diagnosis of haemarthrosis can only be considered when swelling is present. Davidson (1949) puts the onset of swelling a few hours after the appearance of the first symptoms. Swelling is mentioned by Ingram (1974) as one of the usual signs and he states that as bleeding progresses the joint becomes "tightly swollen". Abildgaard (1969) also states that joint bleeding is usually accompanied by swelling. Donaldson and Kisker (1974) however, take a different view and state that periarticular swelling with detectable effusion into the joint is frequently absent unless bleeding had been present for a long time or effusion into the joint was present before the acute bleeding episode. Their clinical observations were made on children and it is therefore possible that age may affect some of the clinical manifestations of haemarthroses.

Tenderness:

Duthie et al (1972) state that tenderness can usually be detected in at least one area when there is bleeding into a joint, and maintain that the absence of tenderness suggests that the swelling is due to an effusion although occasionally they have found haemophiliacs who have presented with chronic joint swelling, painless and non tender, in which blood has been found on aspiration.

Ingram (1974) also claims that tenderness is usual and Davidson (1949) describes exquisite tenderness as a late manifestation of haemarthroses.

Limitation of movement:

This is described as a normal feature of haemarthrosis with progression to immobilisation (Ingram 1974). Restriction of motion is also stated to occur usually by Abildgaared (1969). Duthie et al (1972) state that in all but the mildest bleed the joint is held in an attitude of marked flexion, the preferred position being the one in which the volume of the joint is maximal and the intracapsular pressure minimal. Donaldson and Kisker (1974), and Wintrobe (1974) agree that there is often significant limitation of movement.

Temperature rise:

Haemarthrosis is accompanied by a rise in local temperature (Duthie et al 1972, Ingram 1974, Abildgaard 1969, Donaldson and Kisker 1974, Wintrobe 1974) and frequently by an elevation of body temperature (Duthie et al 1972).

REASONS FOR THE FREQUENCY OF BLEEDING INTO THE KNEE, ELBOW AND ANKLE JOINTS

Mechanical considerations:

The knee, ankle and elbow joint are by far the commonest joints into which bleeding occurs in severe haemophilia (Stuart et al 1966, Gilbert 1977, Rizza and Spooner 1977). These joints are "hinge" articulations and Duthie et al (1972) believe that minor angulatory and rotatory strains which are easily accommodated by the ball and socket joints of the shoulder and hip may cause significant stresses on hinge joints and cause bleeding.

Anatomical and histological considerations:

These major articulations are all synovial joints. The bones where they articulate are covered with articular cartilage. They are held together by the capsule of the joint which consists of an outer layer of strong white fibrous tissue, and a lining of synovial membrane which exudes into the joint cavity (Brash 1948).

This intimal layer of the articular capsule may be regarded as connective tissue which has undergone certain modifications in functional and structural characteristics. It varies from dense fibrous connective tissue to a membrane comprised of many layers of round, oval or cubical cells that are supported by loosely textured and highly vascular connective tissue (Bennett 1948). Gilbert and Glass (1977) define three types of tissue that make up the synovial membrane - areolar, adipose and fibrous and believe that it is the areolar and adipose tissue that make the synovium so susceptible to haemorrhage. The capillaries of these two types of synovium are very superficial, often being separated from the joint cavity by only a single layer of synovial cells with delicate tissue matrix.

Physiological considerations:

Astrup and Sjolin (1958) investigated the synovial membranes

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and fibrous capsular tissue from the knee joints of ten persons dying from disease unrelated to joints. No samples showed more than a trace of thromboplastic activity while all samples showed fibrinolytic activity. The implication is therefore that blood within the joint space requires the intrinsic coagulation pathway to clot and where this is deficient as in haemophilia blood may remain fluid and bleeding will continue. Any inefficient clot that may form is broken down by the fibrinolytic activity demonstrably present within the joint.

THE PATHOGENESIS OF HAEMOPHILIC ARTHROPATHY

The site of primary bleeding into a joint is the synovium (Swanton 1959, Trueta 1966) and Swanton found that the earliest evidence of bleeding into the joints was small synovial tissue haemorrhages. Wolf and Hankin (1965) state that small or isolated haemorrhages may resolve without causing joint damage, but it appears that a single haemorrhage, if severe enough, may ultimately produce degenerative changes (Harris 1970). Some larger synovial tissue haemorrhages may be accompanied by an acute inflammatory reaction. This cellular reaction is maintained by the presence of blood in the joint space or by recurrent haemorrhage into the joint (Duthie et al 1972), and is the early synovial reaction described by Sokoloff (1975). This is characterised by haemosiderin deposition and fibrovascular proliferation (Storti et al 1970), and the synovium becomes so vascular that it appears angiomatoid. Swanton (1959) and Duthie et al (1972) believe that the hypertrophy of the synovium now present with increased vascularity and cellular infiltration is a response to haemosiderin deposition, although Gardner (1965) states that haemosiderin by itself, does not cause any synovial reactions.

The cellular reaction also produces thickening of villi and the formation of nodular projection from the synovial surface. Mechanical trapping by joint movements of these nodular projections may produce patchy areas of necrosis and are a cause of recurrent haemorrhages (Duthie et al 1972). The hypertrophied synovium with the hypervascularity and hyperaemia of the inflammatory response becomes the seat of further and repeated haemorrhages (Gilbert and Glass 1977).

The second stage in the development of arthropathy, that of cartilaginious degeneration (Sokoloff 1975) is a response to severe and repeated episodes of bleeding (Hoaglund 1967) and is characterised by fibrillation of cartilage and

metachromatic change (Gilbert 1977). The joint surface of cartilage is now commonly covered by fibrous tissue which rests on irregularly pitted cartilage. In this situation, it is usual to find an increase in the number of vascular channels perforating the subchondral bone plate and penetrating the calcified cartilage (Woods 1972). This reduces the quantity of bone in the subchondral bone plate and weakens the subchondral tissues. Subchondral bone cysts develop (Swanton 1959) and the epiphyseal ends of the bone enlarge (Gilbert 1977).

By this stage the synovium is becoming progressively more fibrotic (Storti et al 1970) with fibrin becoming organised and incorporated in now permanently thickened, more fibrous, and focally densely hyalinized synovial villi which often show adhesions (Swanton 1959). These adhesions reduce the size of the joint. The end stage of haemophilic arthropathy is a fibrotic, contracted and totally destroyed joint (Arnold and Hilgartner 1977).

This depressing picture is an inevitable consequence of untreated haemophiliac haemarthroses. Modern treatment has greatly reduced the incidence of progressive arthropathy, but there remains a small group of haemophiliacs who progress to end stage arthropathy in spite of receiving adequate and prompt treatment (Hilgartner 1977). The situation is fortunately not as common as stated by Van Creveld et al (1971) because by present standards the treatment his three cases had received would not be regarded as either prompt or adequate. Nevertheless, the morbidity attendant upon this stage of disability in a severe haemophiliac would make research into prevention well worth undertaking.

REVIEW OF THE LITERATURE

2. THE SYSTEMIC TREATMENT OF BLEEDING EPISODES

REPLACEMENT THERAPY WITH WHOLE BLOOD AND PLASMA

The first recorded successful direct transfusion of whole blood into a haemophiliac was reported by Lane (1840). An 11 year old boy who had previously bled copiously from dental extractions, had an operation to relieve a squint. Bleeding from the operation site continued for six days and the boy became moribund. Five and a half ounces of blood from a 'stout, healthy young woman' was transfused, the bleeding stopped and there was no recurrence. The good fortune of finding compatible blood was not repeated over the next few years and operators employing animal blood and permitting air to be injected into the recipient caused blood transfusions to fall into disfavour (Schmidt 1968). Safe blood transfusion did not become possible until Landsteiner (1901) discovered the blood groups.

Weil (1905) found that the therapeutic effect of blood transfusion in haemophilia was due to bringing the coagulation time to or near normal and Addis (1911) put therapy on a more scientific basis with his description of the plasma defect. Blood transfusion thereafter became more routine (Forbes and Davidson 1973). Minot (1916) was a regular user of fresh whole blood in the treatment of haemophilia and the third series of the Surgeon-Generals list in 1926 was the first to carry a section on blood transfusion in the treatment of haemophilia (Ingram 1976).

Payne and Sheen (1929) looked at the effect of a range of 'haemostatic' agents on the coagulation time. They tested 'Haemoplastin', 'Coagulation CIBA', fibrinogen, horse serum, protein shock, citrated human blood and citrated plasma. Only the latter two had any effect and only if given intravenously. They also showed that plasma was more effective than whole blood.

Macfarlane and Barnett (1934) stated that the key to treatment in haemophilia was to promote clotting and four years later Macfarlane pointed out the uselessness of almost all

known remedies in arresting haemophilic bleeding (Macfarlane 1938). He concluded that "only normal blood transfusion has any consistent effect in lowering the coagulation time and improving the condition of the patient and even this effect is sustained for a day or two only". From this time therapy has been directed at replacement of the missing clotting factors by the substitution (infusion) of plasma or a suitable fraction thereof (Breckenridge 1972).

The transfusion of fresh blood, fresh plasma and plasma separated from fresh blood and quickly frozen and stored at low temperature remained the only effectual method of treating haemorrhage in haemophilia (Keckwick and Wolf 1957) and fresh plasma was stated to be the accepted treatment for musculo-skeletal haemorrhage by Biggs (1964). However, only 26 out of 210 haemophiliacs received regular prompt treatment with plasma in the Metropolitan Regional Hospital Board areas of London in 1965 and 1966 (Ali et al 1967).

Plasma donor selection was undertaken increasingly to procure higher levels of factor VIII (Perkins, Rolfs and Acra 1962). Preston and Barr (1964) found that male group 'A' donors have higher levels of factor VIII and Rizza (1961) showed that exercise increased the factor VIII level in normal donors. More attention was focused on conditions of collection, separation and storage. Temperature dependent decay of plasma factor VIII begins in vitro immediately after collection and refrigerated centrifugation soon after donation became widely practiced to minimise the loss (Mason and Ingram 1971). The optimum temperature for storage was found to be - 30° C (Anstall, Grove-Rasmussen and Shaw 1961). at which temperature the plasma factor VIII was stable for long periods (Britten and Grove-Rasmussen 1966). The recommendation of Hawkey and Anstall (1962) that fresh frozen plasma should be thawed at 37° C and used immediately

arose from the observations of Pool and Robinson (1959) which led ultimately to the development of cryoprecipitate and which will be discussed in more detail in the next section.

CONCENTRATED PREPARATIONS OF FACTOR VIII

Patek and Taylor (1937) were the first to report the effect of concentrated preparations of factor VIII. They found that globulin fractions prepared by acid precipitation of diluted cell-free plasma at pH 5.5 contained all the anti-haemophilic properties of the parent plasma and this fraction was named antihaemophilic globulin (Lewis et al 1946).

Animal factor VIII:

Patek and Taylor (1937) showed that plasma fractions active in correcting the clotting time of haemophilic blood could be obtained from the blood of sheep, ox, rabbit and monkey. Pohle and Taylor (1938) used an ox blood plasma fraction as a local haemostatic to control haemophilic bleeding. Spaet and Kinsell (1953) produced a bovine A.H.G. preparation by a method based on the Cohn process (vide infra) but did not use it clinically while Lorand and Laki (1954) prepared material with A.H.G. activity from dog and ox blood by adsorption on to Kaolin. The first preparations used successfully in humans were fraction I preparations prepared from porcine and bovine blood (Macfarlane, Biggs and Bidwell 1954, Macfarlane et al 1957, Fraenkel and Honey 1955). Bidwell (1955a, 1955b) described a simple method for purifying factor VIII from slaughterhouse blood.

Most patients become resistant to animal A.H.G. after 7-10 days and show a progressive fall in their factor VIII response after transfusion (Rizza 1976). Further, both porcine and bovine A.H.G. cause platelet agglutination in vitro and thrombocytopenia in vivo and it is the animal factor VIII molecule which causes the platelets to agglutinate (Forbes and Prentice 1973). Finally, it is possible that these preparations may be more prone to produce factor VIII antibody formation than human A.H.G. preparations (Rizza 1976).

Alcohol Precipitation:

During the war years Cohn separated plasma into six fractions

and later described his method of isolating fibrinogen and factor VIII as fraction I (Cohn 1947). This was essentially the precipitation of plasma that forms at 8% ethanol in the cold and at low ionic strength. Technical pitfalls led to marked loss of factor VIII activity during early attempts to adapt the methods of Cohn to large scale production (Shulman et al 1967). Bidwell, Dike and Snape (1976) have pointed out that these were largely due to failure to recognise the lability of factor VIII with the result that much large scale work was done with plasma that was far from fresh. Blomback and Nilsson (1958) mention contamination with 'thrombokinase' as another reason and also comment on the instability of the fraction. Ahlberg (1965) blames the variable activity on contamination with 'thromboplastin', prothrombin and plasma.

Blomback and Blomback (1956) described a method for purifying the fibrinogen and antihaemophilic globulin obtained by Cohn's method by treating Cohn's fraction I with 1-molar glycine solution containing ethanol and citrate. They obtained a fraction which they called I-O in which 85-90% of the protein consisted of fibrinogen free of active plasmin, practically free of prothrombin and therefore stable in solution. They were able to report the clinical effectiveness of this material in twelve patients with haemophilia A.

In the U.S.A. considerable effort was expended to adapt this Swedish process to a large batch programme, and concentrates up to seven times as potent as plasma were produced (McMillan, Diamond and Surgenor 1961) but the yields could be as low as 16% of the activity of the original fresh plasma (Pool and Shannon 1965).

Ether precipitation:

Keckwick, Mackay and Record (1946) reported their preliminary work on an ether fractionation technique and Van Creveld and Mastenbroek (1946) showed that the product possessed A.H.G. properties both in vivo and in vitro.

However, attempts to separate the A.H.G. from other constituents of plasma were restricted by lack of adequate methods for the assay of A.H.G. activity.

The development of the thromboplastin generation test by Biggs and Douglas (1953) and its expansion into the factor VIII assay made purification studies possible and modifications resulted in the preservation of much of the factor VIII in the fibrinogen fraction (Keckwick and Wolf 1957). They precipitated A.H.G. in the cold with ethyl ether, extracted it with trisodium citrate and NaCl and reprecipitated with ethyl ether. The resultant product was tested successfully on six cases and the A.H.G. rich preparation was made at the Lister Institute, Elstree and used clinically in England and Wales for many years (Bidwell, Dike and Snape 1976).

Cryoprecipitation:

This simple method of fractionation derives from the observation that when frozen plasma is allowed to thaw at a low temperature (0-8° C) a small amount of gelatinous material remains undissolved. Ware, Guest and Seegers (1947) showed that this material contained a high proportion of the fibrinogen of the original plasma and Brinkhous (1954) pointed out that it contained some factor VIII activity. While studying the reasons for low levels of factor VIII in some plasmas, Pool and Robinson (1959) noted that the A.H.G. content of the last few drops of plasma left in a bottle after transfusion was greater than that of the freshly thawed unit. They found that this discrepancy was associated with the presence of cold precipitated fibrinogen and confirmed Brinkhous's observation that this material was rich in A.H.G. No mention was yet made of the possibilities of this material for therapeutic use as a concentrated and partly purified fraction. Indeed, three years later Hawkey and Anstall (1962) were still emphasising the need for redissolving this precipitate in order to raise the factor VIII level of the thawed whole plasma. It was only later that Pool and

Shannon (1965) described their methods for the production of a concentrated and partly purified factor VIII by cryoprecipitation using a plastic bag system. This development revolutionized the possibilities of treating suffers from classical haemophilia but there are drawbacks such as laborious preparation, variable yield and potency, necessity to store in the frozen state and contamination with red and white cells. "The provision of dried, soluble and stable and potent factor VIII preparations remains a valid objective for the special fractionation laboratories" (Bidwell, Dike and Snape 1976).

Cryoethanol precipitation:

Johnson and co-workers used cryoprecipitation accompanied by the addition of ethanol as the first step in preparation of their "Intermediate purity A.H.G." They called this step cryoethanol precipitation (Newman et al 1971). After extracting the factor VIII from this precipitate with very low ionic strength Tris buffer and adsorbing other clotting factors with aluminum hydroxide the stage of intermediate purity was reached. The result was a very soluble product well tolerated in the patient (Bidwell, Dike and Snape 1976).

The factor VIII concentrate currently made in Oxford and at the Lister Institute in Elstree is intermediate purity material made by the above method with some modification.

High potency products:

1) Newman et al (1971) describe further fractionation of intermediate potency product with polyethylene glycol to obtain a highly purified factor VIII preparation.

2) Brinkhous et al (1968) reported a high-potency glycine precipitated A.H.G. with minimal fibrinogen and which yielded concentrates up to 100 times more potent than plasma. They started with cryoprecipitate which was redissolved. Fibrinogen was then selectively precipitated with polyethylene glycol and the remaining A.H.G. precipitated with

glycine.

Highly purified A.H.G. produced by both the above methods is now commercially available. However, it should be pointed out that high purification as at present carried out for factor VIII, greatly reduces the yield on preparation and the best high purity preparations would require at least twice as much blood for their manufacture as cryoprecipitate or the intermediate purity factor VIII (Biggs 1978a).

THE FATE OF TRANSFUSED FACTOR VIII

Before instituting a treatment regime with factor VIII two important considerations arise:-

a) The post-transfusion peak level of factor VIII activity which will be found in the plasma

b) The rate at which that activity will decay.

The recovery of factor VIII immediately after transfusion:
The post infusion level of factor VIII varies with the therapeutic material used and in general the more concentrated the material the less the recovery (Rizza and Biggs 1969). The Oxford workers have devised a formula for the calculation of factor VIII dosage.

$$\frac{\text{Patients weight in Kg.} \times \text{Desired rise of factor VIII(\%)}}{\text{Total units of factor VIII in the dose}} = K$$

'K' was found to be 2.0 for plasma, 1.5 for cryoprecipitate and human A.H.G. concentrates and 1.0 for animal A.H.G. (Rizza 1976). In practical terms this implied that when giving plasma 1 unit/kg would raise the factor VIII level by 2%, when giving cryoprecipitate or concentrated human factor VIII 1 unit/kg would raise the factor VIII level by 1.5% and when giving animal factor VIII 1 unit/kg would raise the factor VIII level by 1%. Data published in a Medical Research Council report (1974) and probably not available to the above authors in time, suggested that concentrated factor VIII was giving a 2% rise per unit/kg with cryo-precipitate giving 1.68% per unit/kg. Later Biggs and Rizza (1978) recommended that a rise of 2% per unit/kg be assumed for cryoprecipitate and other concentrated preparations of factor VIII. A representative view from North America had for some time been stated by Abildgaard et al (1964). He maintained that the in vivo dose response of factor VIII is

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similar regardless of the source, and also stated that 1 unit of factor VIII/kg gives a 2% rise. Other North American authorities have agreed (Hilgartner 1976, Kasper 1976).

Very few authors mention patient weight as a factor influencing the dose response. Biggs and Matthews (1966a) showed that a child weighing 30 kg. responded to a dose of factor VIII with a rise in circulating activity about half that obtained when a 70 kg. adult is given the same dose per unit of body weight. Recent recommendations by Biggs and Rizza (1978) are that 1 unit of factor VIII/kg in a child may be expected to give a rise of 1.5% in vivo. Brinkhous et al (1968) mention better recovery of factor VIII in patients weighing more than 35 kgs. Data suggesting the opposite response has been presented by Barrett (1969) but so far this has not been confirmed.

