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REPORT OF A JOINT WHO/WFH MEETING ON
THE POSSIBILITIES FOR THE PREVENTION AND CONTROL OF HAEMOPHILIA

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1. INTRODUCTION

Physicians from several countries who are active in haemophilia care and in the World Federation of Haemophilia (WFH) conferred together at the Headquarters of the World Health Organization (WHO) to define current principles of haemophilia management and probe ways to improve access to such care in a wider array of countries, as described in this paper. During the 1990s, excellent comprehensive haemophilia care programmes should be found routinely in industrialized countries, and new or expanded programmes should be promoted in countries with evolving health care systems.

2. DESCRIPTION AND DIAGNOSIS OF THE DISEASE

Haemophilia is a hereditary bleeding disorder affecting 15 to 20 of every 100,000 males born, with equal incidence in all ethnic groups and geographic areas that have been surveyed (Table 1). Prevalence, which depends upon survival, varies according to available medical care. The disorder is inherited in a sex-linked recessive pattern, thus, males are affected and females are carriers of the trait and occasionally are affected, usually mildly. Approximately one-third of cases are caused by recent genetic mutations. Excessive, prolonged or delayed bleeding occurs because of the absence, decrease or deficient function of plasma coagulation factor VIII or IX, causing haemophilia A (classic haemophilia, approximately 85% of cases) or haemophilia B (Christmas disease, approximately 15% of cases). Within a given family, affected patients have similar levels of the relevant coagulation factor. Most patients coming to the attention of haemophilia centres have severe deficiencies of the factor and require extensive medical supervision. At any given level of factor deficiency, the two types of haemophilia are clinically indistinguishable. In severe haemophilia, the most common site of bleeding is into the large joints of the limbs (for unknown reasons) and the second most common site is into large muscles. Repetitive episodes of bleeding into the same site are commonly seen. Unless such bleeding is controlled promptly by infusion of the deficient factor, progressive arthropathy and muscle atrophy ensue, leading to serious physical, psychological and social handicaps¹⁻⁴.

Until recently, the foremost cause of death has been haemorrhage, especially in the cranium⁵⁻⁷. In countries with highly-developed haemophilia care programmes, therapy with plasma derivatives has decreased mortality from central nervous system bleeding and from other sites of bleeding. In the past decade, the foremost causes of death have stemmed from side-effects of treatment, including acquired immune deficiency syndrome (AIDS) and liver disease secondary to hepatitis⁸⁻¹¹. Survival in patients who do not suffer from these infections approaches that of the general population. Thus, improvement in survival and increasing average age was seen in populations of haemophiliacs receiving plasma derivative therapy during the 1950s through 1970s, but a decrease in survival was seen in the latter half of the 1980s and is expected to continue into the 1990s because of deaths from AIDS. With introduction of viral-inactivated plasma derivatives in the mid-1980s, excellent life-expectancy can be predicted for patients not previously infected, who include, of course, patients born in the 1980s and coming of age in the early 21st century. This cohort of patients, if treated by current standards, should reach adulthood in good physical condition, autonomous and fully active, and able to take similar positions in society as their non-haemophilic brothers.

The diagnosis of haemophilia is considered if a person with excessive bleeding has a family history of the disorder, or, without such a history, if the bleeding pattern suggests the condition. In families with a history of haemophilia, infants should not be circumcised until the disorder has been excluded by specific laboratory test. Severe haemophilia usually is too obvious to present a diagnostic dilemma.

Persons with mild haemophilia may have prolonged bleeding only after notable trauma or surgical operations. Some persons are found to have mild haemophilia because a routine pre-operative screening test, such as the activated partial thromboplastin time (APTT), is abnormal. Some persons with mild haemophilia have a normal APTT, thus, if the history of bleeding is characteristic, specific clotting factor assays should be performed in experienced laboratories (usually found in specialized centres) which participate extensively in proficiency testing and other quality control measures. Such laboratories also can screen patient plasma for antibodies (inhibitors) to coagulation factors, which develop in some patients after treatment, and often are suspected when a patient does not respond adequately to plasma derivative treatment.

3. CURRENT MANAGEMENT OF HAEMOPHILIA

3.1 Comprehensive centres

Optimum management of haemophilia is achieved through specialized expert interdisciplinary comprehensive care centres, which supervise local medical care and patient self-infusion of plasma derivatives. Centralized supervision gives patients with a rare disease access to knowledgeable experts in an efficient manner. Improved therapies can be instituted quickly.

Centres usually are located within general hospitals, although some successful ones have been established in other settings. A fundamental requirement is a designated physical area where haemophiliacs may expect a sympathetic and knowledgeable reception. Preferably, all staff are based in or near the centre so that patients can receive all needed treatment at one place, on one occasion, a situation of great benefit to patients living at a distance. Typically, staff meet regularly to discuss and plan patient management. Care of acute problems such as bleeding episodes must be prompt, appropriate, and available at all hours.

Frequency and purpose of visits to a comprehensive centre depend on patient circumstances. Newly-diagnosed patients, often babies, are seen often. Routine care such as immunizations may provide an opportunity to educate parents about haemophilia. When a child is a few years old, families are prepared to take over infusion of plasma derivatives. They are taught about signs and symptoms of bleeding, management of emergency situations, decisions about which hemorrhages require centre treatment, preparation of the plasma derivative for infusion, calculation of dosage, safe venepuncture and infusion technique, and the appropriate method of maintaining communication with the centre about bleeding episodes. Such training may take many hours over several days. When a child reaches the age of about 10 years, he is taught to take over his own infusions. Adolescents and adults without complications may be seen at the Centre for routine re-evaluation and advice yearly. Such examinations typically include interval history and physical examination with recommendations from the haematologist for plasma derivative use; evaluation of the musculoskeletal system by a physiotherapist or orthopaedic surgeon with recommendations for fitness programs, therapeutic exercise or orthotic devices; examination by a dentist with plans for appropriate care (because haemophiliacs often have avoided dental care, or have had difficulty finding a willing dentist, for fear of bleeding); a conversation with the social worker to address problems of personal and family adjustment, school or work achievement, and finances of medical care; and a visit with a nurse-coordinator who serves as the primary contact for patient and family, integrates care, and arranges all special consultations. Patients with special problems, such as unstable musculoskeletal disability, poor psychological or social adjustment, or Human Immunodeficiency

Virus (HIV) infection usually require more frequent visits. When care of HIV-infected patients is integrated into centre activities, continuity of care is maintained for the patient. Consultation is obtained as needed from specialists in infectious disease or other fields. Additional funds are needed for care of these patients, including additional laboratory tests (such as counts of CD4 lymphocytes) used to monitor the stage of infection, and drugs, such as zidovudine and pentamidine, which slow the progress of HIV infection or prevent opportunistic infections.

3.2 Haematologic management

Haematologists have been involved intensively with the care of haemophiliacs for decades and protocols for haematologic management have been described in generally-available sources¹². Some issues remain unresolved. One such issue is the minimum effective dose of factor VIII (or factor IX) for hemostasis. Doses of factor VIII in the form of concentrate used in some industrialized nations in the 1970s and 1980s were generous. Through close observation at a boarding school for boys with haemophilia¹³, dosage has been related to the probability of rapid haemostasis depending upon severity and duration of bleeding and on the susceptibility of any particular joint in a particular boy to frequent hemorrhaging, thus suggesting that minimal adequate dosage must be judged for each haemorrhage in each patient. To conserve factor products, close communication between patient and physician or nurse is needed.

Another unresolved issue is the relationship between total dosage of clotting factor received and long-term musculoskeletal condition. Results of the international Orthopaedic Outcome Study as well as studies in the few countries where prophylactic infusions from an early age are standard soon will help define the amount of musculoskeletal damage that can be prevented, and the price of prevention.