The loss of factor VIII activity after its infusion:
There is a steady loss of factor VIII activity from the peak post-infusion level (Pool and Robinson 1959, Biggs 1957, Douglas 1958, Abildgaard et al 1964) and the rate has been stated to be the same regardless of the source of factor VIII (Abildgaard et al 1964, Biggs and Denson 1963) although Nilsson, Hedner and Ahlberg (1976) suggest that the rate of disappearance may vary with the source of factor VIII. Douglas (1958) found that the rate was the same whether patients were bleeding or not. However, the speculation of Pool and Robinson (1959) that there may be early loss of factor VIII into the bleeding site is at variance with this view.

Most authors agree that the disappearance curve of factor VIII is basically biphasic (Pool and Robinson 1959, Abildgaard et al 1964, Shulman et al 1967, Brinkhous et al 1956, Biggs 1957) with an early steep slope and a later more gradual slope. Pool and Robinson (1959) describe another more rapid slope superimposed on these two in the

period immediately following transfusion, while Abildgaard et al (1964) claimed that a rebound phase followed by a relative plateau of activity separated the two major curves with its duration directly related to the level of factor VIII attained clinically.

Many different estimates of the half life of decaying factor VIII in vivo have been given and some confusion appears to arise over terminology. In general, the phrase 'half disappearance time' is used to denote the period of time required for half of the peak level attained to disappear from the circulation. The 'biological half life' is a term used mainly to describe the slope of the final phase of the degradation curve and may represent true degradation of factor VIII. The phrase 'half life of factor VIII' when unqualified may mean either of the above, or a combination of the two.

The half disappearance time has been estimated at 3-6 hours (Abildgaard et al 1964), 4-5 hours (Shulman et al 1967), and 3.8 hours (Adelson 1964). Figures given for the biological half life are more variable and range from 6-8 hours (Arnold and Hilgartner 1977), 10.2 hours (Pool and Robinson 1959), 10-12 hours (Shulman et al 1967), 12 hours (Douglas 1958), 11 hours (Biggs 1957), 13.1 hours (Dallman and Pool 1968), and 15-16 hours (Abildgaard et al 1964). Adelson (1964) gives a biological half life of three days but his work was done on humans with normal factor VIII levels and there is evidence that when a patient is saturated with factor VIII the half clearance time is prolonged (McMillan et al 1970). Nilsson, Hedner and Ahlberg (1976) have reported detectable factor VIII levels for up to two weeks after infusion into severe haemophiliacs, a finding seemingly at variance with those of other workers and as yet unexplained.

Abildgaard et al (1964) have suggested that the initial rapid disappearance represented equilibration of A.H.F. with a

total body pool, but they had not excluded adsorption on to endothelial or other cell surfaces, a change in the reactivity of the factor, the influence of a co-factor or inhibitor and rapid metabolism of a partially denatured protein. Shulman et al (1967) feel that the early phase is a combination of diffusion into extravascular compartments plus degradation. Pool and Robinson (1959) speculated that there might be loss of A.H.F. in clotting at the bleeding site or from adsorption to platelets of vessel walls and emphasized the role of degradation and transport across vascular walls.

THERAPEUTIC REGIMES

There are many variable factors which may be taken into account when planning a therapeutic regime, and a review of the literature is made difficult by the many permutations available.

The administration of factor VIII-containing material to a bleeding haemophiliac may be planned as a single dose or as a course of several doses. The initial dose may be dependent on the site of bleeding, the severity of bleeding or whether there is evidence of previous bleeding into that site. Early bleeds may receive a different dose than later bleeds. The dose recommended may be related to all or some or none of the above factors. Finally, the dose itself may be related to the patients weight or age or it may be a fixed dose irrespective of weight or age.

Treatment of haemarthroses:

During the early days of replacement therapy (1954-1964) limitation of supplies influenced treatment regimes. Infusions were given only for very severe lesions and early haemarthroses were treated with rest and immobilisation - crippling was accepted as an inevitable part of the disease (Duthie et al 1972). Therapeutic regimes in the U.K. have been largely based on the observations made by Biggs and Macfarlane (1958). They found that spontaneous haemarthroses very rarely occurred in patients with more than 5% of factor VIII. To keep the factor VIII level in a severe haemophiliac over this level for twenty four hours would require an initial rise to 20% of average normal and this has been the recommendation of many authors for the treatment of uncomplicated spontaneous haemarthroses (Forbes and Davidson 1973, Lurie 1972, Britten, Harrison and Abildgaard 1974, Dormandy and Madgwick 1970, Mason and Ingram 1971). Forbes et al (1969) had previously recommended a maintenance of the factor VIII level at 30% for minor bleeding episodes.

For some years the practice in North America was to prescribe higher doses for simple bleeds. Until 1967 Abildgaard had prescribed transfusion of 10 units/kg (20% rise) at frequent intervals, but from that date used a single 50% rise for the treatment of haemarthroses (Abildgaard 1969). Shulman et al (1967) recommended the maintenance of a 20% level for several hours which would probably require at least an initial 40% rise, while Dallman and Pool (1968) aimed at a 50% level for most haemorrhagic episodes. Honig et al (1969) treated 47 out of 51 haemarthroses successfully with a single dose which raised the factor VIII level to 50%. Kisker and Burke (1970) used the same regime, but one third of cases needed retransfusion. Breckenridge (1972) recommended a 40% dose for joint haemorrhages while in the same year Miller, Flessa and Glueck (1972) were using a 30% loading dose followed by a 20% dose 12 hourly for spontaneous bleeds. Stengle (1975) and Kasper (1976) aimed at a post-infusion target level of 30%. Hilgartner (1977) used 40-60% and Abildgaard (1975) used 40-50% for acute haemarthroses.

Not all authors have distinguished severe and non-severe haemarthroses, but some have prescribed higher doses of factor VIII for severe bleeds. Duthie et al (1972) recommended a 30% rise for severe haemarthroses while Forbes and Davidson (1973) prescribed 40-50% rises for the more severe spontaneous bleeds. Kasper (1976) gave a 35-50% dose for severe haemarthroses.

Treatment of muscle bleeds:

Dormandy and Madgwick (1970) recommended a 35-50% dose for all muscle bleeds. Gilbert (1977) used 30-40% for mild swelling and 50% when there was significant swelling or spasm. He defined specific high risk sites and maintained a 50% level for calf bleeds as long as there was evidence of acute haemorrhage and for bleeds into the iliopsoas muscle as long as pain and tenderness

persisted. Forearm bleeds were treated with doses of up to 100%. Lancourt et al (1977) prescribed 40-50% doses for early and 70-100% doses for later forearm bleeds.

Fixed dose regimes:

Doses prescribed irrespective of weight have been used particularly with cryoprecipitate (Forbes et al 1969) and as a recent trend in home therapy (Jones et al 1978). While elaborate dosage schedules were being used for cryoprecipitate by some (Prentice et al 1967, Bennett et al 1967) Forbes et al (1969), because of the great variation in activity of cryoprecipitate used a standard dose of 10 bags for minor episodes and 20 bags for major ones. The cryoprecipitate that he used had a mean of 130 units of factor VIII/pack and the mean recovery was 80%.

Patients on home therapy should be treating bleeds early and are usually issued with phials of factor VIII which range from 210-310 units. One third of centres in the U.K. in 1976 and 1977 recommended one or two phials as routine treatment for bleeds irrespective of site and severity. About one quarter differentiated between major joint bleeds and other sites increasing the dose for the former. Only about one fifth of all centres took body weight into account when prescribing doses for home therapy (Jones et al 1978).

The trend to lower doses:

Britten, Harrison and Abildgaard (1974) noted that a dose of 10 units/kg (a 20% rise) was efficacious in the treatment of early bleeds. This was a considerable reduction in dosage compared to other North American regimes in use at that time (Levine and Britten 1973, Stengle 1975). Abildgaard (1975) and Ashenhurst, Langehennig and Seeler (1977) supported this approach to dosage of early bleeds. Penner, Kelly and Boutagh (1977) found a dose of 7-9 units/kg

was effective in mild to moderate but not severe episodes treated early. Ripa, Scaraggi and Ciavarella (1978) claimed that a dose of 3-7 units/kg aborted traumatic haemarthroses if given promptly. Their communication does not state whether any objective signs were present. In any event, only about 1 in 15 traumatic episodes terminate in a bleed (Jones 1980) and in my own experience bleeding usually starts several hours after the incident. It is therefore difficult to evaluate their regime.

Harris and Stuart (1979) found that an average dose of 6.7 units/kg would abort 80% of knee bleeds if given early and an average dose of 5.5 units was as efficacious for bleeds at other sites. Their patients were all adults with haemophilic arthropathy, but no analysis of the actual number of bleeds into the arthropathic sites is presented to substantiate the claim that these doses are adequate for bleeds into joints with arthropathy. Stirling and Prescott (1979) have shown that the results of treatment below these levels are not acceptable.

Allain (1979) has taken a view in opposition to this trend. In a retrospective survey of his patients' responses to treatment with a variety of dosage schedules, he found that a dose of 15 units/kg would abort about 90% of bleeds. However, a dose of around 26 units/kg would be required to suppress 100% of bleeds. He recommends that these higher doses should be given for all bleeds but this is obviously impracticable. A better approach would be to try and identify the 10% of bleeds which require higher dosage.

HOME THERAPY

The subject of home therapy does not fall strictly within the scope of this thesis. However, 60% of severe haemophiliacs in the U.K. treat themselves or are treated at home (Jones et al 1978) and this has produced such a radical change in the lifestyle of haemophiliacs that it should be discussed albeit briefly.

Many authorities have stressed the importance of early treatment of bleeding episodes in the prevention of arthropathy and muscle deformities (Duthie et al 1972, Kasper 1976, Gilbert 1977, Abildgaard 1969, Van Creveld 1970). However, limitation of supplies meant that many early bleeds without objective evidence of bleeding were denied treatment until painful swelling became apparent (Miller, Flessa and Glueck 1972). At this time Duthie et al (1972) in the U.K. were claiming that early haemarthroses no longer needed to be denied treatment and were advocating treatment of bleeds within four hours of onset. These authors found that only with the close co-operation of teachers and employers, the bypassing of family doctors and local hospitals and staffing and equipping of the haemophilia centre to provide an immediate service on the patients own request could this time limitation be met. Once these criteria were fulfilled, no further saving of time could be achieved unless the bleeding episodes were treated at home.

Isolated instances of home therapy programmes were known in the 1950s in North America and Holden started a programme in Texas in 1961 (Levine and Britten 1973). Limitation of supplies prevented general acceptance of this form of management. However, the steady increase in frequency of treatment from 1967 placed such a strain on patients, their families and haemophilia centre staff that the Oxford haemophilia centre initiated a home treatment programme in 1971. Very little therapeutic material was available at that time and only their nine most frequent

bleeders were started on home treatment. By 1975 fifty six severely affected haemophilia A patients were receiving regular therapy from the Oxford centre (Rizza, Biggs and Spooner 1978). Experiences in leading North American institutions were similar and Levine and Britten (1973) reported that forty five out of their sixty one patients with severe haemophilia were on home therapy. Jones (1977) and Jones et al (1978) have collected information from all the U.K. haemophilia centres and presented a comprehensive survey of the use of home therapy in the U.K. during the years 1975 and 1976. At the beginning of 1976 547 patients were either on or awaiting home treatment. By the end of 1976 this figure had risen to 729 - 60% of the potential total. The promptness of treatment following the onset of a bleed which has been made possible by home therapy has enabled smaller doses of factor VIII to be used (Britten, Harrison and Abildgaard 1974, Abildgaard 1975, Ashenhurst, Langehennig and Seeler 1977, Harris and Stuart 1979, Stirling and Prescott 1979). However, even early treatment is not able to abort more than 85% of bleeds (Harris and Stuart 1979, Stirling and Prescott 1979, Jones 1979). The potential for the development of haemophilic arthropathy although much reduced (Jones 1979) is therefore still present (Hilgartner and Sergis 1977).

PROPHYLACTIC TREATMENT

The aims of prophylaxis:

The quality of life in a severe haemophiliac is limited by the frequency with which he bleeds. The primary aim of prophylaxis, therefore, must be to reduce the frequency of bleeding. Dietrich (1975) and Gilbert (1977) used prophylaxis for recurrent haemarthroses. Hilgartner (1977) prescribed continuous prophylaxis for patients who bled more than once per week. Aledort (1977) stated that the recognition of increased bleeding should be followed by a change from episodic to prophylactic treatment. Robinson, Tittley and Smiley (1967) and Shanbrom and Thelin (1969) suggested that prophylaxis would reduce the frequency and each published single case reports in support.

A reduction in the frequency of bleeding is likely as a secondary effect to reduce the incidence of chronic synovitis and ultimately of chronic joint changes. These secondary effects are mentioned as the specific purpose of prophylaxis by several authors (Ahlberg 1965, Harris 1970, Dietrich 1975, Hilgartner 1977, Jones 1977).

History:

The earliest account of prophylactic therapy is given by Johnson (1942) who used lyophilized freshly drawn plasma to try and rehabilitate a patient totally disabled by haemophilia. He gave weekly injections of 125 c.c. plasma for three months and claimed that during the greater part of the treatment the patient was completely free of haemorrhage. We do not know what the patient's bleeding frequency was before this treatment. Alexander and Landwehr (1949) reported a similar experience but with fresh plasma. Following these reports the subject of prophylaxis practically disappeared from the literature and a statement by Macfarlane, Biggs and Bidwell (1954) that the ultimate goal of treatment with A.H.G. was continuous replacement, stood out almost alone during the fifties.

Trials of prophylaxis:

Few comparative trials of prophylaxis appear in the literature and an M.R.C. report (1974) stated that at that time no properly controlled trial of prophylaxis had been carried out.

Robinson, Tittley and Smiley (1967) gave one unit of cryoprecipitate twice daily for three months then daily for three months to one patient. Bleeding was less frequent on the daily regime and absent on twice daily treatment. Kasper, Dietrich and Rapaport (1970) reported a trial comparing four different regimes:-

a) 250 units per day
b) 2,000 units per week
c) 1500 units three times per week
d) 500 units per day

Schedule 'c' using the most factor VIII gave the best results. By choice, however, they use schedule 'a' and have halved the bleeding frequency in their patients. The trial of Ramsey and Parker (1973) compared nine months on demand therapy with nine months in which six bags of cryoprecipitate were infused prophylactically every week. They found no significant difference in bleeding frequency on the two regimes. The first double-blind controlled trial of prophylaxis was carried out at the Treloar haemophilia centre (Aronstam et al 1976) and showed that infusions needed to be given at least on alternate days to be effective. This work is reported in detail in a later chapter of this thesis. Another controlled trial was carried out by Schimpf, Fischer and Rothmann (1977). They administered 36 units of factor VIII/kg/week to six patients either as a single dose, twice weekly or three times weekly. The results from the last regime were significantly superior to the others.

Other regimes:

The Swedish school maintained that chronic arthropathy could

be prevented if the plasma level of factor VIII could be kept above 3% (Ahlberg 1965). Their first reports were of prophylactic doses of fraction I-O given every two weeks, later modified to individually titrated doses to raise blood levels of factor VIII to 40% and stop them falling below 1% (Nilsson, Hedner and Ahlberg 1976). 300-600 units of antihaemophilic factor at 7 to 10 day intervals was the usual regime. The persistence of factor VIII at measurable levels for 7 to 10 days has not been confirmed by other workers. Further, while many other prophylactic regimes have been described in the literature, only Shanbron and Thelin (1969) have claimed success with an infusion schedule as infrequent as once per week.

Other authors have reported success with prophylactic doses administered more frequently than once weekly. Hirschman, Itscoitz and Schulman (1970) gave infusions 4 to 5 times per week. Levine and Britten (1973) gave 15 units/kg on alternate days. Arnold and Hilgartner (1977) gave infusions 2-3 times weekly, aiming to keep the plasma level about 10% during prophylaxis.

The effect on resources:

It is apparent that most physicians who prescribe prophylaxis use a schedule of at least twice and usually thrice weekly infusions (vide supra). The consequent drain on scarce resources was foreseen by Dallman and Pool (1968) and Abildgaard (1969). Britten (1970) saw prophylaxis as a logistic rather than a scientific problem raising questions about potential supplies of factor VIII. Duthie et al (1972) predicted that it would be economically difficult to provide prophylaxis for many and Breckenridge (1975) maintained that a prophylactic programme would quadruple blood requirements. Aronstam et al (1976) calculated that to reduce bleeding frequencies by two-thirds would require two and a half times more therapeutic material. Arnold and Hilgartner (1977) cited high costs and limitation of supplies as the reason why they could not

recommend prophylaxis for all their patients.

The constraints on supplies of factor VIII have led many physicians caring for haemophiliacs to use prophylaxis predominantly for limited periods to cover increased bleeding frequency, chronic synovitis and intensive physiotherapy (Aronstam et al 1977, Levine and Britten 1973, Hilgartner 1977). Ahlberg (1965) suggested regular prophylaxis between the years 5 and 15 in order to prevent chronic arthropathy although the potential for regular prophylactic therapy appeared remote in the late sixties (Dallman and Pool 1968). The use of prophylaxis in the United Kingdom increased explosively between 1975 and 1976 (Jones et al 1978) and the ideas put forward by Ahlberg (1965) were tentatively supported by Jones (1977). If the statistical evidence the latter author awaits should materialise, then he would recommend a move to a regular prophylactic programme between the years 5 and 15 in the United Kingdom. This would severely test the availability of resources in this country, but the postulated benefits may well outweigh these reservations.

FACTOR VIII SUPPLY AND DEMAND

Biggs (1978a) and Cash and Spencely (1976) have estimated the requirements of factor VIII in the United Kingdom to be around 50,000,000 units/annum. Both these authorities have based their calculations on the annual usage of factor VIII up to and including 1975. For reasons documented below, I believe this figure to be now a very serious underestimate of future requirements:-

a) An explosive growth in prophylaxis (negligible in 1975 in the U.K.) has taken place from 1976 (Jones et al 1978). The use of prophylaxis has been shown to substantially increase the usage of factor VIII; two to four times the amount of factor VIII in current use being required for a prophylactic programme (Breckenridge 1975, Aronstam et al 1976, Arnold and Hilgartner 1977, Schimpf, Fischer and Rothmann 1977).

b) The number of patients on home therapy in the U.K. increased by one third in 1976 (Jones et al 1978). Rizza and Spooner (1977) have shown that patients on home therapy use 15% more factor VIII than those on hospital-based treatment. This increase in material usage may be balanced out by the trend to lower dosages for early bleeds treated at home (Penner, Kelly and Boutagh 1977, Ripa, Scaraggi and Ciavarella 1978, Harris and Stuart 1979). However, the 15% failure rate at low dosage (Harris and Stuart 1979, Stirling and Prescott 1979, Jones 1979), which is not very different from the retransfusion rates for boys at Lord Mayor Treloar College (Rainsford and Hall 1973, Aronstam, McLellan and Turk 1979) cannot be ignored. As the majority of bleeds occur into the knees, elbows and ankles, it is disturbing to contemplate the effect of lowering the dose of factor VIII still further in the 15-20% of joint bleeds which would

have failed to respond even to standard dosage. One must speculate that the arthropathy engendered by the increased amount of blood present for a longer period in these joints would generate chronic arthropathies which, in their initial stages at least, would result in more frequent bleeding.

c) The lengthening haemophiliac life-span is likely to lead to a doubling of the haemophiliac population (Biggs 1978a, Carter et al 1976). The leading of normal lives by haemophiliacs will result in the fathering of many more carriers and thus a second increment of increase in the haemophilic population in two generations (Biggs 1978a).

d) It is self evident that most haemophiliacs who were able to produce children in the past were likely to have been suffering from milder forms of the disease. Because the severity of the disease breeds true in families (Macfarlane 1966) an improvement in survival and therefore of reproductive capacity is likely to bias the haemophiliac population to the severer forms. As the severest 20% of the haemophilic population use 80% of the blood resources (Carter et al 1976) this will have a considerable impact on demand of factor VIII in the future.

e) The treatment of patients with inhibitors to factor VIII has changed in certain respects over the past four years. Patients with low antibody rises following treatment with factor VIII now receive factor VIII for almost all bleeds (Biggs 1978a). This group of patients is not mentioned in recommendations from the same unit two years before (Biggs and Denson 1976).