Of major importance is elimination of blood-borne infections, which has become possible through physical or chemical viral inactivation processes, such as heat or solvent detergent treatment applied to clotting factor concentrates¹⁴⁻¹⁵. Furthermore, various chromatographic processes are being used to produce factor VIII and IX concentrates of very high purity. Highly purified factor IX concentrate is specific replacement therapy for haemophilia B, avoiding the excess thrombogenicity (for example, deep vein thrombosis) sometimes associated with concentrates containing other clotting factors in addition to factor IX. Factor VIII concentrates prepared by recombinant DNA techniques have been developed recently and have now entered large scale clinical trials. Efficacy has been demonstrated, but long-term safety studies continue. Advances in production technique will affect cost and may determine whether recombinant coagulation factors will replace treatment with plasma derivatives to a large extent. This methodology also permits production of segments of the native proteins, or mutants thereof, in the hope that they might circulate longer or prove less antigenic.

Blood-borne infections also can be avoided in patients with mild hemophilia A (and in patients with von Willebrand's disease) by use of the synthetic vasopressin analogue, desmopressin ("DDAVP") which stimulates release of factor VIII and von Willebrand factor from storage sites. The drug was given initially by the intravenous route, but recently more convenient routes of administration, including subcutaneous injection and nasal sprays, are proving to be effective.

Inhibitor antibodies that arise against the deficient factor create major impediments to control of bleeding. In a majority of patients, inhibitors can be suppressed with regimens of immune tolerance induction, which utilize regular

administration of the factor concentrate, sometimes together with immunosuppressive drugs. Ways to control bleeding in patients with inhibitors are being studied intensively. Concentrates used include high doses of human factor VIII, or porcine factor VIII (because human inhibitors inactivate non-human factor VIII to a much lesser extent than they inactivate human factor VIII), or activated prothrombin complex concentrates (which may contain activated factors or complexes of factors that bypass the need for factor VIII), and, currently under trial, separate components of prothrombin complex that also bypass factor VIII, most notably, factor VIIa, now made by recombinant technology. Reduction of inhibitor levels by adsorption of antibodies from extracorporeal plasma during plasmapheresis also is available in some sites.

The future holds the hope of cure. A few patients undergoing liver transplantation subsequently have produced normal levels of the formerly-deficient factor. The mortality rate of that procedure is substantial and patients must endure life-long immunosuppressive therapy, so such a procedure is justifiable only for selected patients with end-stage liver disease. Organ transplant may not be reasonable, but gene transplant may become possible. It is already possible to introduce the factor VIII or factor IX gene in human cell lines which then synthesize functional coagulation factors¹⁶⁻²¹. If the many technical problems of gene transplants are solved by the end of the decade, such procedures may put an end to the need for plasma derivative therapy.

3.3 Management of musculoskeletal problems

Functional disorders caused by the sequelae of joint and muscle haemorrhages can cause long-lasting problems²². Centre personnel try to reduce the incidence of early impairments, to limit or reverse disability and prevent the progression of disabilities into handicaps that limit the patient's ability to fulfill the role normal to his social circumstances (Table 2). Amongst the permanent staff of comprehensive care centres should be included persons (such as a physiotherapist, an orthopaedic surgeon, a rehabilitation specialist, a rheumatologist, or the like) dedicated to prevention and treatment of musculoskeletal disorders. Such staff should examine patients at least once a year, assessing range of motion of joints and strength of muscles, so that problems may be brought to attention at a stage at which prevention of impairments is still possible.

The patient with haemophilia should be advised to undertake regular physical activities and participate in sports to develop and maintain a strong musculature, for muscular patients are less likely to sustain joint or muscle haemorrhages and, if such injury does occur, recover more rapidly, than patients with weak muscles. Parents of young patients, of course, also must be instructed about the benefits of exercise. Education is undertaken during visits to the centre and re-inforced by publications easily understood by families and by local paramedical personnel, with diagrams. The sports advised for the patient are those with the least likelihood of trauma and the greatest potential for good activity for all joints and muscles (Table 3). Of these sports in which most haemophiliacs can participate safely, swimming is the most beneficial for the development of all muscles. Boys do not want to be different from their peers, so sports also must be considered in which the physical, psychological and social benefits may outweigh the risk of trauma. These sports should be supervised by experts who give the haemophiliac proper training using reliable equipment. The patient also should be taught exercises to be done at home.

To prevent or reverse early impairment of function due to acute haemorrhage, the musculoskeletal specialist should use and teach such strategies

as immobilization of the limb and use of ice during an acute haemorrhage, and, after hemostasis is secured, use of muscle setting exercises followed by active mobilizing exercises and active stretching. In some instances, such technology as pulsed short wave diathermy, ultrasound, and interferential currents may be useful. For patients with disabilities such as unstable or painful joints or muscle wasting, the facilities to produce orthoses (splints, braces and the like) should be available²³. Stabilizing a joint by taping or similar inconspicuous means is more acceptable to youngsters than heavy braces. Useful modifications of shoes include heel lifts (when one leg is shorter than the other) or shock-absorbing soles (of great benefit for arthritis of the ankle). Wheelchairs and adaptations to other mobility devices such as bicycles and automobiles should be made, and adaptive furniture or architectural changes made at home or work to accommodate the patient.

When pain or contractures are causing disabilities, the orthopaedic surgeon should have facilities for operative interventions such as osteotomies, joint replacement or whatever operation in his experience will give the best functional result in that particular patient. Haematological care (laboratory facilities and plasma derivative therapy), operating rooms, post-operative facilities and care should be of a high standard. A centre familiar with the operative treatment of haemophilia patients is essential. The orthopaedic surgeon should use procedures with which he has experience and should choose proven prosthetic models.

Several orthopaedic rehabilitative procedures have proven useful in haemophilia. When haemorrhages are recurrent and synovitis has developed that does not respond to conservative management (such as prophylactic factor replacement, anti-inflammatory medications, and a combination of protective splinting with a graded exercise programme, radionuclide synoviorthesis or arthroscopic synovectomy should be considered. When there is angular deformity at a painful deformed joint, osteotomy may be a useful procedure. A painful arthritic elbow with restricted range of motion may benefit from excision of an enlarged radial head. A painful, severely arthritic ankle joint with restricted range of motion is best treated with arthrodesis. Good range of motion in the hip and knee are important for the activities of daily living, thus, if one of these joints is painful due to advanced arthritis, total joint replacement seems to be the treatment of choice.

Rehabilitation is not the work of the musculoskeletal specialist and haematologist alone. The social worker assesses the patient at the centre and also visits the patient at home, contacts local authorities, school or work, and educates them about haemophilia, to try to achieve integration of the person with haemophilic in his society. Advice as to choice of school and vocation should be given in collaboration with a psychologist, who may want to test the patient. If there are disabilities that hinder the patient during his education or work, advise about possible adaptations, or other forms of schooling, or retraining, should be done as a joint effort of several centre staff members.

4. GENETIC SERVICES

4.1. Genetic counselling

The aims of genetic counselling are to communicate the features and recurrence risks of the disorder with information about possible alternatives such as prenatal diagnosis and selective abortion in a non-directive way. Emotional support for the consultant and the family must be provided during and after counselling regardless of the decisions which may have been made. In

order to make decisions about reproduction, it is not sufficient to be armed with technical information, it is also necessary to work through the emotional gamut of guilt, resentment, anger and fear.

Ideally, the potential carrier should know of her possible carrier status from an early age, through the haemophilia centre and with peer groups. Personal decision about marriage and childbearing can then be based on a firm foundation.

Haemophilia centres provide the most appropriate setting for genetic counselling. Parents also can be offered guidance on introducing their daughters to an understanding of inherited disorders and their own potential to be carriers. Sisters should be invited to support groups arranged for adolescent haemophiliacs and their parents. More definitive counselling should be offered to girls after puberty. They should be invited to bring prospective partners in parenthood to counselling sessions so that decisions about reproduction are made together, avoiding subsequent guilt, blame and resentment wherever possible. Women who request investigation and counselling for the first time when they are already married should be urged to attend with their husbands for the same reasons.

Counselling sessions should not take the form of a lecture where the carrier is flooded with information which is difficult to absorb under stress. Drawing the family tree is an easy and non-threatening way to start the session. The carrier's understanding can be ascertained through simple questions which encourage her to think about the problems. It is important to find out whether there are pressures for a couple to have children and who might be disappointed if a son proved to have haemophilia. Hypothetical, future-oriented questions help the couple understand some of the long-term implications of having a child with haemophilia, such as questions about expected help with child care, or the ability to reside near a centre.