Meeting the demand:

The Medical Research Council Working Party which reported in 1974 estimated that 550,000 to 750,000 donations of

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blood would be needed to satisfy demands using only the resources of the voluntary Blood Transfusion Service of the National Health Service. Biggs (1978a) calculated that 900,000 donations would be needed to meet the 50,000,000 units of factor VIII which she estimated had been used in 1975. This would require as much as one third to a half of all donations to be fractionated. In the present economic climate the prospects of the National Health Service becoming self sufficient in factor VIII are poor even if the predicted 50,000,000 units per annum are sufficient. If this figure is indeed an underestimate, the prospects are remote.

OTHER FORMS OF TREATMENT

Many different modes of treatment, mainly empirical, have been tried through the years in attempts to control bleeding episodes. They have almost all fallen into disuse, but will be briefly discussed as a group. Only the antifibrinolytics, the vasopressins and the corticosteroids have some credence in current practice and these will be discussed in separate sections.

Earlier treatment:

Otto (1803) maintained that 'an ordinary purging dose of Sulphate of Soda administered two or three days in succession generally stops the bleeding and by more frequent repetition is certain of producing this effect'. It is apparent from a paper by Lane (1840) that leeches were used to treat haemarthroses which at that time were thought to be gout. Not suprisingly, Lane reported some difficulty in staunching the bleeding after removing the leeches!

Legg (1872) in a wide ranging view of practices then current mentioned Lead Acetate, Alum, Mineral Acids, Oil of Turpentine, Gallic Acid, Strychnine, Creosote, Opium, Tincture of Shepherds Purse and Ergot. He himself felt that Tincture of the Perchloride of Iron was the most beneficial especially when accompanied by Magnesium Sulphate. He also emphasized the beneficial effect of the waters of Harrogate "especially as the air there is dry and bracing". Wright (1893) used lime salts and demonstrated shortening of the coagulation time of a haemophiliac for two days following treatment. By the 1920s a range of 'haemostatic' agents were in use mainly consisting of animal protein and producing 'protein shock'. Payne and Sheen (1929) tested the effect of horse serum, calcium, 'Haemoplastin' and 'Coagulation Ciba', and found that none had any effect on the coagulation time.

In more recent times, Lucas (1970) has reported that

hypnosis lessened blood loss after dental extraction. Green and Smith (1972) felt that the well known relief afforded to Alexis the Tsarevich by Rasputin (Massie 1968) may have been due to hypnosis.

Antifibrinolytic therapy:

The active principle of peanuts is a protease inhibitor with an antifibrinolytic activity similar to Epsilon-Amino-Caproic Acid (Astrup et al 1961). Verstraete and Ruys (1967) conducted a six month long double-blind controlled trial on the haemostatic value of an aqueous extract of peanuts on 92 severe haemophiliacs. They found no statistically proved benefit on the bleeding incidence. Strauss, Kevy and Diamond (1965) found no significant reduction in the severity or frequency of bleeding between patients taking E.A.C.A. and those taking a placebo. Others have reported some clinical improvement in patients taking E.A.C.A. (Abe et al 1962, Gordon et al 1965, Mainwaring and Keidan 1965), or Tranexamic Acid (Rainsford, Jouhar and Hall 1973).

Following a carefully controlled trial carried out by Walsh et al (1971) the use of antifibrinolytics as an adjunct to factor VIII therapy has become standard practice in the management of dental extraction in haemophiliacs. These agents have also been recommended for other mouth bleeding episodes such as a bleeding tongue or lacerated frenulum (Hilgartner 1976, Kasper 1976). Antifibrinolytic therapy should not be used in the treatment of haemarthroses since a clot formed with E.A.C.A. or Tranexamic Acid adsorbed to the fibrin strands may not dissolve for many months and may contribute to fibrosis and so to joint destruction (Hilgartner 1976).

Adrenocortical steroids:

Ozsoylu, Strauss and Diamond (1962) found a shortened partial thromboplastin time, prothrombin time and a high level of A.H.G. in a patient with Cushings Syndrome and a high level of A.H.G. in three patients who had been on Prednisolone 60 mg. per day for at least ten days. They put three patients with haemophilia on this regime and demonstrated a marginal increase in the factor VIII levels of the two who had measurable factor VIIIs to start with, but not in the third who did not. Later a controlled trial of steroids showed no effect on the severity of bleeding or the disability (Canale et al 1967). A trial of long term steroid treatment was carried out by Bennett and Ingram (1967) who found the incidence of bleeding in children was reduced. Nevertheless, they felt that the long term side effects did not justify continued use of steroids.

A different approach was adopted by Kisker and Burke(1970). They conducted a double-blind study on the use of steroids in the treatment of acute haemarthroses and demonstrated a clinical effect both on the usage of factor VIII and the time taken for bleeds to resolve. Hilgartner (1976) also maintains that steroids used with replacement therapy at the onset of the haemarthroses are effective particularly in those joints where synovial hypertrophy and synovitis have developed. The use of steroids in the management of chronic synovitis is recommended by Dietrich (1976).

Some authors feel that Prednisolone has a role in the management of haematuria. Gourdeau and Denton (1970) found that the treatment of haematuria with Prednisolone alone was nearly as effective as combined treatment with Prednisolone and Cryoprecipitate. Hilgartner (1976) recommended both. Dietrich (1976) felt that a short course of Prednisolone as an adjunct to factor VIII therapy could be helpful. On the other hand, Biggs and Rizza (1978) stated that in their experience Prednisolone did

not control haematuria.

Vasopressins:

Desamino-Cys-1-8-D-Arginine Vasopressin (D.D.A.V.P.) is a structural analogue of the natural antidiuretic hormone with two changes (Ferring 1977). Mannucci et al (1977) reported that the intravenous infusion of D.D.A.V.P. raised the level of factor VIII in mild and moderate haemophiliacs, allowing surgery to be undertaken without factor VIII cover. No effect on the level of severe haemophiliacs has been found. Other authors have confirmed these findings (Lowe et al 1977, Ingram and Hilton 1977), and there is now a definite place for this material in the management of bleeding episodes in mild and moderate haemophilia but not in severe haemophilia.

REVIEW OF THE LITERATURE

3. THE HAZARDS OF TREATMENT

TRANSFUSION REACTIONS

Plasma and to a lesser extent concentrates of factor VIII contain all manner of substances which may result in transfusion reactions (Hilgartner 1976). The purification techniques used in the preparation of factor VIII concentrates have resulted in a decrease in clinical problems due to reactions (Breckenridge 1975). Nevertheless, reactions to concentrates do occur (Davis, Grizzle and Bryan 1973, Eyster, Bowman and Haverstick 1977) and may be severe (Ahrons et al 1970). A discussion of this subject is therefore presented and the various types of reactions will be reviewed in relation to the component thought to cause them.

Whole plasma:
The sheer volume of plasma required to achieve safe haemostatic levels of factor VIII using plasma infusions occasionally led to a patient suffering from hypervolaemia (Biggs 1978b). The use of concentrated preparations of factor VIII has eliminated this problem.

The 'protein load':
Hilgartner (1976) believes that headache and abdominal pain are directly related to the speed of transfusion and are probably due to the protein load infused. She suggests that the change in plasma osmolarity induces a vascular fluid expansion responsible for the immediate distress and therefore advocates a slow infusion of concentrate. Anaphylactic and febrile reactions occurring more frequently in plasma than in cryoprecipitate and occasionally in other concentrates were thought by Davis, Grizzle and Bryan (1973) to be due to denatured protein.

White blood corpuscles (W.B.Cs):
Urticaria, pyrexia, bronchospasm, pulmonary congestion and even death have been reported following plasma infusions and have been attributed to white cell antibodies (Kernoff et al 1972). Fever, chills and urticaria have been

attributed to white cell and platelet contamination of infused plasma by Hilgartner (1976). Reese, McCullough and Craddock (1975) have reported an acute pulmonary disorder said to be due to white cell antigens in cryoprecipitate.

Pyrogens:

Pyrexia may be due to pyrogens in the anticoagulant fluid or infusion apparatus. If unaccompanied by back pain or urticaria it is unlikely to be serious, but if more severe it may be the first sign of sensitivity to plasma protein (Tovey and Bird 1974). Injections of crude concentrates of animal factor VIII commonly caused pyrogenic reactions in the early days of specific coagulation factor therapy. These reactions were probably due to materials extracted from rubber tubing (Biggs 1978b).

Immunoglobulins:

The presence of antibodies reacting with antigens carried by human gamma-globulin is found not infrequently after transfusions (Tovey and Bird 1974). Prentice et al (1971) reported a haemophilic patient with an anti-GM(1) antibody who following plasma transfusions had repeated severe reactions and exacerbations of proteinuria. Although the reactions no longer developed when GM(1) plasma was avoided, he developed a nephrotic syndrome and died of renal failure. At autopsy extensive amyloid deposition was found in liver and kidneys and the authors postulate repeated stimulation of the immune system as a cause. Breckenridge (1975) also noted a patient with fatal amyloid kidney disease who had received more than 1,000 transfusions during his life. The relationship of these phenomena to the raised IgM and IgG levels described by Wardle (1967) in 25% of haemophiliacs is unclear.

Anti-IgA is present in low titre in the serum of 2% of persons (Tovey and Bird 1974), and is potent in the serum of some patients suffering from conditions in which there is a low level or total absence of IgA globulin (Vyas,

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Perkins and Fudenburg 1968). Multitransfused haemophiliacs may develop anti-IgA to an antigenic determinent of IgA globulin which they do not themselves possess. When transfused with plasma containing incompatible IgA the patient with high-titre anti-IgA may react alarmingly with severe erythema and anaphylaxis (Tovey and Bird 1974). The severity and danger of these reactions was stressed by the Medical Research Council's blood transfusion research committee (1974).

Insoluble debris:

Eyster and Nau (1978) showed that both cryoprecipitate and freeze-dried concentrates of A.H.F. contained a significant amount of debris which could be filtered out when the material was passed through 40 μ screen. The standard 170 μ screen did not filter the material. Boese, Tantum and Eyster (1979) were able to demonstrate a significant decrease in the single breath carbon monoxide diffusing capacity (D_L CO_{SB}) in five of six patients thirty minutes and six hours after infusion of factor VIII-containing material. Two patients restudied using a 40 μ filter showed no such reduction.

Reactions consisting of bronchospasm, dyspnoea, chest pain and hypotension which have occurred following infusion of A.H.F. concentrate could be an allergic reaction to some component of the concentrate or could possibly be due to pulmonary embolization from the abundant insoluble debris known to be present in the A.H.F. (Eyster, Bowman and Haverstick 1977). The D_L CO_{SB} could usefully identify the blockage of pulmonary capillaries, as by emboli, in this situation (Boese, Tantum and Eyster 1979).

Haemolysins:

Factor VIII concentrates are derived from large pools of plasma and contain Anti-A and Anti-B haemolysins which cannot be totally removed during processing. Large infusions of factor VIII can therefore produce haemolysis in patients with A, B or AB type blood (McMillan, Diamond

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and Surgenor 1961, Marder and Shulman 1966, Shulman et al 1967, Aledort 1977).

TRANSFUSION-INDUCED BLEEDING DIATHESIS

A secondary bleeding diathesis may occur in haemophiliacs during intensive therapy with factor VIII (Hilgartner 1977, Bark and Orloff 1972, Hathaway et al 1973). Abnormalities of platelet function and parameters of coagulation have been described.

Platelet function abnormalities:

Borchgrevink (1961) showed that haemophiliacs developed a prolonged bleeding time after multiple transfusions which took about two weeks to return to normal following cessation of transfusion. In-vivo platelet adhesion was markedly reduced. Hathaway et al (1973) found prolonged bleeding times, diminished adhesion and diminished release of platelet factor 3 (PF3) following intensive transfusion of cryoprecipitate or lyophilised commercial concentrates. They administered cryoprecipitate during a non-bleeding state and demonstrated a prolonged bleeding time, diminished adhesiveness and abnormal aggregation of platelets with adenosine-diphosphate (ADP). Gamba et al (1975) studied five patients with severe haemophilia after replacement therapy and showed diminished adhesion and aggregation of platelets.

Abnormalities of coagulation:

Hathaway et al (1973) found prolongation of the thrombin time (TT) and partial thromboplastin time (PTT) in association with high levels of fibrinogen and fibrin split products (FSP). Gamba et al (1975) found high levels of fibrinogen and FSP after intensive factor VIII therapy which was partially reduced by the administration of Epsilon-Aminocaproic Acid (EACA). Bark and Oloff (1972) also found a prolonged TT and PTT in a patient whose factor VIII level was being maintained between 60% and 130% by intensive transfusion. Their patient had an unexplained episode of bladder haemorrhage while the factor VIII levels were near 100%.

Underlying mechanism:

Most preparations of factor VIII for clinical use contain a high proportion of fibrinogen (Bidwell, Dike and Snape 1976). Fibrinogen has a half life of about 80 hours and thus the fibrinogen concentration would rise steadily when A.H.G. is given frequently over a prolonged period (Forbes et al 1969, Hilgartner 1977). Platelets have diminished adhesion and aggregation in the presence of high levels of fibrinogen, probably because the fibrinogen coats the platelets, changing their surface and making them non-adhesive and non-aggregable in vivo (Borchgrevink 1961, Hathaway et al 1973).

Takeda and Chen (1967) using autologous ^{131}I-Fibrinogen studied the metabolism and distribution of fibrinogen in ten patients with haemophilia A and concluded that the deviation from normal which he noted was due to the host condition of increased fibrinogen breakdown. This may at least partially account for the high levels of FSP noted in haemophiliacs during intense transfusion with factor VIII (Hathaway et al 1973, Gamba et al 1975). FSP are known to interfere with platelet function (Kowalski, Kopel and Wegrzynowicz 1964, Hardisty 1976, Pitney 1974).

Grignani et al (1978) showed that high levels of factor VIII concentrate produced a significant increase in the maximum amount and the speed of aggregation and could cause releast of ^{14}C Serotonin. Factor VIII concentrate may, therefore, have a direct stimulating effect on human platelets and the presence of 'exhausted' platelets may contribute to the bleeding diathesis.

Finally, high levels of fibrinogen, FSP or fibrin monomers may interfere with the polymerization of fibrinogen and thus interfere with the basic clotting tests such as TT, PT and PTT (Hathaway et al 1973).

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haemophilia centre Directors remained constantly between 6 and 7% (Biggs and Spooner 1977a). A study funded by the National Heart and Lung Institutes Blood resource programme (1973) gave a figure of 4.3% while Kasper (1976) stated that about 8% of patients in her practice developed antibodies. An incidence of 5-10% (Pool 1975) appears to encompass current views. Earlier discrepancies may be related to differences in the laboratory methods and could reflect different referral patterns.

Type of material transfused:

The first demonstration of an anticoagulant in the plasma of a patient was made long before the advent of concentrated preparations of factor VIII (Lawrence and Johnson 1942). The first reports of antibodies developing after cryoprecipitate appeared shortly after its introduction (Hattersley 1966, Besselaar et al 1966), and of course most severe haemophiliacs who develop antibodies at the present time would have received other concentrated preparations of factor VIII. Thus antibodies may develop after plasma, cryoprecipitate or other concentrates of factor VIII being infused. Patients who have received concentrates appear to be no more liable to develop antibodies to factor VIII than those who have received plasma only (Brinkhous, Roberts and Weiss 1972).

Amount of material transfused:

Strauss (1969) showed that all his cases of high level antibodies developed after 20-90 exposure days to factor VIII while the milder forms arose after 100 exposure days. There appears, therefore, to be some relationship between the amount of exposure to factor VIII and the development of an antibody (Abildgaard 1976). It is thus possible that a greater incidence of antibody might have resulted from increased use of factor VIII over the past decade. However, Biggs (1978b) has pointed out that the incidence of anti-factor VIII antibodies in the U.K. did not rise between 1969 and 1974 although the amount of treatment

A small number of patients with haemophilia A will develop a substance in their plasma which progressively neutralises or destroys factor VIII, and which is undoubtedly an antibody (Biggs and Denson 1976). This development presents serious problems in the management of affected patients (Abildgaard 1976). Shapiro (1975) has pointed out that it is probably the single condition most often associated with fatal outcome of a bleeding episode. The same author has stressed that with almost no exceptions factor VIII antibodies arise in haemophiliacs only after transfusions of factor VIII-containing materials. It is thus an important potential hazard of factor VIII therapy in haemophiliacs. The incidence of this complication and development in relation to the type and frequency of transfusion will therefore be reviewed. The important questions of the kinetics of the antigen-antibody reaction and the clinical management of patients with antibodies are beyond the scope of this thesis.

Incidence:

Strauss (1969) found an overall incidence of 12% of patients with antibodies to factor VIII in his 143 patients. This figure rose to 21% when he considered only those patients with no demonstrable factor VIII. It is possible, however, that some of his patients may have had demonstrable factor VIII before their antibodies developed. Margolius, Jackson and Ratnoff (1971) gave the incidence as 21% out of 84 haemophiliacs while Biggs and Macfarlane (1962) found only 6 patients with antibodies out of 300 families. Hardisty and Ingram (1965) agreed substantially with these figures, but by then the incidence of antibodies in the practice of Biggs and Macfarlane had risen to 7% (Biggs 1966). These figures were based on in-patient attendances and therefore dealt with the more severely affected patients. The true incidence could well have been lower. Over the years 1969 to 1974 the incidence in the U.K. based on the observed incidences of antibodies to factor VIII reported by

given to patients did. The development of antibodies in individuals therefore appears to increase over the first 100 exposure days but then drops off.

ACUTE HEPATITIS

In this section acute hepatitis is taken to mean a clinical syndrome characterized by jaundice, gastro-intestinal symptoms and pyrexia, associated with transfusions and of presumed viral etiology. It may rarely be due to type A or short incubation hepatitis. It is often due to type B hepatitis and is recognised increasingly frequently as being due to a type or types of hepatitis which are neither A nor B.

Hepatitis has always been a risk for the patient with haemophilia who required therapy with plasma or plasma products (Breckenridge 1975, Hasiba, Spero and Lewis 1977, Biggs 1974), but the risk increased markedly with the introduction of pooled concentrated preparations of factor VIII (Bryan et al 1969, Kasper and Kipnis 1972). Many of the earlier reports of transfusion-related hepatitis concerned patients who had received concentrates derived from large plasma pools (Davidson 1949, Cronberg, Belfrage and Nilsson 1963).