For some haemophiliacs and their relatives, abortion and attempted prevention of transmission of the defective gene are unacceptable on moral grounds. Some carriers regard selective abortion as implied rejection of a much-loved relative, such as a haemophilic father, brother or son.

Carriers are faced with difficult decisions. Families have differing priorities and choose different courses of action. Whether a carrier has decided to have selective abortion or have opted to take the chance of having a haemophilic son, she should not be made to feel guilty about that choice by staff members who might have chosen differently for themselves.

4.2 Carrier detection and prenatal diagnosis

Accurate carrier detection and early prenatal diagnosis are very effective forms of control of an inherited disease. For every haemophiliac, there are between five and six women at risk of being carriers (potential carriers). Obligate or proven carriers (daughters of haemophiliacs, mothers of haemophiliacs with antecedent haemophilic relatives) can be identified easily from the family pedigree. Among potential carriers are those with a maternal haemophilic relative and those women (about 30% of mothers of haemophiliacs) with one haemophilic son and no further family history. Most of the latter women have carried the trait unwittingly, due to a recent mutation in germ cells of their parents or grandparents, but some may have produced a unique ovum with the mutation. Some women may have somatic or germline mosaicism, complicating attempts at accurate diagnosis.

Phenotypic diagnosis of the carrier state is based on several observations²²⁻²³. Obligate carriers of haemophilia have, on average, 50% of the normal plasma level of factor VIII or IX measured biologically. Immunological measurements (factor VIII or factor IX coagulant antigen) show concomitant reductions except in cases where, in the patient, normal plasma levels of biologically inactive factor are present, that is, in cross-reacting-material-positive (CRM+) haemophilia. Because of the large normal range of factor VIII and IX in plasma and the process of lyonization (random inactivation of one of the X-chromosomes in females) a significant overlap between plasma factor levels found in normal women and obligate carriers is found. In haemophilia A, the evaluation can be improved by also measuring the plasma level of von Willebrand factor (vWF), which serves as a carrier of factor VIII in plasma and also protects unactivated factor VIII from proteolytic degradation. Thus while the ratio of vWF to factor VIII is 1.0 in normal plasma, in carriers of haemophilia A it is close to 0.5. Determination of this ratio is the best phenotypic discriminant for carrier detection. Complex statistical analysis of these measurements has been reported. Even so, some five to ten percent of obligate carriers of haemophilia A still appear to be phenotypically normal given the best estimates of plasma factor VIII and vWF levels.

Phenotypic prenatal diagnosis by measurement of factor VIII or IX levels in fetal blood obtained at fetoscopy at 18-20 weeks gestation has been very effective in skilled hands²⁴. However, since sampling is only possible in the second trimester, any resulting termination of an affected fetus is at a gestational age that many find unacceptable.

The ideal method for carrier detection and prenatal diagnosis is identification of the affected gene in possible carriers and in fetuses at risk, that is genotypic analysis, which is rapidly supplanting phenotypic analysis wherever possible^{25,26}. Identification and tracking of the defective gene can be performed in two ways. **FIRSTLY**, the identification of normal polymorphic DNA variations within or close to the gene can serve as markers for that gene. Such polymorphic changes generally are single nucleotide alterations. Those most readily detected are changes which alter the cutting site of a restriction endonuclease and thus change the fragment pattern of DNA digested with such an enzyme. Such polymorphisms are termed restriction fragment length polymorphisms (RFLP). Restriction enzyme fragments are generally visualized by the Southern blot procedure using specific gene probes. The usefulness of an RFLP depends on several factors, including frequency within a specific population. For a series of RFLPs the overall usefulness is related to the level of linkage disequilibrium between them (i.e., the tendency for one allele of one RFLP to associate with a particular allele of a second RFLP). In general the lower the level of linkage disequilibrium the more useful a second RFLP will be. Crossovers may also occur between the locus of the RFLP and the gene locus if the RFLP is not within the gene but linked to it. In haemophilia A, five intragenic RFLPs, all diallelic, detected by restriction enzymes BclI, BgII, XbaI, MspI and HindIII have been described. Details of frequency are given in Table 4, with an indication of significant ethnic variations. Linkage disequilibrium means that the overall usefulness of these intragenic RFLPs within populations of European descent is 70-80%. In addition, two linked polymorphic loci close to the the factor VIII gene locus have been observed. The loci, detected by probes DX 13 and ST 14, contain BgIII and TaqI/MspI RFLPs, the latter being multiallelic. A crossover rate of about five percent between the DX13/ST14 loci, which are close together, and the factor VIII gene limits the usefulness of these markers. In haemophilia B, six intragenic factor IX RFLPs and one useful linked RFLP have been described (Table 5). All are a result of single nucleotide changes except for the DdeI polymorphism which results from the presence or absence of a 50 bp nucleotide inset. The