The introduction of cryoprecipitate in 1965 (Pool and Shannon 1965) was followed by a spate of reports of hepatitis following the administration (Besselaar et al 1966, Del Duca and Eppes 1966, Forbes et al 1969). Davis, Grizzle and Bryan (1973) applying maximum likelihood methods of statistical analysis showed that glycine precipitated A.H.F. and fibrinogen fraction A.H.F. prepared from large donor pools carried a higher risk than cryoprecipitate which in turn carried a higher risk than whole plasma. The incidence of hepatitis in patients using the Swedish factor VIII rich fraction I-O incorporating plasma from 600-1,000 donors was reported in 1963 as 14% (Cronberg, Belfragg and Nilsson 1963). The incidence in the U.K. over the years 1969-1971 on the other hand was reported as 3.48% for all patients (Biggs 1974). These figures are not comparable with the Swedish figures as they included patients treated only with single donor plasma.

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Hepatitis B:

Blumberg (1964) first described an unusual antibody in the serum of a transfused haemophiliac which was also found in the blood of a proportion of patients having viral hepatitis. It was in fact found to be directed against the surface of an antigen associated with the long incubation type of virus hepatitis infection. The antigen is now called HB_sAg and its antibody HB_sAb. The development of increasingly sensitive screening tests for HB_sAg and the exclusion of positive blood from plasma pools has greatly reduced the incidence of hepatitis B in haemophiliacs (Biggs 1978b). However, using counter-electrophoresis to exclude positive donors, Alter et al (1972) still found a 3.7% incidence of hepatitis of which six out of ten were HB_sAg positive. Even using the more sensitive radio-immunoassay (R.I.A.) only 60-80% reliability may be expected (Hilgartner 1976) and the radio-immuno assay gives an undefined proportion of positive results in samples that apparently do not contain virus (Biggs 1978b). Other outbreaks of HB_sAg positive hepatitis following the use of lyophilised concentrates (Craske, Dilling and Stern 1975) emphasize this continuing problem.

The exposure of multitransfused patients to HB_sAg is far more widespread than the incidence of acute hepatitis would lead us to suspect. Seeff and Hoofnagle (1977) pointed out that while less than a quarter of adult haemophiliacs had a history of acute hepatitis, more than three quarters of them could be shown by serologic tests for HB_sAg or Ab to have been exposed to type B hepatitis. Breckenridge (1975) stated that 100% of his patients were positive for HB_sAb or Ag. This high degree of exposure in the presence of routine screening is likely to be due to the use of very large pools for production of starting plasmas for concentrated preparations of factor VIII (Hilgartner 1977) and to the concentration of the antigen in cryoprecipitates of plasma (Gocke and McIntosh 1973, McIntosh, Koss and Gocke 1976) which apart from their use as single units for treatment, are often the starting points

for the preparation of concentrates (Keckwick and Wolf 1957, Pool and Shannon 1965, Newman et al 1971). Perhaps screening of the cryoprecipitates of donor plasmas for HB_sAg would produce more satisfactory exclusions.

Because exposure to HB_sAg is so widespread in multitransfused patients, the implications need to be considered in a much broader concept than just that of HB_sAg positive acute hepatitis.

The consequences of exposure to HB_sAg:

There are a variety of responses to exposure to hepatitis B virus in human beings (London 1977).

a) Acute hepatitis which may resolve completely or progress to chronic hepatitis

b) Asymptomatic infection with little or no liver damage, transient production of HB_sAg and the development of protective titres of anti HB_s. This result is obviously the ideal.

c) Asymptomatic infection with little or no liver damage, persistent production of HB_sAg, minimal synthesis of anti HB_s and a minimal or no cellular immune response to HB_sAg. These patients become chronic carriers.

d) Chronic hepatitis including chronic persistent hepatitis (C.P.H.) and chronic aggressive hepatitis (C.A.H.) Post-necrotic cirrhosis and probably primary hepato-cellular carcinoma may occur as sequelae.

e) Persistent production of hepatitis B viral antigen and antibody to surface (and probably core) antigens. Antigen/antibody complexes develop that bind and activate complement producing tissue damage primarily in the vascular system. A number of disease syndromes may result, and are now briefly reviewed.

Immune complex diseases associated with HB_sAg:

a) Mixed cryoglobulinaemia:
HB_sAg or HB_sAb or both were found in the cryoprecipitates of fourteen out of 19 patients with this condition (Levo et al 1977). The major complaints were purpuric rash, arthralgia and weakness and rapidly progressive glomerulonephritis was the most serious aspect of their disease.

b) Polymyalgia rheumatica (P.M.R.):
Nine out of twelve patients with this condition were positive for HB_sAg (Bacon, Doherty and Zuckerman 1975). They presented with raised immunoglobulins which fell on treatment with steroids suggesting an immune basis for this disease. The vasculitis of P.M.R. is thought to be due to the deposition of immune complexes of HB_sAg and Ab.

c) Membranous glomerulonephritis:
Combes et al (1971) described a patient with persistent HB_sAg post-transfusion hepatitis who developed membranous glomerulonephritis. Immunofluorescent scanning of kidney tissue revealed glomerular deposits of IgG, C_3 components of complement and HB_sAg in a pattern characteristic of immune complex deposition.

d) Polyarteritis Nodosa:
Four out of eleven patients with this condition were also found to be HB_sAg positive (Gocke et al 1970). They exhibited a typical polyarteritis syndrome and also had evidence of mild hepatic damage. Circulating immune complexes were demonstrated in the sera of three of these patients and these complexes were found to be composed of HB_sAg and immunoglobulin. Immunofluorescent studies of tissue from one of these patients revealed depositions of HB_sAg, IgM and B_1C in vessel walls and this deposition was presumably the cause of the diffuse vasculitis.

e) Papular Acrodermatitis of childhood:

This is an infective disease characterized by a recognisable skin eruption localised to the face and limbs, by lymphadenopathy and by an acute hepatitis always associated with HB_sAg (Gianotti 1973). Thirty-two children had liver biopsies which showed acute hepatitis during the dermatitis phase and six months later were either normal or showed C.P.H. (Jean et al 1967). This condition occurs almost exclusively in children who are initially HB_sAg negative and thus appears to represent the naturally occurring form of hepatitis B. Possibly manifestations may only appear when the infection is acquired by cutaneous or mucous membrane routes and may be of little consequence in the multitransfused haemophiliac.

Non-A, Non-B hepatitis:

Alter et al (1972) described four cases of short incubation, HB_sAg negative hepatitis following transfusion of blood previously screened for HB_sAg by counter-electrophoresis. The introduction of commercial factor VIII lyophilised concentrates was followed by at least three separate outbreaks of hepatitis among haemophilic recipients and both hepatitis B and non-hepatitis B varieties were implicated and two patients contracted both types (Craske, Dilling and Stern 1975). Nine episodes of short incubation hepatitis were observed during five years in six haemophiliac children after infusion of commercial factor VIII concentrates prepared by two different manufacturers (Hruby and Schauf 1978). Cytomegalovirus, Epstein-Barr virus and Toxoplasma virus were excluded as were hepatitis A and B. They suggested infection with one or more non-A, non-B hepatitis agents associated with factor VIII concentrates. One form has been called hepatitis E (Hilgartner 1977). Whatever the nomenclature, this form of hepatitis is as likely to progress to chronic hepatitis as the hepatitis B variety (Spero et al 1978, Seeff et al 1975) and is therefore at least as important.

CHRONIC HEPATITIS

Disordered liver function tests:

Mannucci et al (1975) studied 91 severely affected patients who had not been transfused for at least two weeks. All had been exposed repeatedly to factor VIII preparations. They found a high incidence of abnormal liver function tests (L.F.Ts) which increased with age, was not correlated with a history of jaundice and was not associated with overt illness. 8% of their patients were positive for HB_sAg and 66% were positive for HB_sAb. Hilgartner and Giardina (1977) found that while 2% of their patients had overt liver disease 52% had chemical liver dysfunction. Levine et al (1977) reported that 68% of their patients had persistently abnormal L.F.Ts and Preston et al (178) found persistently abnormal L.F.Ts in 53% of their patients. Out of 120 patients studied by Spero et al (1978) 40% had persistently abnormal L.F.Ts.

Relationship to frequency and volume of transfusions:

Levine et al (1977) compared 100 patients treated with a variety of large pool concentrates in North America with 33 English haemophiliacs treated only with wet frozen cryoprecipitate from selected HB_sAg negative donors. Within each group the presence of abnormal L.F.Ts was not correlated with intensity of treatment. However, 68% of the American group had abnormal L.F.Ts and they received 34,500 units of factor VIII per patient per annum. The British group who only received 25,630 units per patient per annum had only 48.5% L.F.T. abnormalities. The significance of this difference is uncertain because the two groups were receiving two different types of preparation.

Hilgartner and Giardina (1977) compared patients receiving episodic treatment with those receiving prophylaxis and concluded that abnormal liver function tests occurred more frequently in those patients receiving prophylaxis at high levels than those on lower doses of prophylaxis and those

on episodic treatment. Mannucci et al (1975) found that the incidence of liver function abnormalities increased with age and presumably, therefore, with increasing exposure to factor VIII-containing preparations.

Histological abnormalities:

With the proliferation of reports detailing abnormal liver function tests it has become increasingly important to study the relationship of the histological appearance of the liver to the chemical abnormalities in the blood. There has been understandable reluctance to undertake a procedure such as liver biopsy in severe haemophilia. However, the safety of the procedure under adequate A.H.G. cover was demonstrated by Lesesne et al (1977) and three other series of liver biopsies in severe haemophiliacs were reported in the following year (Preston et al 1978, Mannucci et al 1978, Spero et al 1978). A total of 38 biopsies were studied in these four series, all done on severe haemophiliacs who had persistently abnormal L.F.Ts for at least the previous six months. One hundred per cent showed histological abnormality of which 47% showed the appearances of C.P.H. 34% showed C.A.H. and 18% showed at least some progression to cirrhosis.

It appears therefore that at present about half of all severely affected haemophiliacs have persistently abnormal liver function tests and more than half of these will have histological evidence of serious chronic liver disease. This bleak picture has developed in spite of the use of increasingly sophisticated screening tests for HB_sAg and donor blood. We now know that blood containing HB_sAg diluted to such an extent that the antigen is no longer detectable by R.I.A. may nevertheless induce hepatitis in laboratory animals (Alter et al 1978). We also know that even if HB_sAg could be eliminated non-A, non-B hepatitis would still be capable of inducing chronic liver damage (Spero 1978). The addition of a further chronic disabling disease to the lot of patients already suffering from

severe haemophilia is a therapeutic catastrophe and will be a major concern to those concerned with the transfusion therapy of haemophiliacs for some time to come.

EFFECT OF TRANSFUSION ON OTHER SYSTEMS

Urogenital system:

The effect of large volumes of protein load on multiple organs in the body is unknown. Since the kidney is the ultimate filter of proteins, renal dysfunction secondary to deposition of these proteins in the glomeruli has been postulated (Lazerson 1976). Combes et al (1971) had earlier described a patient with persistent HB_sAg after post-transfusion hepatitis who developed membranous glomerulo-nephritis. Immununofluorescent staining of kidney tissue revealed glomerular deposits of IGg, the C_3 component of complement and HB_sAg in a pattern characteristic of immune complex deposition. Later Levo et al (1977) stated that rapidly progressive glomerulonephritis was the most serious aspect of their patients with essential mixed cryoglobulinaemia, many of whom were positive for HB_sAg or HB_sAb.

Cardiovascular system:

Weisz and Kasper (1977) reported a retrospective survey from three large centres which compared blood pressure measure-ments in 233 haemophiliac patients with factor VIII:C levels of under 3% with published studies of blood pressure measure-ments in normal males. They found significantly higher diastolic blood pressures in 10-39 year old group of haemophiliacs, which were not correlated significantly with haematuria or the amount of factor VIII used. They suggested that hypertension might be a significant contributing factor to the high incidence of death from central nervous system bleeding in haemophilia. Although these authors do not implicate blood products as a cause, they advance no other theory and if their results are confirmed, the role of blood products is not yet excluded.

Reticulo-endothelial system:

Splenomegaly was found in more than 25% of patients and was correlated significantly with the volume of treatment by Levine et al (1977). They postulated that continuous bombardment with foreign antigens and possibly antigen/

antibody complexes caused reticulo-endothelial hyperplasia leading to splenomegaly. The long term effects of reticulo-endothelial hyperplasia are not clear, but one obvious disadvantage to the haemophiliac would be the effect of hypersplenism on the haematological system.

Endocrine system:

Bem et al (1979) found a positive correlation between the height and bleeding frequency in adolescent haemophiliacs. While it is possible that taller boys exercise more stress on their joints and muscles, it is also possible that tall posture could be the result, not the cause, of more frequent bleeds. Pierson and Temin (1972) have shown the presence of growth factors in plasma, which could contaminate factor VIII-containing preparations.

REVIEW OF THE LITERATURE

SUMMARY AND DISCUSSION

SUMMARY AND DISCUSSION

Haemophilia - The Disease:

Having traced the history of the disease and the growth of understanding of its nature we find predictions of a steady increase in the haemophiliac population possibly biased towards the severer forms. Meticulous observations have revealed a clear link between the clinical severity of the disease and the factor VIII level, an observation which has played a central role in current therapeutic regimes. There is general agreement that the commonest sites of bleeding are the knees, elbows and ankles. Most authors put the knee at the head of the list, but it appears that the relative frequency of bleeds into the ankles and elbows varies with age, ankle bleeds declining and elbows bleeding increasing. Age appears to play a role also in the severity of bleeds which are worst in adolescence. A composite clinical description of the acute haemarthroses is given, the reasons for the frequency of bleeding into the knees, elbow and ankle is explored and finally the literature on the pathogenesis of haemophilic arthropathy is reviewed.

Systemic treatment of bleeding episodes:

The history of replacement therapy with whole blood and plasma is traced from the first transfusion into a haemophiliac in 1840 to the observations which led to the development of cryoprecipitate in 1965. The literature on the development of concentrated preparations of factor VIII is traced from the observations of Keckwick and Cohn in 1946 to the recent development of high potency concentrates. The post-transfusion level of factor VIII achieved and the decay of that activity have major implications for therapeutic regimes of which there are many. The important inter-related developments of home therapy and prophylaxis are discussed and the major demands prophylaxis makes on therapeutic resources are emphasized. A discussion on the supply of and demand for factor VIII

follows and predictions of increasing demand plus limited resources paint a gloomy prospect. Finally, other forms of treatment are reviewed and the conclusions are drawn that while steroids, anti-fibrinolytics and vasopressins have some role to play to play in the treatment of haemophilia, there is no drug available to replace factor VIII in the treatment of bleeding episodes in severe haemophiliacs without inhibitors.

Hazards of treatment:

Transfusion reaction due to plasma volume, the 'protein load', antibodies to white blood corpuscles, immuno-globulins and haemolysins are reviewed. Some authors claim that insoluble debris may cause pulmonary embolisation and there is an appreciable amount of literature covering transfusion-induced bleeding diatheses. The role of transfusion in the induction of antibodies to factor VIII is discussed before the major problem of hepatitis is reviewed. Acute hepatitis may be due to type A, type B or non-A, non-B types of hepatitis virus. The widespread exposure to HB_sAg is commented on and various disease syndromes associated with the presence of HB_sAg are reviewed. The subject of chronic hepatitis is considered under the headings of disordered liver function tests, their relationship to frequency of transfusion and the histological appearances as shown by liver biopsy. The final section deals with the effect of transfusion on the urogenital, cardiovascular, reticulo-endothelial and endocrine system.

DISCUSSION

It is apparent from this literature review that the natural history of severe haemophilia is relentless progression to crippling. The institution of replacement therapy was at first reserved for life threatening bleeds and then gradually became more freely available to treat bleeds involving the locomotor system. However, crippling continued to be an

accepted consequence of the disease until the principles of early and adequate treatment became widely understood.

As preparations of factor VIII became more freely available, so reports of undesirable side effects became more and more frequent, culminating in the realisation that widespread parenchymal liver disease appeared to be a direct consequence of transfusion therapy. Many other immediate and delayed hazards have been described. While no really convincing evidence has been presented to link the majority of undesirable side effects to the quantity of factor VIII transfused, it is logical to look for the lowest dose of factor VIII likely to be clinically effective.

Further constraints on the amounts of factor VIII that should be used are imposed by the increasing haemophiliac lifespan, the predicted bias towards severer forms in the haemophiliac population and the increased usage of factor VIII brought about possibly by home treatment and certainly by prophylaxis.

A scarce and potentially harmful preparation must be used rationally and the enormous benefits to the haemophiliac of adequate factor VIII make the sensible use of this preparation vital. It is against this background that the work on this thesis is presented. The study of patterns of bleeding and transfusion requirements in adolescent haemophiliacs has been undertaken to identify situations where intensive treatment may make the long term outlook more favourable. The double-blind controlled trials of prophylaxis have been undertaken to crystallize the benefits and rational use of this expensive form of treatment.

Finally, the double-blind controlled trial of different dose regimes and the analysis of the effects of site, severity, targeting and movement restriction on these regimes is intended to identify both high risk situations where a higher initial dose of factor VIII may be indicated and also low risk situations where lower initial doses may be effective.

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ORIGINAL WORK

1) THE ENVIRONMENT IN WHICH THE WORK HAS BEEN DONE

THE TRELOAR HAEMOPHILIA CENTRE

Introduction:
The component parts of the Treloar Haemophilia Centre are found in the Lord Mayor Treloar College and the Lord Mayor Treloar Hospital. Information about the history and development of these institutions has been obtained from "The story of the Lord Mayor Treloar Trust" (Evans 1968) and from the Lord Mayor Treloar College Prospectus (1978). College and hospital records have also been studied, and several ex-college haemophiliacs responded to an appeal for information about the treatment of the first haemophiliacs at the College.

Lord Mayor Treloar:
William Purdie Treloar was born on the 13th of January 1843 in Southwark, the son of "an entirely honest merchant". He worked his way through every department of his father's factory and entered public life in his late thirties when he was elected to the Common Council. The beginning of his public work for the poor and disabled children of London came in 1892 with the Christmas Hamper Fund, a small project which involved the sending of hampers of food and drink to disabled children in London in the New Year. In the same year Treloar was elected Alderman of the Ward of Farringdon and seven years later he was appointed Sheriff of London. He became Lord Mayor of London in 1906 and during his mayoral year he raised £60,000 to found an institution which would do lasting good for London's disabled children.

The Lord Mayor Treloar Cripples Hospital and College:
Two blocks of wooden buildings which had been erected as a hospital for soldiers wounded in the South African war were standing empty at Alton in Hampshire in 1907, and were transferred to the Treloar Fund. The old buildings were first named the Lord Mayor Treloar Cripples Hospital and College. The hospital opened on September 7th 1908 with Dr. Henry Guavain as the first resident medical officer. Shortly afterwards on the 26th of October 1908, the first boys entered the College and after a few months the full

complement of 60 was reached. The twin institutions grew steadily, the hospital being completely rebuilt between 1930 and 1936. Treloar himself died in 1923. The College and hospital establishments worked side by side complementing each others work until the coming of the National Health Service in 1947.

The independent College:

When the hospital passed into the control of the Ministry of Health in 1947, the College remained independent under the control of the trustees and was then known as the Lord Mayor Treloar College. It remained for six more years in its original buildings in the hospital grounds and then in 1953 moved from the old wooden buildings at Alton to new premises in nearby Froyle. The first term at Froyle began with 44 boys - one for each full year of the College's previous existence. By 1954 there were 61 boys in the College new buildings, which had been planned to accommodate another 70 boys, were opened in 1956. The new larger intake in September of that year included for the first time three haemophiliac children.

The Florence Treloar School for girls was built at Holybourne, in between Froyle and Alton and opened in 1965. The school was named after Sir William Treloar's adopted daughter and provided accommodation and education for 60 handicapped girls with the possibility of expansion to 100. The two schools became one co-educational unit in 1978 with the upper school at Holybourne and the lower school at Froyle. The whole unit is now named the Lord Mayor Treloar College.

The Lord Mayor Treloar Hospital:

The transfer of the hospital to the National Health Service in 1947 did not alter its fundamental commitment to the practice of orthopaedics. Up until the present time the hospital has remained primarily an orthopaedic hospital and has developed into the Wessex Regional Orthopaedic Centre, with consultants coming from all over the Wessex

Region to operate on their own patients at Treloars. At various times since 1948 the hospital has had beds for general medicine and general surgery and the Lord Mayor Treloar College sent its haemophiliacs for treatment to the hospital until 1978.

The Treloar Haemophilia Centre:

The first haemophiliacs entered the College in 1956 and their numbers grew steadily over the next ten years. Thirty one cases, many with major deformities of long standing, boarded at the College in 1965 (Britten et al 1966). Treatment with plasma was available on request at Lord Mayor Treloar Hospital and a local general practitioner undertook the care of the boys at the College usually without any form of replacement therapy for a bleed. With the appointment of Dr. S.G. Rainsford as Research Fellow in 1968, the treatment of haemophilia at the College entered the modern era. The post was created with the support of Doctors Rosemary Biggs and Kathleen Dormandy and was linked with the Oxford Haemophilia Centre. Approximately 900 transfusions were given to College pupils during the years 1970 and 1971, about 90% of which were given at the Lord Mayor Treloar Hospital (Rainsford and Hall 1973). During these years, Dr. Rainsford bore this considerable clinical commitment on his own and at the same time, established a haemophilia research laboratory at Lord Mayor Treloar Hospital. By this time, the number of boys with haemophilia at the College had reached 40.

The Treloar Haemophilia Centre was established in 1972 under the Directorship of Dr. P.G. Arblaster with Dr. A. Aronstam as Associate Director.

Over the next five years the number of haemophiliacs at the College increased to over 50 and by 1977, 2,000 transfusions were being given annually. A haemophilia ward had been established at the hospital shortly after the designation of the Centre and the majority of bleeds were treated there having first been seen by medical staff

at the College. In 1977, Dr.A. Aronstam became Director of the Centre, and one year later all treatment facilities were transferred to the Upper School at Holybourne.

The Haemophilia Centre at present is directed by Dr. A.Aronstam with two full-time medical officers assisting. The Treloar College Upper School Sick Bay is staffed with one Sister and thirteen part-time nurses. Four of these are dedicated to the treatment of haemophilia and are competent to transfuse haemophiliacs. Boys with fresh bleeds or those being followed up are seen by medical staff in the Sick Bay wing. Those needing transfusions either transfuse themselves or are transfused by nursing staff. Those needing bed rest are admitted to the 10 bedded sick bay unit. The haemophilia laboratory and secretarial suite are located at Lord Mayor Treloar Hospital and the laboratory and clinical facilities of a district general hospital are available at Basingstoke. A consultant orthopaedic surgeon, Mr. F.J. Moynihan, sees cases at a joint clinic weekly and major orthopaedic and bleeding problems may be referred to the Haemophilia Centre and the Nuffield Orthopaedic Centre at Oxford.

ORIGINAL WORK

2) BLEEDING EPISODES IN HAEMOPHILIACS AT THE LORD MAYOR TRELOAR COLLEGE BETWEEN 1973 AND 1977

INTRODUCTION

The frequency of bleeding in haemophiliacs is known to change with age (Stuart et al 1966). An important time for these patients may be during the physical strains of adolescence. Teenage haemophiliacs are likely to be more active nowadays than those included in earlier surveys because modern treatment has increased the physical capabilities of young adolescents. The pattern of bleeding in young haemophiliacs has therefore been examined in the hope that it would yield new information which might influence their management.

The transfusion requirements of haemophiliacs in this country have been escalating steadily (Biggs and Spooner 1977a, 1977b) thus rapidly outdating successive forecasts of future requirements. A haemophiliac population bulge exists between the ages of 10 and 19 years (Biggs and Spooner 1977a) and close observation of the transfusion requirements of a group of severely affected adolescent haemophiliacs should yield information which may help in the prediction of future requirements. An analysis of the transfusion requirements for bleeds at specific sites may also be helpful in the planning of dose requirements for bleeds at those sites.

During school terms, the haemophiliac boys at Lord Mayor Treloar College are under constant medical supervision and all bleeding episodes and transfusions are fully documented. All bleeding episodes occurring in severely affected pupils with haemophilia A between the years 1973 and 1977 have been analysed and the patterns of bleeding and transfusion requirements have been documented.

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PATIENTS AND METHODS

Eighty two boys with haemophilia A were studied. All had less than 1% of average normal factor VIII:C detectable in their plasma. Haemophilia was diagnosed on the basis of a classical family history or the presence of normal amounts of factor VIII:RAG, or both, associated with a reduction of factor VIII:C and a normal aggregation response of platelets to ristocetin.

All the case records of the boys with severe haemophilia A who spent some time at the College between 1973 and 1977 have been reviewed. Each bleeding episode has been documented and the following information recorded with each episode has been extracted:-

Name
Age
Weight
Site of bleed
Number of transfusions
Units of factor VIII given at each transfusion

Each transfusion was of cryoprecipitate, National Health Service factor VIII concentrate or commercial factor VIII concentrate and was recorded as a single transfusion irrespective of dose. The strength of cryoprecipitate which was supplied by the Wessex Regional Transfusion Service at Southampton was monitored by frequent assays of recovery in vivo and assay of the bags in vitro. On this basis each donor unit was assumed to contain 75 international units of factor VIII in the years 1973 to 1975 and 100 international units in 1976 and 1977.

Bleeding frequency was calculated by recording all episodes that occurred while the boys were at the College and expressing them as the number of bleeding episodes/100 boy-days observed (Rainsford and Hall 1973). A boy-day is defined

as a day on which an individual boy was under observation at the College, and thus differs from a day on which all the boys at the College on that day were observed. When bleeding occurred at more than one site simultaneously, it was recorded as a single episode, but the sites were recorded separately and transfusions given were recorded under each site. No attempt was made to distinguish whether bleeding into hands and feet affected joints or soft tissues. The most common sites of bleeding are listed separately while less common sites are grouped together.

Factor VIII:C assays were carried out by a two-stage method based on that of Denson (1972).

The levels of factor VIII aimed at in vivo to treat bleeding episodes were dependent on the site and severity of the lesion. As a general rule for an uncomplicated joint bleed the factor VIII level was raised to 20% of average normal while for severe or complicated joint bleeds and muscle bleeds, a level of 30% of average normal was aimed at. The amount of factor VIII required to achieve the desired rise was derived from the formula:-

$$\text{Dose(units)} = \frac{\text{Patients wt(kg) x desired rise in F.VIII (\%)}}{K}$$

In the present study, 'K' was taken to be 1.5.

All bleeds and their subsequent progress were assessed by one of the medical staff attached to the Centre. Although several boys were able to transfuse themselves, the decision to transfuse was always a medical one.

Indications for retransfusion within twenty four hours were evidence of extension of bleeding at 12 hours or poor progress after twenty four hours. Further transfusions were given to cover rehabilitation or for complicated or

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poorly resolving bleeds.

All boys were weighed at the beginning of each term. The average of all their mean weights for the year was taken as the overall mean for that year.

Seven of the boys had antibodies to factor VIII. Their bleeds were excluded from analyses of bleeding frequency and transfusion requirements, but not from those of the sites of bleeding.

Prophylactic infusions of factor VIII were given to several boys for limited periods during the time of the study. Bleeds occurring while on prophylaxis were excluded from analyses of bleeding frequency and prophylactic transfusions were excluded from analyses of transfusion requirements. Those bleeds which occurred while on prophylaxis, were, however, recorded under sites of bleeding.

When more than one spontaneous bleeding incident presented simultaneously this was called a multiple bleed. This definition did not include bleeds which developed during the course of treating another bleed nor of those following trauma. Multiple bleeds occurring in haemophiliacs with inhibitors or on prophylaxis were excluded from the analyses of multiple bleeds.

RESULTS

PATTERNS OF BLEEDING:

Annual bleeding frequency at the College (Table 1)

Four thousand, nine hundred and thirty five bleeding episodes were recorded in patients who did not have inhibitors to factor VIII and who were not on prophylaxis.

Year	Patients	No. of Bleeding Episodes	No. of Boy-Days	No.of Episodes/ 100 Boy-Days
1973	39	639	7690	8.31
1974	43	708	9160	7.73
1975	49	948	11151	8.50
1976	54	1249	10786	11.58
1977	51	1391	11016	12.63

TABLE I

Annual Bleeding Frequency at the College

The number of bleeding episodes rose steadily from 1973 to 1977. The actual bleeding frequencies of the boys at the College rose sharply from a mean of 8.50 episodes/100 boy-days in 1975 to 11.58 episodes/100 boy-days in 1976 and again to 12.63 episodes/100 boy-days in 1977.

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Commonest Sites of Bleeding (Table 2)

A total of 5450 bleeding episodes were recorded. Of these 1302 (24%) were into the elbow joint, 1213 (22%) into the knee joint and 801 (15%) into the ankle joint.

	No. of boys	No. of bleeds	Percentage of all bleeds
Elbow	59	1302	(24)
Knee	59	1213	(22)
Ankle	63	801	(15)
Shoulder	57	322	(6)
Thigh	62	242	(4)
Forearm	61	197	(4)
Hand	38	181	(3)
Upper Arm	55	177	(3)
Foot	39	154	(3)
Wrist	41	141	(3)
Lower Leg	59	132	(2)
Others	75	589	(11)
	TOTAL	5450	(100)

TABLE 2

Commonest sites of bleeding

The Effect of Age on the Bleeding Frequency (Table 3)

Analyses by age showed a small but steady drop in bleeding frequency from 10.44 episodes/100 days in 10-11 year olds to 9.63 episodes/100 days in 16-17 year olds.

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Age	Patients	No. of Bleeding Episodes	No.of Days	No.of Episodes/ 100 Boy-Days
10-11	38	557	5335	10.44
12-13	72	1636	16070	10.18
14-15	73	1532	15579	9.83
16-17	41	839	8714	9.63

TABLE 3

The effect of age on the bleeding frequency

The effect of age on the sites of bleeding:

The effect of age on the distribution of bleeding among the four commonest sites is shown in table 4. There was a steady decline in the incidence of knee bleeds from 28% at age 10-11 to 18% at 16-17. A similar decline occurred in episodes of bleeding into the ankle. By contrast, episodes of bleeding into the commonest upper limb sites increased steadily - in the elbow from 19% at age 10-11 to 27% at 16-17 years and in the shoulder from 4% at age 10-11 to 8% at 16-17 years.

Age	Knee	Ankle	Elbow	Shoulder
10-11	28	20	19	4
12-13	24	16	23	6
14-15	22	13	26	6
16-17	18	11	27	8

TABLE 4

Percentage of bleeding episodes in major joints at various ages

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An analysis by age of all bleeding episodes into the upper and lower limbs is shown in table 5. At the ages studied bleeding at these sites always accounted for about 90% of all bleeds. The incidence of bleeding into the lower limbs, however, fell steadily from 60% of all bleeding episodes at 10-11 years to 39% at 16-17 years. By contrast, bleeding episodes into the upper limbs rose steadily from 32% at 10-11 years to 50% at 16-17 years.

Age	No.(%)of bleeds into Lower Limb	No.(%)of bleeds into Upper Limb	Total
10-11	315 (60)	169 (32)	484
12-13	929 (52)	728 (40)	1657
14-15	739 (45)	752 (46)	1491
16-17	346 (39)	444 (50)	790

TABLE 5

Proportion of all bleeding episodes affecting upper and lower limbs

Multiple bleeds:

One hundred and eighty one bleeding episodes (3.7%) involved two separate sites and 9 (0.2%) involved three separate sites. This analysis is confined to those bleeds occurring in two sites. The sites most frequently involved in multiple bleeds are shown in table 6, the elbow, knee and ankle being the most commonly involved in multiple bleeds. The commonest combinations of sites involved in multiple bleeds is shown in table 7.

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Fifty three boys out of seventy five had at least one multiple bleeding episode during the study. The number of multiple bleeds in each of the 53 was adjusted to multiple bleeds/100 boy-days under observation and this was plotted against the bleeding frequency (figure 1).

Elbow	76
Knee	59
Ankle	50
Shoulder	33
Thigh	17
Fingers	17
Forearm	14
Calf	14
Upper Arm	11
Wrist	10

TABLE 6

Commonest sites involved in multiple bleeds

A highly significant correlation was found ($r = 0.613$, $p = <.001$). When multiple bleeds/100 days were plotted against days under observation there was no significant correlation ($r = 0.047$, $p = N.S.$). The mean bleeding frequency of those boys who had multiple bleeds was 12.36 ± 4.52 while the bleeding frequency of those boys who had not was 8.06 ± 4.29. The difference between these two groups was not significant.

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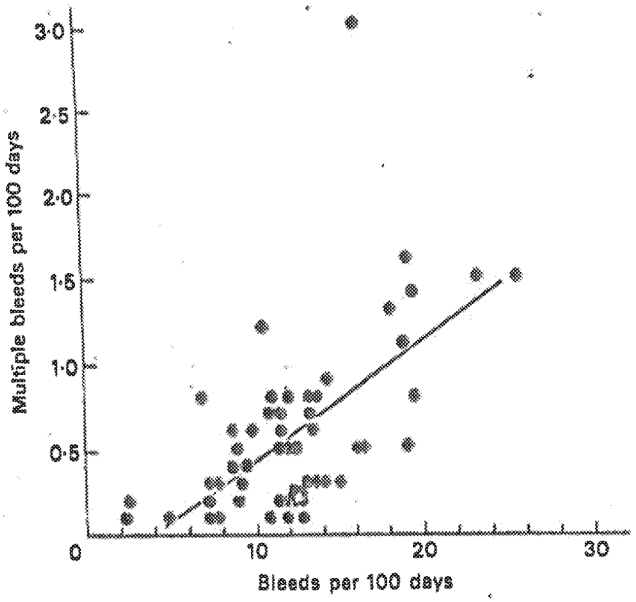

FIGURE 1

Multiple bleeding frequency plotted against original bleeding frequency $r = 0.613$, $p < 0.001$.

When the bleeding frequency of the boys who had not experienced a multiple bleeding episode while at the College was plotted against the days spend under observation a highly significant negative correlation emerged ($r = -0.742$ $p = < .001$). (Figure 2).

Site	Site	Bleeds
Elbow	Knee	21
Elbow	Ankle	15
Elbow	Shoulder	13
Knee	Ankle	10
Elbow	Elbow	8
Knee	Shoulder	7
Ankle	Ankle	5
Knee	Knee	4

TABLE 7

Commonest combinations in multiple bleeds

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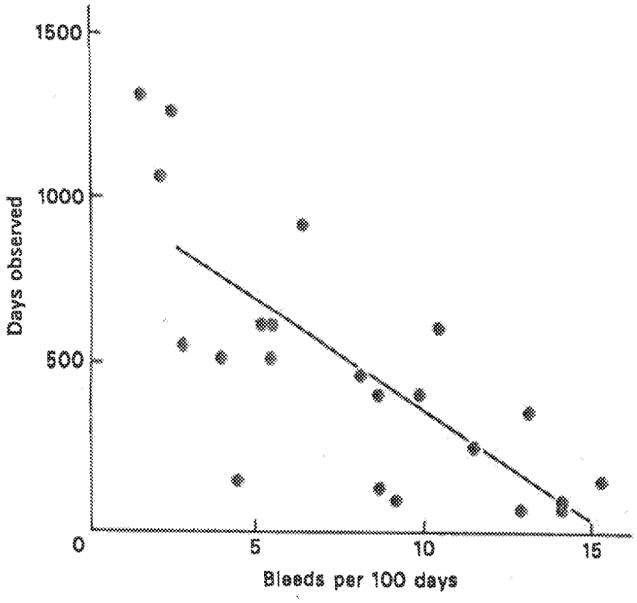

FIGURE 2

Bleeding frequency of boys who had not had multiple bleeds plotted against days under observation.
$r = 0.742$, $p = < 0.001$.

TRANSFUSION REQUIREMENTS:

Transfusions given annually at the College

A total of 6726 transfusions of factor VIII were given for the 4935 bleeding episodes in patients without inhibitors and not on prophylaxis, an average of 1.36 transfusions per bleeding episode.

Year	No. of Patients in each year studied	No. of Bleeding episodes	No. of Transfusions	No. of Transfusions /bleeding episode
1973	39	639	782	1.22
1974	43	708	873	1.23
1975	49	948	1359	1.43
1976	54	1249	1781	1.43
1977	51	1391	1931	1.39
TOTAL		4935	6726	1.36

TABLE 8

Number of episodes and transfusions each year

While the number of bleeding episodes rose by a factor of 2.2 from 639 in 1973 to 1391 in 1977 (table 1) the number of transfusions rose by a factor of 2.5 from 782 in 1973 to 1931 in 1977. The major change in the number of transfusions given per bleeding episode took place in 1975 when 1.43 transfusions were given per bleeding episode with 1.23 transfusions/bleeding episode given in the previous year. This figure remained reasonably constant

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in 1966 and 1977 (table 8). The number of bleeding episodes and transfusions by age is shown in table 9. The number of transfusions/bleeding episode rose to a peak in the 14-15 year age group and then fell back.

Age	No.of Patients in each year studied	No. of Bleeding episodes	No. of Transfusions	No. of Transfusions / bleeding episode
10-11	38	557	669	1.20
12-13	72	1636	2126	1.30
14-15	73	1532	2245	1.47
16-17	41	839	1131	1.35

TABLE 9

Number of episodes and transfusions by age

During the years of the study the amount of therapeutic material used rose by a factor of 2.5 from 561,640 units of factor VIII in 1973 to 1,153,340 in 1977 (table 10). The average weight of the haemophiliacs during each year of the study is shown in table 11 which also shows the annual usage of factor VIII/bleed and per Kg/bleed as well as the annual usage of factor VIII/transfusion and per Kg/transfusion. The annual usage of factor VIII per bleed has risen from 879 in 1973 to 1045 in 1977, a factor of 1.2. This increase occurred between 1974 and 1975 and was sustained in the three years 1975 to 1977.

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The units of factor VIII given per Kg/bleed increased by a factor of 1.2 from 19.1 in 1973 to 22.7 in 1977. There was no significant change in the units per dose and the units/Kg/dose over the years of the survey.