alanine/threonine dimorphism at amino acid 148 in the factor IX activation peptide can be detected by digestion with M_nII, use of specific oligonucleotide probes or by specific monoclonal antibody based immunoassays. The recently described HhaI RFLP is very useful but can be detected only using DNA amplified by the PCR reaction since the cytosine residue in the HhaI site in genomic DNA is methylated, so blocking HhaI activity. Overall, by combined use of the intragenic RFLPs, some 90 percent of females of European descent are heterozygous. This figure is considerably lower in other ethnic groups.

The SECOND method of gene tracking is by detection of the specific defect at the DNA level that causes haemophilia in a particular individual. In the past, such detection has required a considerable amount of work, particularly for haemophilia A because of the size and complexity of the factor VIII gene (181 kb in length with 26 exons). Specific mutations causing haemophilia A include total and partial deletions, insertions and point mutations, detected in the factor VIII gene in about ten percent of patients studied. Many of the point mutations involve the CpG dinucleotide mutation hotspot where a C to T change occurs. For haemophilia B, the ability to detect DNA defects has improved dramatically in the past two years with the introduction of the polymerase chain reaction (PCR) technique of DNA amplification. With PCR, complete DNA sequencing of the eight exons within the factor IX gene has allowed the defect to be found in almost all patients examined. As with haemophilia A, a series of deletions, insertions, and, in particular point mutations have been described, 30% of which involve C to T transitions in CpG dinucleotides.

Genotypic analysis has a considerable advantage over phenotypic analysis since it generally gives an absolute diagnosis when informative. Carrier detection by intragenic RFLP analysis can be considered to have a very high level of accuracy as, of course, has direct defect detection. Single tests are generally required and modern PCR technology means that only very small samples of blood or other tissue are required. Importantly, prenatal diagnosis can be performed in the first trimester, between ten and twelve weeks gestation, by analysis of DNA obtained from chorionic villi samples. RFLP analysis, because it does not detect the gene defect but only a polymorphic marker close to it, does have certain limitations. Essential family members must be available to allow for unambiguous tracking, and certain females within the family must be heterozygous for at least one of the RFLPs available. Although linkage disequilibrium reduces the overall usefulness of the combined RFLPs, among females of European descent 70-80% will be heterozygous for the known intragenic RFLPs for haemophilia A and up to 90% for haemophilia B (these figures are lower in certain other ethnic groups studied). Extragenic linked RFLPs significantly increase these figures but also introduce a crossover error rate of up to 5%. Mistaken paternity can also occasionally cause errors of interpretation. RFLP analysis is of limited use in families with sporadic haemophilia (that is, no prior history of haemophilia) where it can diagnose the non-carrier state in some females but cannot rule out the carrier state in others. The advantages of RFLP analysis are that it is applicable to all types of haemophilia irrespective of the gene defect, and, with PCR technology, it is becoming a relatively simple, inexpensive and quick procedure. In contrast to direct defect detection, RFLP analysis may be informative when none of the haemophiliacs in the kindred are alive or available.

DNA is extremely stable and can be stored for many years. Because genotypic analysis by direct defect detection invariably requires DNA from an affected haemophiliac, it is very important to obtain and store suitable samples, particularly in view of the current high mortality rate from AIDS in haemophiliacs.

5. HAEMOPHILIA PROGRAMME DEVELOPMENT

5.1 General observations

The development of a haemophilia programme requires, firstly, recognition of need, and then the knowledge and enthusiasm necessary to secure and develop resources. Evidence of need is gathered by creating a registry of patients with haemophilia and related coagulation disorders, identifying their demography, severity of illness and unmet needs. Haemophilia care is an impossible financial burden for the affected individual and his family, thus, public funding is needed. In applying for such funding, it may be helpful to point out that appropriate haemophilia care has proven to prevent handicaps. In terms of outcome, therefore, the treatment of haemophilia may be considered a highly effective use of resources. In considering costs, it is important to assess the costs of non-treatment or under-treatment, for example, dependency of the patient and his parents, which result in long-term economic burdens falling directly or indirectly on government authorities.

Whenever possible, the mechanism for providing haemophilia care should be linked with that for other major health problems in a country or region, e.g., sickle cell disease, thalassaemia or thrombotic disorders. This linkage mechanism will not only strengthen the programme for the control and prevention of these associated disorders, but also has the potential to improve health care generally, particularly in the areas of public health, blood transfusion services and diagnostic laboratory capacities and facilities.

Funding of a haemophilia programme can be met in different ways. In countries with national health systems, haemophilia care is assumed to be covered. Supplementary funds, however, may be needed for specialized haemophilia centres. Systems requiring patient co-payment for medications and medical care must exempt persons with expensive lifelong disorders such as haemophilia. In some countries, intravenous infusion of blood products at home is forbidden by law, thus, legislation is needed to exempt haemophiliacs. In some countries without national health systems, only employed persons have health insurance, thus excluding most haemophiliacs. In these countries, governments may be asked to list haemophilia amongst diseases causing exceptional social and financial burdens, thereby entitling patients to free medical care. Funding haemophilia care must be the responsibility of governments.

Haemophilia programme development requires determined leaders. Typically, the initiator or developer of a programme is a specialist physician with a main commitment within the fields of haematology and/or blood banking. Lay organizations (such as haemophilia societies, often led by parents of affected children and by adult patients) sometimes are the driving forces. Whichever the case, successful programmes are difficult to establish and maintain without the financial and other support of government authorities.

Delivery of comprehensive care requires active collaboration of a variety of health care professionals. Ways must be found of interesting such persons in haemophilia-related problems, persuading them to make commitments of time and effort, and educating them in the principles of haemophilia management. The motivation for such staff is rarely financial. More usually, they are attracted by the intrinsic interest of the work, the potential for recognition of their expertise and contribution to a field of medicine in which relatively few people can be regarded as experts, and opportunities for academic studies.

The concept of the "haemophilia centre" is now well-established as essential, but the specifications and functions of centres may differ greatly according to local circumstances. In countries with evolving health care systems, haemophilia centres are highly likely to be part of larger haematology services or be closely associated with blood banks. As programmes mature, the organizational framework may shift towards fewer but larger centres with expanded functions requiring high levels of expertise and technology, but with less involvement in day-to-day aspects of primary care. A major cause is improvement in education of the patient, the family and local health practitioners, and expansion of supervised self-infusion programmes in which family members or local medical personnel administer plasma derivatives quickly at the onset of haemorrhages. Self-treatment programmes have the advantage of providing rapid hemostasis and thus minimal damage to tissues, minimal sequelae, and little disruption of normal schedules and activities. On the other hand, new problems may arise with such programmes, in particular, a shift of control and responsibility away from the physician towards the patient and family. The former may be unhappy to lose control and the latter may not be prepared to accept responsibility.

The mainstay of haemophilia care is adequate availability of lyophilized virus-inactivated concentrates of plasma clotting factors. Cryoprecipitate and plasma, which are not viral-inactivated, sometimes are still used but are not ideal²⁷. Concentrate availability entails an adequate supply of plasma (which may be obtained through separation of blood components or through plasmapheresis) and the necessary technology to fractionate it. Some countries develop and use their own fractionation facilities, either private or state-owned. Other countries contract with external fractionation facilities, which may be a good means to avoid unnecessary duplication of expense and effort. The type of concentrate produced for each country is decided therein, taking into consideration scientific evidence of benefit, counsel of local haematologists, amount of plasma available and fractionation technologies available. The goal is to make enough concentrate available to prevent most handicaps in all the haemophiliacs in the country.