Year	Patients	Units F_3VIII ($\times 10^3$)
1973	39	562
1974	43	600
1975	49	865
1976	54	1238
1977	51	1453
TOTAL	75	4718

TABLE 10

Annual usage of factor VIII at the College

Retransfusion at Specific Sites:

The transfusion requirements for bleeds into the eighteen commonest sites are shown in table 12. More iliopsoas bleeds needed retransfusion within 24 hours (61.6%) than bleeds into any other site, followed by retroperitoneal (58.8%) and abdominal wall bleeds (42.3%). The least retransfusions were needed for bleeds into the hands (8.1%), feet (6.7%) and toes (2.9%). Retroperitoneal bleeds required most transfusions/bleed (3.6) followed

Year	Patients	Average weight (Kg)	UNITS FACTOR VIII			
			Per bleed	Per Kg per bleed	Per transfusion	Per Kg per transfusion
1973	39	46	879	19.1	718	15.6
1974	43	47	848	18.0	687	14.6
1975	49	44	912	20.7	637	13.0
1976	54	45	991	20.0	695	15.4
1977	51	46	1045	22.7	753	16.4
Mean		45.6	956	21.0	701	15.4

TABLE 11

Dosage of Factor VIII

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Site	No. of bleeds	Bleeds retransfused in 24 hours		Transfusions per bleed
		No.	Percentage	
Iliopsoas	73	45	61.6	2.5
Retroperitoneal	17	10	58.8	3.6
Abdominal wall	26	11	42.3	1.6
Buttock	59	18	30.5	1.7
Thigh	224	58	25.9	1.4
Hip	59	13	22.0	1.6
Calf	121	25	20.7	1.4
Wrist	139	25	17.3	1.2
Knee	1184	187	15.8	1.2
Shoulder	317	45	14.2	1.2
Ankle	758	105	13.9	1.2
Forearm	185	21	11.4	1.2
Elbow	1279	143	11.2	1.2
Upper Arm	171	18	10.5	1.1
Fingers	85	8	9.4	1.1
Hand	86	7	8.1	1.1
Foot	75	5	6.7	1.1
Toes	70	2	2.9	1.0
Total	4928	745	15.1	1.2

TABLE 12

Retransfusions for bleeds into the 18 commonest sites

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by iliopsoas bleeds (2.5 transfusions/bleed) and bleeds into the buttocks (1.7 transfusions/bleed). Bleeds into the upper arm musculature, hands, fingers, feet and toes required the least retransfusions per bleed.

	Bleeding Episodes	Transfusions	Transfusions /bleed
All Bleeds	4935	6726	1.36
Two-Site Bleeds	181	221	1.22
Three-Site Bleeds	9	11	1.22

TABLE 13

Transfusions per Bleed

Multiple Bleeds:

The number of transfusions given per bleed is shown in table 13. An average of 1.2 transfusions were needed for each multiple bleeding episode. The transfusion requirements for bleeds involving various sites are shown in table 14 which also shows the transfusion requirements for single bleeds at those sites. The thigh, upper arm, elbow and shoulder were most frequently involved in the multiple bleeds needing most transfusions.

	Bleeds	Transfusions	Transfusions/ bleed	Transfusions /bleed Single Site
Thigh	17	24	1.4	1.4
Upper Arm	11	15	1.4	1.1
Elbow	76	97	1.3	1.1
Shoulder	33	44	1.3	1.2
Knee	59	72	1.2	1.2
Fingers	17	20	1.2	1.1
Ankle	50	58	1.2	1.2
Forearm	14	16	1.1	1.2
Calf	14	16	1.1	1.3
Wrist	10	10	1.0	1.2

TABLE 14

Transfusion Requirements of Commonest Sites involved in multiple bleeding episodes

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DISCUSSION

The boys studied were under continuous medical care. Other surveys have been based on attendances at Haemophilia centres and have necessarily excluded bleeding episodes which were not reported or were treated elsewhere. An attempt was made to document the bleeding frequencies while the boys were at home during holidays, but not all haemophilia centres responded and the data collected was insufficient to compare with that collected at the school.

Over the five years of the survey the number of bleeding episodes more than doubled. Treatment policy remained the same, the presumption being, therefore, that the haemophiliacs entering the College towards the end of the period were more severely affected. Facilities for home management have improved over the past few years (Jones et al 1978) and so fewer haemophiliacs have to travel long distances in order to obtain treatment for bleeding, which was previously a major reason for residence at a special school. The College is probably now seeing only the worst cases which cannot be managed at home, many of whom also have social problems at home.
Other reports show that bleeding frequency declines with advancing age (Veltkamp 1975) and this survey confirms that a steady decline occurs through adolescence.

The finding that the elbow joint was the commonest site of bleeding differs from those of other surveys (Stuart et al 1966, Ramsay and Khoo 1975). This study was confined to adolescence whereas others have included all age groups. Stuart et al (1966) showed a preponderance of knee bleeds in patients aged 12-21 but the number of episodes studied was less than 5% of those in the present series. A comparable number of patients was studied by Rizza and Spooner (1977) but they considered haemophiliacs of all ages and were concerned only with episodes of bleeding

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treated at home.

Bleeding at 10-14 years occurred more often into the knee joint than into the elbow joint. From 15-17 years the elbow was the commonest site. This difference may be due to the boys using their arms more as they became less physically active and to more academic work, or it may simply result from a relative decrease in the use of legs because of the predominance of leg bleeding in earlier life. However caused, the increase of bleeding into the arm in severely affected adolescent haemophiliacs between the ages 10 and 17 should warrant special measures to manage and where possible to prevent these bleeds. In response to these findings present policy at the College in treating elbow bleeds in pre or early adolescence is to:-

a) treat these bleeds vigorously

b) pay scrupulous attention to restoration of function

c) give limited prophylaxis when recurrent bleeds occur

d) develop a programme of physical treatment aimed at strengthening the muscles protecting the elbow joint.

The 14-15 year age group had a higher rate of transfusions per bleeding episode than all other age groups. This implies that bleeds in this group were more severe and the progressive increase in severity from the youngest age groups suggests an increase in activity not yet tempered with greater care.

There was a marked increase in the use of therapeutic material at this Centre between 1973 and 1977. A large part of this can be accounted for by the increased bleeding frequency of pupils at the College. The average amount of factor VIII per dose and the units of factor VIII per Kg per dose have remained relatively constant over the 5 years

while the number of transfusions has risen by more than the number of bleeds. An increase in the number of transfusions rather than the amount of factor VIII per transfusion therefore accounts for some of the increased usage of factor VIII. This is confirmed by the increase in units of factor VIII per bleed and units of factor VIII per Kg per bleed, each up by a factor of 1.2 over the period of the survey. The implication is that the transfusions given per bleed have increased by 1/5th between 1973 and 1977.

Analyses of transfusion requirements at various sites have shown that iliopsoas, retroperitoneal and abdominal wall bleeds were the commonest bleeds which needed retransfusions within 24 hours, while bleeds into the extremities of the upper and lower limbs needed least retransfusions within 24 hours. Retroperitoneal bleeds needed more retransfusions per episode followed by iliopsoas, buttock, abdominal wall and hip joint bleeds. It is striking that the transfusion requirements of bleeds below the diaphragm appear to diminish steadily the more peripheral they become, apart from calf bleeds which require more transfusions per bleed than those into the knee joint. This relationship does not hold for upper limb bleeds and may be related to weight bearing. It may highlight the need for non-weight bearing during the acute phase of bleeds into the lower half of the body.

The incidence of bleeds into two sites simultaneously is seen to be uncommon but not rare. Bleeds into three sites are rare and during the 5 years of the survey no bleeds involving more than three sites were noted. The sites most frequently involved in multiple bleeds reflect the frequency of single bleeds at those sites (Aronstam, McLellan and Turk 1979). It would thus be reasonable to predict that the most frequent combinations of bleeds would be at the sites most frequently affected. However, the incidence of bilateral elbow and knee bleeds is much lower than one would expect were the relationship a simple

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arithmetical one. Other factors such as mechanical interdependence of various sites may play a role in determining the combinations of multiple bleeds.

The overall transfusion requirements for multiple bleeds are less than for single bleeds. It is striking that most multiple bleeds involving upper limbs required more transfusions per bleed than single bleeds into the upper limb sites. This is not altogether surprising as single bleeds in the upper limb require less transfusions per bleed than most bleeds into other sites.

The number of multiple bleeds was correlated significantly with the bleeding frequency and not with the number of days under observation. Its incidence appears therefore to be a function of the severity of the disease rather than a function of time. If this proposition is true than those boys who had not yet experienced a multiple bleed were likely to be predominantly the newer arrivals at the College and with increasing time under observation, more multiple bleeding episodes should be noted. This is confirmed by the negative correlation between bleeding frequency and days under observation which is well shown in figure 2. It is suggested therefore, that the severe haemophiliac who bleeds frequently, will sooner or later experience a multiple bleeding episode, and that the incidence of multiple bleeds reflects the severity of the disease.

ORIGINAL WORK

3) PROPHYLACTIC TREATMENT

A. A DOUBLE-BLIND CONTROLLED TRIAL OF ONCE WEEKLY PROPHYLAXIS

INTRODUCTION

The quality of life in a severe haemophiliac is limited by the frequency with which he bleeds. Current therapy is aimed at treating established bleeding episodes, although several attempts at prevention of bleeding have now been documented (Bellingham et al 1967, Robinson, Tittley and Smiley 1967, Shanbrom and Thelin 1969, Nilsson, Blomback and Ahlberg 1970, Kasper, Dietrich and Rapaport 1970, Hirschman, Itscoitz and Shulman 1970, Van Creveld 1971, Ramsay and Parker 1973).

Widely different regimens have been instituted and marked variations in the time between prophylactic doses and the amount of factor VIII in a given dose have been tried. The results have not been consistent. Nilsson, Blomback and Ahlberg (1970) used doses of 300 I.U. every 2-4 weeks and claimed a reduction in frequency of bleeding episodes. In contrast Robinson, Titley and Smiley (1967) gave one unit of cryoprecipitate,about 70 I.U. of factor VIII, twice daily and reduced a bleeding frequency of eight in three months to nil over a similar subsequent period, but this was in only one patient. Ramsay and Parker (1973) gave six units of cryoprecipitate weekly in two patients and were not able to demonstrate an overall reduction in bleeding frequency.

No controlled trial of prophylactic treatment had been reported when this work was undertaken. Several sources of potential bias require elimination in an attempt to evaluate such a regimen, e.g. a patient may gain sufficient assurance to ignore symptoms which would ordinarily cause him to seek treatment and advice. He might be prompted to exert himself more strenuously than otherwise and thereby provoke a bleeding episode. The effects of psychological influences on bleeding have been stressed (Lucas 1970). Furthermore, observer bias cannot be eliminated if diagnosis of a marginal bleeding episode is left to an observer who wishes to show that prophylaxis is beneficial and who knows

that the patient is on a prophylactic regime. His management of a patient may also be affected if he knows that a dose of therapeutic material will shortly follow the presentation of an equivocal bleed, as he may be tempted not to treat that bleed routinely. These sources of potential bias can be controlled by designing a trial with three specific requirements. Firstly, the variation among patients is eliminated by a cross-over design whereby each patient serves as his own model for comparison.. Secondly, the individual patient should not know whether he is or is not receiving prophylaxis; this may be achieved by using a placebo or an extremely low dose of factor VIII and employing a double-blind method. Thirdly, the clinician responsible for the diagnosis of a bleeding episode should not know whether the patient is receiving factor VIII or a placebo. Personnel facilities exist for separating clinical management and trial administration at the Treloar Haemophilia Centre and it is therefore an ideal location for carrying out such a trial.

MATERIALS AND METHODS

Clinical management of the boys on the trial was carried out at various times by a Research Fellow, a GP Clinical Assistant, a College Medical Officer and a Senior House Officer. These were at all times blind to the particular trial dosage of the different boys, although they were aware that any given boy was on the trial. Diagnosis of a bleeding episode requiring treatment was made at the College, routine treatment was given at either the College or the Haemophilia Unit at the hospital and prophylactic treatment was given at the hospital. These infusions were all given by nursing staff.

Eligibility Criteria:
Only classical haemophiliacs over 7 years of age and with a factor VIII concentration of less than 1% of average normal were selected. Before admission to the trial each boy was observed for at least two school terms and had to have a baseline bleeding frequency of at least seven bleeding episodes per 100 days during those terms. Patients with antibodies to factor VIII were excluded.

A bleeding episode was defined as any spontaneous discrete episode of joint, muscle, subcutaneous, genito-urinary or nasal haemorrhage which required treatment with factor VIII-containing material. Only patients who were potentially available for at least four school terms were considered.

The nature of the trial was fully explained to the eligible boys and their parents or guardians were asked to give their consent; if this was obtained the boys were admitted to the trial.

Trial Design:
An attempt was made to give once-weekly infusions of either a factor VIII concentrate calculated to raise the boys' factor VIII level to at least 25% of average normal or a

concentrate calculated to raise the level of factor VIII by not more than 1% of average normal.

The concentrates were made in the Blood Products Laboratory of the Lister Institute for Preventive Medicine and they were as nearly indistinguishable visually as possible. As an added precaution the bottles were covered during the infusions. The hope was that each eligible boy would be on the trial for four consecutive school terms. For two of these terms he would receive a low-dose and for the other two a high-dose regimen. The random allocation of trial subjects to the different regimens at the beginning of each term was made by the Wessex Medical Information Unit. At the beginning of each trial term screening for factor VIII inhibitors and HB_sAg was carried out. During each trial term the recovery of factor VIII after a prophylactic dose was tested on each boy, usually on two occasions.

Strength of low-dose prophylactic material was discussed and debated fully at a meeting of the Directors of the Haemophilia Centres of Great Britain. The consensus was that it would be wrong to give any possibly therapeutically effective dose during the control regimens and that this would call the validity of the trial into question. The amount of factor VIII in the control material was therefore limited to that which was calculated to raise the level of factor VIII in the boys' blood by less than 1% of average normal. The patients and staff concerned with their routine management were aware that the only safe assumption to make was that they were in a low-dose group.

Administration of Prophylactic Materials:

This was carried out on weekday afternoons at about 16.00 hours to interfere as little as possible with the boys' schooling and leisure. The fractionated material was reconstituted in distilled water and administered by drip infusion. Scheduled prophylactic doses were delayed until at least 24 hours had elapsed from the last therapeutic

administration of factor VIII. No trial infusions were given during weekends or holidays.

Factor VIII assays:
were carried out by the two-stage method described by Denson (1972). The technicians carrying out the assays were at all times blind to the patient's schedules and did not know the names of the patients whose plasma they were assaying. All samples were taken on the ward and assigned a number. Pre and post samples were obtained immediately before and thirty minutes after the completion of the infusion. All assays were commenced within two hours of venepuncture. Random assays were also carried out on each batch of materials at the Lister Institute.

Factor VIII inhibitor screens:
were carried out by the method described by Biggs and Bidwell (1959).

Prophylactic material (high dose):
was prepared by the method of Newman et al (1971). The method was modified in that the addition of ethanol to 3% concentration at the cryoprecipitation stage was omitted. Fractionation was taken to the 'intermediate potency' stage. Two strengths of bottle were used; a full volume bottle containing 400 I.U. of factor VIII which was reconstituted in 50 ml of sterile water and a half bottle containing 200 I.U. of factor VIII which was reconstituted in 25 ml of distilled water.

The dose of factor VIII required to raise each boys' factor VIII level by 25% of average normal was calculated using the formula:

$$\text{Dose(units)} = \frac{\text{Patients Wt(Kg)} \times \text{Desired rise in F.VIII(\%)}}{K}$$

'K' is a factor depending on the nature of the therapeutic

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material used and expresses the percentage rise in factor VIII per unit/kg of dose. In the present study 'K' was taken to be 1.5.

To avoid wastage and for convenience the dose was made up to the nearest 200 I.U. As the boys' weight increased during this trial, the dosage was recalculated and adjusted as necessary.

Prophylactic material (low dose):
consisted after reconstitution of a full bottle to 50 ml of 2% human albumin plus the above concentrate to give an estimated 10 I.U. of factor VIII per bottle. The same volume of material was administered as during high-dose periods.

PATIENTS:

Patient 1:
Born GRO-A 1960, weight 43 Kg on admission to trial. Had frequent bleeds involving knees, elbows, ankles and sometimes the muscles on both upper and lower limbs. The right knee was most frequently involved and was the only joint showing any signs of permanent disablement. Radiological appearances typical of haemophilia seen in both knee joints and elbow joints.

Patient 2:
Born GRO-A 1958, weight 37 Kg on admission to trial. Two maternal uncles suffered from this disease. Bled into most joints and muscles of all limbs. Radiological changes typical of haemophilia seen in elbows, knees and ankles.

Patient 3:
Born GRO-A 1961, weight 33 Kg on admission to trial. No family history. Both elbow and knee joints showed some permanent disablement. Radiological changes typical of haemophilia seen in knees, ankles and elbows. He had never presented with a muscle bleed.

Patient 4:
Born GRO-A 1958, weight 60 Kg on admission to trial. One brother suffered from severe haemophilia with a factor VIII inhibitor. His maternal grandfather had haemophilia and died from intracranial haemorrhage. Had suffered from numerous bleeds involving elbows, knees and ankles and sometimes the muscles of both upper and lower limbs. Radiological changes typical of haemophilia could be seen in the elbow, knee and ankle joints. Clinically these joints showed some degree of permanent disablement.

Patient 5:
Born GRO-A 1958, weight 30 Kg on admission to trial. No family history. Frequent bleeds had affected his knees, elbows, shoulders, wrists and ankles. He had never suffered from a muscle bleed. Both knee joints showed some degree of permanent disablement. Radiological appearances typical of haemophilia seen in most joints.

Patient 6:
Born GRO-A 1958, weight 57 Kg on admission to trial. One brother had severe haemophilia. Most haemorrhages had involved knee joints and elbow joints. He occasionally suffered from muscle bleeds. Radiological appearances typical of haemophilia seen in elbow and knee joints.

Patient 7:
Born GRO-A 1958, weight 50 Kg on admission to trial. No family history. Had suffered from numerous bleeds involving joints of elbows, knees and right shoulder. Did not suffer from muscle bleeds. The right elbow and both knees showed some degree of permanent disablement. Radiological appearances typical of haemophilia seen in the joints of both knees and the right elbow.

Patient 8:
Born GRO-A 1961, weight 33 Kg on admission to trial. No family history. Had numerous bleeds into his knees and ankles. His left knee was the worst affected and was the

only joint which showed some degree of permanent disablement with wasting of the quadriceps. He had bled into the muscles of his limbs. Both knee joints showed radiological changes typical of haemophilia.

Patient 9:

Born GRO-A 1962, weight 30 Kg on admission to trial. No family history. Had numerous bleeds into both elbows and both knee joints. Both elbows and the right knee joint showed some degree of permanent disablement. The right elbow joint was very distorted in outline due to the presence of a number of haemophilic cysts. Radiological changes typical of haemophilia seen in both elbows, right knee and left ankle. He also suffered from occasional bleeds involving the muscles of his limbs.

RESULTS

Nine boys were studied for a total of 27 boy-school terms. A 'boy-school term' is defined as the whole or any part of any school term during which an individual boy was under observation; the whole study took place during five school terms. The boys' bleeding frequencies with high-dose material were studied during 14 boy-school terms and with low-dose material during 13 boy-school terms. Ninety-seven infusions of high-dose and 95 of low-dose material was given.

Overall Bleeding Frequencies:
The findings during the two pre-trial and trial terms are shown in table 15. There is a small but statistically significant reduction in the number of bleeds per 100 days amongst those on high dosage ($p = < 0.05$). The mean difference for all boys is a reflection of a fairly consistent difference for each individual child; eight out of the nine boys had a lower proportion of bleeds when on high-dose compared with low-dose prophylaxis.

Distribution of first bleeds on individual days:
Table 16 shows the number of bleeds which occurred on each individual day following a planned infusion. Only the first bleeds that followed each infusion have been recorded. It is assumed that any subsequent bleed before the next prophylactic infusion was no longer related to the original infusion.

In order to obtain comparable data from the high and low dose groups the number of bleeds on each day has been expressed as a percentage of possible first bleeds on that day (table 17). Ninety-five infusions of low dose material were given during the trial thus creating a potential 95 first bleeds. Of the 95 possible bleeds on day 1 only three took place, which is expressed as a percentage of 95. On day 2 there were 92 possible first bleeds or days at risk. This is because it was no longer possible to have first bleeds

Case	Pre-trial terms			Low-dose terms			High-dose terms		
	No. of bleeds	Days under observation	Bleeds per 100 d	No. of bleeds	Days under observation	Bleeds per 100 d	No. of bleeds	Days under observation	Bleeds per 100 d
1	17	169	10.0	19	143	13.3	15	124	12.1
2	27	169	16.0	6	27	22.2	24	125	19.2
3	31	169	18.3	22	147	15.0	10	94	10.6
4	17	169	10.0	11	79	13.9	5	60	8.3
5	27	169	16.0	16	79	20.3	9	52	17.3
6	12	148	8.1	8	139	5.8	6	151	4.0
7	27	176	15.3	11	64	17.2	7	56	12.5
8	22	168	12.3	6	37	16.2	8	72	11.1
9	25	168	14.1	8	72	11.1	6	45	13.3
Mean	22.8	167.2	13.6	11.9	87.4	13.6	10.0	86.6	11.6

TABLE 15

Overall bleeding frequencies

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related to the three infusions which were followed by bleeds on day 1. Twenty one bleeds occurred on day 2 which is expressed as a percentage of 92. On day 3 there were only 71 possible bleeds because by now 24 of the original 95 infusions had been followed by first bleeds. The 14 bleeds which occurred on day 3 are thus expressed as a percentage of 71 and so on.

DAY	HIGH DOSE	LOW DOSE
1	1	3
2	4	21
3	6	14
4	9	8
5	13	7
6	12	5
7	22	10

TABLE 16

Distribution of first*bleeds on individual days following high or low dose infusions

* Only the first bleed following an infusion has been recorded; any subsequent bleed occurring before the next prophylactic infusion is no longer related to the previous prophylactic dose.

The difference in bleeding frequency following high and low doses is significant on day 2 and day 3 and approaches the 5% level of significance on day 1, even though it is only based on bleeds after 16.00 hours. The daily mean bleeding frequency following the low dose infusion is 15.5 and the frequency of 22.8 on day 2 is significantly higher than this ($p = \leq 0.05$). However, if the bleeds during the 8 hours of

Day	High-dose infusion			Low-dose infusion			Significance of difference (P value)
	Bleeds recorded	Possible bleeds	Percentage bleeds	Bleeds recorded	Possible bleeds	Percentage bleeds	
1	1	97	3.0*	3	95	9.5*	0.06
2	4	96	4.2	21	92	22.8	<0.001
3	6	92	6.5	14	71	19.7	0.02
4	9	86	10.5	8	57	14.0	0.57
5	13	77	16.9	7	49	14.2	0.69
6	12	64	18.8	5	42	11.9	0.32
7	22	52	23.0+	10	37	16.2+	0.42

* Adjusted from 1/3 to 1 day

\+ Adjusted from 1 2/3 to 1 day

TABLE 17

First bleeds on individual days expressed as a percentage of possible bleeds

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Pre-trial terms			Low-dose infusion			High-dose infusion		
ys under dical care	Days under observation	Morbidity per 100 d	Days under medical care	Days under observation	Morbidity per 100 d	Days under medical care	Days under observation	Morbidit per 100
310	1505	20.6	171	787	21.7	130	779	16.7

TABLE 18

Morbidity

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day 1 are added to those in the 24 hours of day 2 and the appropriate adjustments made, then the difference in bleeding frequency is no longer significant.

Time to first bleed:

The interval times from administration of high or low dose material to the first bleeds thereafter have been pooled and compared. When an infusion was followed by a clear week, all subsequent infusions until the next bleeding episode were ignored, for example, if an infusion was followed by two clear weeks and the next bleed occurred on day 2 of the subsequent cycle, it was recorded as one infusion, with an interval time of 16 days to the first bleed thereafter. The mean interval times were significantly longer ($p = \leqslant 0.05$) in the boys on high dose (8.3 days) than in those on low dose prophylaxis (6.6 days).

Clear weeks:

Twenty nine out of 95 administrations of low dose material (30.5%) were followed by a clear week. Thirty nine out of 97 high doses (40.2%) were followed by a clear week. The difference is not significant ($p = 0.16$).

Morbidity:

The time spent either in the College Sick Bay or at the hospital during high and low dose regimens was recorded. More than 3 hours under medical care was noted as 1 day. The total figures are shown in table 18. The children on high dose spent significantly less time confined to bed ($p = \leqslant 0.05$).

Factor VIII assay:

Twenty three random assays on blood taken 30 minutes after the infusion of low dose material were undertaken. All but three of these were over 0.2 I.U./ml (mean 0.26 I.U./ml). Random assays were carried out on each batch of materials at the Lister Institute and each confirmed the predicted strength.

DISCUSSION

The raising of the factor VIII level in severe haemophiliacs to at least 20% of average normal once weekly has been shown to reduce the overall bleeding frequency from 13.6 to 11.6 bleeds per 100 days. This small but significant reduction in bleeds amongst the high dose group is due to a modest reduction in bleeds amongst eight out of the nine boys on the high dose prophylaxis. A 15% reduction in the overall bleeding frequency of severe haemophiliacs can therefore be achieved by weekly prophylaxis. The dose of factor VIII-containing materials normally used for spontaneous, uncomplicated, bleeds was selected. On this dose each spontaneous bleed needs an average of 1.2 doses of therapeutic material per 100 days (Rainsford and Hall 1973). Weekly prophylaxis reduces the bleeding frequency to 11.6 bleeds per 100 days. If 1.2 doses of therapeutic material are used to treat each bleed then 13.9 doses per 100 days will be needed to treat 11.6 bleeds per 100 days. In addition, 14.3 prophylactic doses would be given in 100 days (one prophylactic dose each week for 100 days), making a total of 28.2 doses of therapeutic material on 100 days. Thus a 73% increase in therapeutic materials is required to reduce by 15% the frequency of bleeding in a group of severe haemophiliacs.

The reduction in bleeds occurs predominantly in the first 3 days after infusion. The difference in the bleeding frequencies on high and low dose prophylaxis is statistically significant on the second and third days and nearly so on the first day. It is difficult to explain the increased bleeding frequency on day 2 following the low dose. The possibility that the boys became over confident, believing themselves to be protected cannot be excluded, although they denied this. It should also be stressed that these were a group of boys who bled frequently. At least 24 hours had to elapse from the last therapeutic infusion before a prophylactic dose was given and no prophylaxis was given during

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the weekends. This meant that the second day after a low dose infusion was often the fourth or fifth day since the last bleed and many of the boys on this trial would expect a fresh bleed at about that time. Whatever the reason, this increased bleeding frequency following the low dose infusion must cast some doubt on the validity of comparing the high and low doses and is one example of the difficulties associated with the use of a placebo in this trial.

The mean bleeding frequency during the first three days after the high dose infusions was approximately two-fifths of the mean bleeding frequency over all 7 days following a high dose. It is about one-third of the mean bleeding frequency in the 7 days following a low dose. Taking the most optimistic view, it might be predicted that a prophylactic dose of the order used in this trial, given every third day, would reduce the bleeding frequency in severe haemophiliacs by two-thirds. Four point five bleeds would then occur in 100 days. Assuming 1.2 doses of therapeutic material was used on average per bleed then 5.4 doses of therapeutic material would be needed to treat these bleeds in 100 days, making a total of 38.7 doses of therapeutic material. This is nearly 2.5 times more material than the 16.3 doses needed to treat the average of 13.6 bleeds per 100 days occurring in the boys on the trial. It thus appears that a substantial reduction in bleeding frequency by prophylaxis is likely to require a great increase in the supply of therapeutic materials. In view of the implications for the limited financial and human resources needed to service such a commitment, it is important that further trials are undertaken to establish the lowest dose which might be beneficial and what the optimum frequency should be.

There were many problems in this trial. Some bleeds were bound to occur shortly after infusions of low dose material and sooner or later a crop of bleeds will occur. On one occasion four boys were together in the Sick Bay within 24 hours of low dose infusion. They concluded that the material was the cause for their bleeding and it was difficult to persuade them to remain in the trial. Two, in fact, dropped

out soon after this episode. The giving of a dose interferes with a boy's leisure and schooling and when inert material is being given this may not now be easily justified. In my view, future trials should compare only probably effective prophylactic regimens, and should not include placebo doses.

ORIGINAL WORK

3) PROPHYLACTIC TREATMENT

B. A DOUBLE-BLIND CONTROLLED TRIAL OF TWICE WEEKLY PROPHYLAXIS

INTRODUCTION

The first double-blind controlled trial of prophylactic treatment carried out at the Treloar Haemophilia Centre showed that the weekly administration of factor VIII-containing material calculated to raise the factor VIII level to 25% of average normal reduced the overall bleeding frequency in nine severe haemophiliacs by 15%. Analysis of the results on each individual day after a prophylactic dose showed a two-thirds reduction of bleeding frequency over the first two and one-third days. It was calculated that a two and a half fold increase in therapeutic materials would be needed to achieve this substantial reduction in bleeding frequency.

In view of the implications for the limited financial and human resources available to service such a commitment, it is important to confirm these findings and to establish the lowest dose which might be beneficial. A second double-blind controlled trial reported here is a step along that path.

TREL0000517_0136

MATERIALS AND METHODS

Clinical management of the boys on the trial was shared between the College Medical Officer, a Research Senior Registrar and an S.H.O. These were at all times blind to the particular trial dosage of the different boys although they were aware that any given boy was on the trial. Diagnosis of a bleeding episode requiring treatment was made at the College. Routine treatment was given at either the College or the haemophilia ward at the hospital and prophylactic treatment was given at the hospital. All these infusions were given by nursing staff.

Selection of Cases:

Those boys who had been on the first double-blind controlled trial and were still available for a further two terms were selected. There were four such boys, patients 1, 3, 8 and 9, of that trial. The boys selected had each had at least one full school term off prophylaxis before entering the second trial.

All cases suffered from classical haemophilia and had no detectable factor VIII in their plasma. During their stay at the College, while not on prophylaxis, their baseline bleeding frequencies were observed to be 14.6, 18.3, 15.3, and 13.1 bleeds per 100 days. A bleeding episode was defined as any discrete episode of muscle, joint, sub-cutaneous, genito-urinary or nasal haemorrhage which required treatment with a factor VIII-containing material.

Trial Design:

Twice-weekly infusions of factor VIII-containing material, calculated to raise the boys' factor VIII levels to either 15% or 30% of average normal, were given. The material given was either cryoprecipitate, prepared by the Wessex Regional Transfusion Centre or a factor VIII concentrate marketed by Serological Products Ltd (Kryobulin). The boys were allocated to different treatment schedules at random at the start of the trial and the dose schedules

were reversed during the second term.

At the beginning of each trial term screening for inhibitors to factor VIII and hepatitis B surface antigen (HB_sAg) was carried out. During each trial term the response to the prophylactic material was tested on each boy on two separate occasions.

Administration of prophylactic materials:
This was carried out on Monday and Thursday afternoons at about 1600 hours so as to interfere as little as possible with the boy's schooling and leisure. The boys were not aware that there was any difference in the dose schedules over the two terms. A bleeding episode occurring on the day of the scheduled dose was treated in the standard way with a dose of therapeutic material 'topped up' to the trial dosage level if necessary.

Laboratory Methods:
Factor VIII assays, inhibitor screens and tests for HB_sAg were carried out as previously described.

Prophylactic materials:
The strength of the cryoprecipitate used at this Centre is constantly monitored. The strength of each preparation of Kryobulin is recorded on the pack, and random assays confirmed these.

RESULTS

Eighty three infusions of high dose material and 71 of low dose material were given to the four boys on the trial over the two school terms. The number of infusions given to each individual boy is shown in table 19.

Case	Infusions to 15%	Infusions to 30%
1	24	17
2	21	13
3	16	22
4	22	19

TABLE 19

Number of infusions given to raise the factor VIII level to 15% or 30%

The number of bleeds on each individual day after an infusion is shown in table 20. It is possible to calculate the percentage bleeding frequency from the data in tables 19 and 20 and the result of these calculations is shown in table 21. In no case did any boy show a significant departure from baseline bleeding frequencies on any individual day.

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The individual boys were compared by their baseline bleeding frequency. It emerged that boy 1 (14.6 bleeds per 100 days), boy 3 (15.3 bleeds per 100 days), and boy 4 (13.1 bleeds per 100 days) were not statistically different from each other when tested by a binomial test on their respective number of observed days. (Fliess 1973).

Case	15%			30%		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1	3	2	1	1	2	1
2	1	6	1	1	2	3
3	0	0	3	0	1	4
4	1	2	3	0	0	0

TABLE 20

Bleeds on each individual day after a prophylactic dose raising the F. VIII level to 15% or 30%

Boys 1, 3 and 4 were therefore pooled and the average taken which was obtained by adding all their days of observation and all their bleeding episodes for separate days 1, 2 and 3 following either a 15% or a 30% dose.

The baseline bleeding frequency for this group was 14.5 bleeds per 100 days and the average percentage of bleeding frequencies is shown in table 22 together with the significance of the drop in bleeding frequencies from the baseline.

Case	Baseline	15%			30%		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1	14.6	12.5	8.3	4.2	5.9	11.8	5.9
2	18.3	4.8	28.6	4.8	7.7	15.4	23.1
3	15.3	0	0	18.8	0	4.5	18.2
4	13.1	4.5	9.1	13.6	0	0	0

TABLE 21

Bleeds per 100 days observed on each individual day after a prophylactic dose raising the F.VIII level to 15% or 30%

The 30% dose produced a more significant reduction in bleeding frequencies ($p = < 0.01$) than the 15% dose ($p = < 0.05$) on the first day, but reductions were equally significant on day 2 ($p = < 0.05$). There was no significant reduction on day 3.

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Development of Inhibitors:

No case developed during the trial.

Hepatitis:

No case developed during the trial.

Day	15% Dose	Significance (p)	30% Dose	Significance (p)
1	6.2	<0.05	1.7	<0.01
2	6.2	<0.05	5.2	<0.05
3	11.3	N/S	9.6	N/S

TABLE 22

Average of boys 1, 3, and 4: percentage of bleeding frequencies and significance of the drop in bleeding frequency from baseline (14.5%)

Factor VIII Assays:

The factor VIII levels achieved after a prophylactic dose were assayed on two occasions on each boy during each term. The mean of the eight assays done on the high dose schedule, expressed as a percentage of average normal, was 28.37 $\pm$ 3.50. The mean of the eight assays done on the low dose schedule was 16.94 $\pm$ 3.82.

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DISCUSSION

These results demonstrate an initial superiority of the 30% dose which rapidly returns to the same level as the 15% dose, and neither dose seems to have any major effectiveness after the second day. This broadly confirms the results of the last trial in which no significant effect could be demonstrated after two and a third days. It appears therefore that a reduction in bleeding frequency of about 60% can be achieved by raising the factor VIII level to 15% every 48 hours. The standard therapy for a spontaneous bleed is to raise the factor VIII level to 20% of average normal(Rizza 1972) and at this Centre 1.2 standard doses are needed to treat each spontaneous bleeding episode (Rainsford and Hall 1973). The average baseline bleeding frequency of 14.5 bleeds per 100 days would therefore need 17.4 standard doses in 100 days. The prophylactic dose regime mentioned above would reduce the bleeding frequency by 60% to 5.8 bleeds per 100 days, requiring seven standard doses in 100 days to treat those bleeds. In addition, prophylaxis every 48 hours would require 50 doses of material calculated to raise the factor VIII level to 15% or the equivalent of 37.5 standard doses. This, together with the seven standard doses required to treat the reduced bleeding frequency, makes a total of 44.5 standard doses in 100 days. A two and a half fold increase in therapeutic materials would therefore be needed to reduce the bleeding frequency by 60%. This conclusion agrees substantially with earlier work.

From the data presented, it might reasonably be concluded that the 24 hourly prophylactic administration of a dose of factor VIII, calculated to raise the level to 30% would reduce the bleeding frequency by 90%. The application of a similar calculation to that explained above suggests that such a commitment would need nearly nine times the amount of therapeutic material currently in use for haemophiliacs with comparable bleeding frequencies.

Clearly, this sort of commitment is not possible with known therapeutic materials, given the current limitations of human and financial resources, particularly in the United Kingdom. Indeed, the two and a half fold increase in therapeutic materials needed to reduce the bleeding frequency by 60% is not within our compass. Further work in this field should be directed towards the possible benefits of limited periods of prophylaxis. The possibility that a badly affected joint might improve on short-term prophylaxis and reduce the bleeding frequency in the long-term appears the most fruitful line to be evaluated at the present time.

ORIGINAL WORK

3) PROPHYLACTIC TREATMENT

C. PROPHYLAXIS AT THE LORD MAYOR TRELOAR COLLEGE IN 1976 AND 1977

Prophylactic factor VIII was given to 15 of the boys for limited periods during 1976 and 1977. Prophylaxis was administered twice weekly to five boys during 1976 and three times weekly to 13 boys during 1976 and 1977. The bleeding frequency before prophylaxis was taken as that over the previous two school terms.

The effect of prophylaxis on transfusion requirements and bleeding frequencies is shown in Tables 23 and 24. Twice weekly prophylaxis was able to reduce the bleeding frequency from 13.4 to 9.4 bleeds per 100 days. On this regime 795 units per dose were used and each dose averaged 17.0 units per kilogram; 1657 units were used for each bleed at a dose of 36 units per kilogram per bleed. Thrice weekly prophylaxis reduced the bleeding frequency of 13 boys from 16 bleeds per 100 days to 5.9 bleeds per 100 days. On this regime, 730 units per dose were used and each dose averaged 15.0 units per kilogram- 4809 units of factor VIII were used for each bleed at a dose level of 101 units per Kg per bleed.

The use of prophylaxis resulted in an overall increase of about one-quarter in the factor VIII used during 1976 and 1977. While on prophylaxis the boys consumed about four times more factor VIII per bleed than the average for all boys not on prophylaxis. Twice weekly prophylaxis resulted in a reduction in bleeding frequency from 13 to 9 bleeds per 100 days - about 30%. To achieve this reduction 1657 units per bleed were needed compared with an average of 1018 units per bleed used by boys not on prophylaxis. In this group of boys, 13 bleeds which might be expected to occur while not on prophylaxis would need 13,234 units of factor VIII, while the nine bleeds expected to occur while on prophylaxis would use 14,913 units - an increase of about 12%.

Thrice weekly prophylaxis resulted in a reduction of bleeding frequency from 16 to 6 bleeds per 100 days - about 60%; 4809 units per bleed were needed to achieve this reduction.

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	Patients	Days	Bleeds	Bleeds/ 100 days	Previous bleeds /100 days
1976	7	1351	88	6.5	15.1
1977	13	1240	78	6.3	15.8
Twice weekly	5	374	35	9.4	13.4
Thrice weekly	13	2217	131	5.9	16.0

TABLE 23

Effect of prophylaxis on bleeding frequency

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	No. of transfusions	UNITS F.VIII				
		X 10^3	per transfusion	per Kg. per transfusion	per bleed	per Kg. per bleed
1976	447	339	758	17	3852	86
1977	489	349	714	14	4474	91
Twice weekly	73	58	795	17	1657	36
Thrice weekly	863	630	730	15	4809	101

TABLE 24

Consumption of factor VIII on prophylaxis

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In this group of boys 16 bleeds which might be expected to occur while not on prophylaxis would require 16,288 units of factor VIII while the six bleeds expected to occur while on prophylaxis would use 28,854 units - an increase of 77%.

These observations confirm the steeply escalating requirements for factor VIII when attempting to increase the efficacy of prophylaxis predicted in the two controlled trials previously carried out at the Centre. The increase in materials required is less than predicted, but some of this is due to the increased amount of transfusion now used in normal practice. Only 18% of Haemophilia Centre Directors in the United Kingdom used prophylaxis in 1975 (Aronstam, Inwood and Arblaster 1977) while recent information (Jones et al 1978) suggests an escalation in this form of treatment which is likely to be responsible for an upsurge in the usage of factor VIII over the next few years.

ORIGINAL WORK

4) A DOUBLE-BLIND CONTROLLED TRIAL OF THREE DOSAGE REGIMES IN THE TREATMENT OF BLEEDS INTO THE KNEES, ELBOWS AND ANKLES OF SEVERE HAEMOPHILIACS.

INTRODUCTION

The cornerstone of the modern management of haemarthroses in severe haemophiliacs is early and adequate replacement of the missing clotting factor. Low or inadequate treatment will predispose the joint to chronic synovitis, more frequent bleeding and progressive arthropathy (Rizza 1970). However, the adequacy of the dosage of factor VIII is threatened by the cost of this material and by the shortfall in human resources (Aronstam 1980). There is also growing awareness that chronic hepatitis is a not uncommon complication of transfusion with factor VIII-containing materials (Hasiba, Spero and Lewis 1977) and may bear some relation to the degree of exposure to therapeutic materials (Hilgartner and Giardina 1977, Mannucci et al 1975). It is clearly important to find the correct dose of factor VIII for different situations.

The use of home treatment for haemophiliacs in the United Kingdom has grown explosively in recent years (Jones et al 1978) and the promptness of treatment thus obtained has allowed smaller doses of factor VIII to be used. However, even this early treatment does not abort more than 85% of bleeds (Harris and Stuart 1979, Stirling and Prescott 1979). This does not differ greatly from retransfusion rates at the Lord Mayor Treloar College between 1973 and 1977 when rather higher doses were used (Aronstam et al 1979) implying that the 15% of bleeds which would not respond to standard doses of factor VIII are now being subjected to even lower doses. The effect of this on bleeds into the major joints is likely to be chronic synovitis, more frequent bleeding and chronic haemophilic arthropathy (Rizza 1970). One approach to this problem is to try and identify those bleeds which are likely to do badly on a low dose.

A double-blind controlled trial of three dosage regimes in the treatment of haemarthroses of knees, elbows and ankles has been carried out at the Lord Mayor Treloar College. Results are presented here to show the effect of site,

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severity and previous patterns of bleeding on the response to different doses of factor VIII.

PATIENTS AND METHODS

Forty six boys who boarded at the Lord Mayor Treloar College during 1978 and 1979 were studied. The potential for separating activities concerned with transfusion from clinical assessment before and after transfusion, makes the College an ideal situation for conducting such a controlled clinical trial.

Selection of Bleeding Episodes:

All spontaneous bleeds into the knee, ankle or elbow in boys with haemophilia A and without inhibitors were graded according to limitation of movement by goniometry. Grade 0 was assigned where no limitation was detected, grade 1 bleeds had more than 50% of their normal movement, grade 2 bleeds had less than 50% of their normal movement, and grade 3 bleeds were associated with no movement at all. Bleeding episodes in patients who had been transfused in the previous 48 hours were excluded. The progress of grade 0 bleeds could not be objectively assessed and it was not considered ethical to subject patients with grade 3 bleeds to low doses of factor VIII. The present study is therefore confined to bleeds graded 1 or 2. These two grades, in fact, accounted for 90% of all bleeds seen.

Conduct of the Trial:

A set of randomised envelopes containing instructions for doses of 7, 14 or 28 units/kg for each site and grade of bleed was held by nursing staff. All bleeds into the knee, ankle or elbow which satisfied the above criteria were graded according to limitation of movement, and the presence or absence of tenderness was recorded by medical staff. The information was passed to the nursing staff, who opened the appropriate envelope and prepared and administered the indicated dose of factor VIII. The range of movement and degree of tenderness were assessed thereafter every 12 hours by medical staff unaware of the initial dosage. The time taken to complete restoration of function and the number of extra transfusions given was recorded.

Management of Bleeds:

All bleeds were treated on the assumption that a dose of 14 units/kg had been given initially. The majority of bleeds (90%) were seen and treated within 2 hours of the start of bleeding. Local management and rehabilitation were carried out according to standard procedures. Repeat transfusions of factor VIII were usually given for bleeds that were worsening after 12 hours or progressing poorly after 24 hours. For this study only repeat transfusions given within 48 hours were considered relevant to the initial dose.

Patient consent and participation:

Consent was obtained from the parents and the boys themselves. The boys were not told which dose regimen they were on, and because of the wide variety of factor VIII preparations in use at the College, it would be difficult for them to glean such information from the amount of material used.

Therapeutic Materials:

A wide range of commercial concentrates as well as material from the Lister Institute was used during the trial, thus enabling the dose to be made up in every situation to within 1 unit/kg of the required dose. The recovery of factor VIII in vivo was checked after 57 bleeding episodes following the infusion of approximately equal numbers of intermediate and high-potency products.

Target Joints:

During a one year period that included the study reported here, 909 bleeds occurred into the knees, elbows or ankles of the 46 boys who took part in the trial. Of these bleeds, 446 occurred into 143 joints (3.1 bleeds per joint per year) and 463 bleeds occurred into 35 joints (13.2 bleeds per joint per year). The joints in the second group were designated target joints.

Restricted Joints:

Baseline measurements of all joints were taken in the non-bleeding state. Those with limitation of movement demonstrated by goniometry were designated restricted joints.

RESULTS

Three hundred and thirty nine bleeding episodes were studied. Of these, 142 were into the knee, 118 into the elbow and 79 into the ankle. 119 doses of 7 units/kg, 134 doses of 14 units/kg, and 86 doses of 28 units/kg were administered.

Grade 1 knee bleeds lost tenderness at the same rate whatever the dose, but at lower doses it took longer for movement restriction to disappear. Grade 2 knee bleeds showed a definitely worse response to the lowest dose (Table 25).

There was no difference in the response of grade 1 elbow bleeds to the three dose regimens. However, grade 2 elbow bleeds responded worse to a low dose. On a dose of 7 units /kg tenderness and movement restriction took much longer to disappear, the mean time to discharge was significantly longer than after 14 units/kg ($p = < 0.05$), and a much higher percentage of patients needed repeat transfusion within 48 hours than after 14 or 28 units/kg (Table 26).

Ankle bleeds of grades 1 and 2 showed no disadvantage in terms of tenderness, movement, time to complete resolution or repeat transfusion when a dose of 7 units/kg was given (Table 27). The highest dose (28 units/kg) was not obviously superior for bleeds into any of the three sites.

Eighty six bleeds were into restricted joints, 91 were into target joints, 85 were into joints which were both restricted and target and 77 into joints which were neither ('normal' joints).

Grade 2 bleeds into 'normal' joints fared worse on low doses than on higher doses but the difference was non-significant (Table 28). The marginally worse response to low dose seen in grade 1 target bleeds was also non-significant (Table 29). There was no apparent difference in the response of grade 1 or 2 bleeds into restricted joints to all three dosage

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regimes (Table 30). When joints showed both restriction and targeting, then lowering the dose of factor VIII produced an obviously worse response in grade 1 bleeds which was accentuated in grade 2 bleeds (Table 31). The difference in restoration of function at 48 hours reached statistically significant levels ($p = < .05$).

N	DOSE (units /kg).	RESIDUAL TENDERNESS 12h	24h	36h	48h	RESIDUAL MOVEMENT RESTRICTION 12h	24h	36h	48h	D	T
						GRADE I BLEEDS					
43	7	14	10	7	7	79	64	57	31	3.1	26
37	14	17	8	3	3	81	47	25	25	2.6	16
17	28	6	6	6	6	56	47	40	25	2.1	12
						GRADE 2 BLEEDS					
6	7	40	50	33	33	100	100	100	67	4.8	33
20	14	50	26	17	5	94	68	50	45	3.6	20
19	28	44	21	11	0	89	76	53	41	3.4	21

TABLE 25 KNEE BLEEDS

D = Mean days to complete resolution of bleed

T = Percentage of bleeds requiring retransfusion within 48 hours

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N	DOSE (units /kg).	RESIDUAL TENDERNESS 12h	24h	36h	48h	RESIDUAL MOVEMENT RESTRICTION 12h	24h	36h	48h	D	T
						GRADE I BLEEDS					
26	7	24	8	12	0	84	52	33	21	2.7	15
24	14	23	17	8	4	82	54	33	22	2.7	8
12	28	25	17	0	8	75	36	27	18	2.4	8
						GRADE 2 BLEEDS					
12	7	44	42	27	18	100	100	100	91	5.6	50
25	14	33	12	8	8	91	90	70	39	3.4	28
19	28	50	22	17	0	100	87	59	24	3.5	21

TABLE 26 ELBOW BLEEDS

D = Mean days to complete resolution of bleed

T = Percentage of bleeds requiring retransfusion within 48 hours

TREL0000517_0160

N	DOSE (units /kg)	RESIDUAL TENDERNESS 12h	24h	36h	48h	RESIDUAL MOVEMENT RESTRICTION 12h	24h	36h	48h	D	T
						GRADE I BLEEDS					
16	7	19	0	0	0	37	12	0	0	1.5	0
13	14	31	15	8	8	23	8	8	8	1.5	8
6	28	20	20	17	0	20	20	17	17	1.5	17
						GRADE 2 BLEEDS					
16	7	67	37	31	19	93	44	31	19	2.6	25
15	14	47	29	15	13	73	53	38	33	3.1	27
13	28	64	54	42	17	82	62	42	23	2.7	31

TABLE 27 ANKLE BLEEDS

D = Mean days to complete resolution of bleed

T = Percentage of bleeds requiring retransfusion within 48 hours

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N	DOSE (units /kg).	RESIDUAL TENDERNESS 12h	24h	36h	48h	RESIDUAL MOVEMENT RESTRICTION 12h	24h	36h	48h	D	T
						GRADE I BLEEDS					
15	7	27	13	7	7	80	60	43	20	2.4	20
14	14	54	31	8	8	69	54	31	23	2.5	15
7	28	33	33	29	14	50	40	29	14	1.9	29
						GRADE 2 BLEEDS					
9	7	22	22	22	11	87	67	56	44	3.2	22
19	14	42	11	0	0	89	72	43	19	2.6	16
13	28	58	23	8	0	67	46	8	8	2.0	8

TABLE 28 'NORMAL' JOINTS

D = Mean days to complete resolution of bleed

T = Percentage of bleeds requiring retransfusion within 48 hours

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N	DOSE (units /Kg).	RESIDUAL TENDERNESS 12h	24h	36h	48h	RESIDUAL MOVEMENT RESTRICTION 12h	24h	36h	48h	D	T
						GRADE I BLEEDS					
29	7	14	4	10	7	61	45	39	20	2.8	14
18	14	6	6	6	6	59	35	24	12	2.1	11
9	40	0	0	0	0	44	22	25	11	1.8	11
						GRADE 2 BLEEDS					
6	7	83	50	17	17	100	50	50	33	3.5	33
15	14	50	36	33	27	92	85	82	67	4.5	20
14	28	67	50	43	14	100	93	77	36	3.4	43

TABLE 29 TARGET JOINTS

D = Mean days to complete resolution of bleed

T = Percentage of bleeds requiring retransfusion within 48 hours

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N	DOSE (units /kg).	RESIDUAL TENDERNESS 12h	24h	36h	48h	RESIDUAL MOVEMENT RESTRICTION 12h	24h	36h	48h	D	T
						GRADE I BLEEDS					
28	7	19	0	0	0	67	46	26	11	2.1	18
14	14	7	7	0	0	71	43	36	21	2.2	7
7	28	14	14	14	14	71	57	50	29	2.6	14
						GRADE 2 BLEEDS					
11	7	60	45	30	10	100	80	67	50	4.0	27
13	14	38	25	9	15	77	69	50	54	2.8	38
13	28	67	33	18	0	100	89	64	44	4.2	23

TABLE 30 RESTRICTED JOINTS

D = Mean days to complete resolution of bleed

T = Percentage of bleeds requiring retransfusion within 48 hours

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N	DOSE (units /kg).	RESIDUAL TENDERNESS 12h	24h	36h	48h	RESIDUAL MOVEMENT RESTRICTION 12h	24h	36h	48h	D	T
						GRADE I BLEEDS					
14	7	14	21	14	0	71	64	50	43	3.7	29
28	14	24	11	7	4	81	43	30	26	2.7	14
12	28	18	8	0	0	64	33	27	20	2.2	0
						GRADE 2 BLEEDS					
7	7	40	57	57	57	100	100	100	100	6.4	57
13	14	38	15	8	8	92	58	50	33	3.4	23
11	28	9	9	9	0	90	64	45	45	3.5	18

TABLE 31 RESTRICTED AND TARGET JOINTS

D = Mean days to complete resolution of bleed

T = Percentage of bleeds requiring retransfusion within 48 hours

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DISCUSSION

In the treatment of haemarthroses that are not frozen, high doses (28 units/kg) of factor VIII do not appear to offer any advantage over lower doses (14 and 7 units/kg).

Ankle bleeds of grades 1 and 2 (and by implication grade 0) can safely be given 7 units/kg. Knee bleeds of grades 1 and 2 are adversely affected by lowering the dose of factor VIII from 14 to 7 units/kg: No inference can be drawn about the correct dose for knee bleeds of grade 0. Elbow bleeds of grade 1 and therefore also grade 0 may be treated with 7 units/kg without harm, but grade 2 elbow bleeds seem to need a higher dose.

When a haemophiliac's joint is restricted in movement even in the non-bleeding state it is presumed that previous bleeding episodes have occurred into that joint, that the genesis of haemophilic arthropathy has begun and that synovial adhesions are probably present (Swanton 1959). Recurrent bleeding into such a joint implies that the synovium is hypertrophied and hyperaemic (Gilbert 1977). It is apparent from these results that bleeding in such a situation responds poorly to a low dose of factor VIII. The emergence of increased bleeding frequency into the previously restricted joint should therefore alert both Physician and patient to the need to avoid low dose regimes until the situation has resolved.

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ORIGINAL WORK

5) SUMMARY OF ORIGINAL OBSERVATIONS AND CONCLUSIONS

SUMMARY OF ORIGINAL OBSERVATIONS AND THEIR CONTRIBUTION TO THE RATIONAL USE OF FACTOR VIII:

1) Bleeding frequency declines through adolescence. Intensive care during early adolescence may be well worthwhile in terms of saving joints from the ravages of frequent bleeding.

2) Bleeding into the elbow joint becomes increasingly frequent through adolescence. Scrupulous attention should therefore be paid to restoration of function, limited prophylaxis should be given when recurrent bleeds occur and a programme of physical treatment aimed at strengthening the muscles protecting the elbow joint should be instituted.

3) Bleeds increase in severity through adolescence and and peak at age 14-15. Bleeds at this age should therefore be treated vigorously. This is not the time for low dose unsupervised regimes.

4) Increased use of therapeutic materials has resulted from more frequent transfusions during 1973 and 1977. Higher initial doses for 'high risk' bleeds may therefore not result in more usage of factor VIII.

5) Iliopsoas, retroperitoneal, abdominal wall and buttock bleeds were transfused more frequently than other bleeds. Higher initial dosage in these situations may therefore reduce morbidity.

6) The more frequently single bleeds occur, the more likely is the occurrence of multiple bleeds.

7) Multiple bleeds do not require more factor VIII than would the severest of their component bleeds.

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8) Once weekly prophylactic infusions of factor VIII raising the level to 25% of average normal will reduce the bleeding frequency by about 15%.

9) Twice weekly prophylactic infusions raising the level to 20% of average normal will reduce the bleeding frequency by about 30%.

10) Alternate day prophylaxis raising the level to 15% of average normal will reduce the bleeding frequency by about 60%.

11) Daily prophylaxis raising the level of factor VIII to 30% of average normal is likely to reduce the bleeding frequency by about 90%.

12) The requirements of factor VIII escalate steeply with increasingly frequent prophylaxis usage.

13) Most ankle bleeds do well if treated with doses of 7 units/kg of factor VIII.

14) Most knee bleeds do badly when treated with doses of less than 14 units/kg of factor VIII.

15) Most grade 2 elbow bleeds do badly if treated with doses of less than 14 units/kg of factor VIII.

16) Joints with baseline restriction of movement and increased bleeding into the joint will respond poorly to doses of less than 14 units/kg of factor VIII.

The observations made at this Centre and reported in this thesis have identified high risk situations in adolescence which may be overcome by higher initial doses of factor VIII for bleeding episodes. Expectations of multiple bleeds and the effect of dose levels for these bleeds have been predicted. The effective-

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ness of prophylactic regimes of different frequencies has been shown together with a clear indication of the escalating consumption of factor VIII required by the more effective prophylactic regimes.

Finally, the effect of site, severity and patterns of previous bleeding into joints on the response of those joints to lower doses of factor VIII is emphasized.

A logical extension of this work which delineates situations where lowering the dose of factor VIII is likely to be harmful would be to identify the high risk bleeds which are likely to do badly on standard doses. Stirling and Prescott (1979) and Harris and Stuart (1979) agree that 5-6 units/kg will abort 85% of bleeds. However, the effect of this low dose on the other 15% of bleeds is likely, when major joints are involved, to initiate the very progression to arthropathy which early treatment regimes set out to avoid. These arthropathic joints are likely to bleed more frequently and negate the resource saving aims of low dose programmes. Allain (1979) suggests that a dose of 26 units/kg is required to suppress all bleeds. It is obviously impractical to apply this dose to all haemophilic bleeds, but if the high risk bleeds could be identified, a high initial dose of factor VIII could be selectively used. It is intended to utilize the experience gained whilst doing the work reported here to develop this concept.

Meticulous data collection will form the base for careful analyses of the characteristics of these bleeds which do badly. A statistical package linked to computerized analysis would be the ultimate extension of this project and should identify a large proportion of high risk bleeds.

If Allain's hypothesis is true, then such a project developing from this thesis may finally bring about the elimination of haemophilic arthropathy and allow the home therapy programme to achieve its highest potential - the true normalisation of haemophiliac life.

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