5.2 The role of transfusion services

Countries without adequate transfusion services are not ready for initiation of modern haemophilia care. Such care can be developed only where there is a well organized and efficient blood transfusion network continuously providing adequate, safe blood products on an equitable basis. Cryoprecipitate and fresh-frozen plasma, the simplest blood products used to treat haemophilia, can be prepared easily as by-products from whole blood donations with elementary technology within the grasp of all countries. To prepare viral-inactivated products, the introduction of freeze-drying technology and heat-treatment is important. The League of Red Cross and Red Crescent Societies (LRCS), WHO and the International Society of Blood Transfusion (ISBT) stand ready to assist developing countries shape their blood transfusion capabilities and establish an integrated quality assurance programme. Problems in providing adequate transfusion services have increased because of the AIDS epidemic for an additional financial burden is entailed to test for HIV. An international group, the Global Blood Safety Initiative (GBSI), initiated by WHO with input from LRCS and ISBT, has published its first recommendations on the structuring of safe and effective blood transfusion organizations, on the equipping and supply of laboratories and blood banks, and optimal use of essential blood components, plasma derivatives and substitutes. Recommendations for training personnel (and funding such training) are being formulated.

Self-sufficiency is becoming the goal of national transfusion services. Human blood for transfusion should be regarded as a national resource to be shared by all on an equitable basis. The community is the basic shareholder and the medical profession is the principal protector of the resource. All appropriate segments of the population should be motivated to donate blood voluntarily. National health authorities should accept their fundamental responsibility to protect the blood donor and the patient by instituting good standards of practice and a mechanism for inspection, control and registration.

A national blood transfusion policy should be instituted and extended to regional and local levels. Items covered in the policy should include donor recruitment, donor selection, blood collection methods, component production and preservation, plasma fractionation, creation of reserves and education of the medical community on the appropriate use of blood and its components. A well organized network of regional blood transfusion services should be supported. Quality assurance is the primary responsibility of regional services.

A national fractionation policy is needed to facilitate production of the needed amount of quality plasma products such as purified and safe factor VIII preparations, albumin and gamma globulin, whether processed within the country or at another reliable location. One or more national reference laboratories should be organized and maintained for development of blood bank technology and for training and ongoing education of all blood bank personnel.

5.3 Specific proposals for pilot programmes for haemophilia care

Pilot programmes for the establishment or betterment of haemophilia care have been a major interest of WFH. Such programmes are small in scale and, of course, may not be successful in every instance. A country targeted for such a programme should meet certain pre-requisites, including the presence of a functioning blood transfusion system which has the potential for, or includes, some blood component production, and the presence of a key person who has espoused interest and willingness to provide haemophilia care. Pilot programmes may be applied at two levels, at a primary level in a country that is about to initiate haemophilia care or at a secondary level in a country with an existing haemophilia programme that wants to increase its degree of sophistication in haemophilia care. The strategies for primary and secondary level programmes differ, and emphasis varies according to the specific needs of the target country. Inherent in any strategy for a pilot programme must be mechanisms for assessment of effectiveness: if a pilot programme is satisfactory, the next logical step would be introduction of a major or model programme for haemophilia care in that country.

Selection of potential target countries is difficult. At the primary level, certain countries which have expressed a special interest in haemophilia care and where some blood transfusion activities are undertaken are considered. At the secondary level, several countries well recognized by WFH could meet necessary criteria for further development, including existence of a haemophilia care programme, a functioning transfusion service, some dedicated medical and paramedical personnel and an expressed desire to increase their level of expertise and degree of clinical and laboratory sophistication with regard to the delivery of haemophilia care. If such countries are also strategically placed in a particular geographic area, they might then serve as a reference centre for that area and undertake the task of developing and improving haemophilia care in neighbouring lands.

At the primary level, consideration should be given to countries, where a transfusion service is present and a key person is identified. In Zimbabwe,

Zambia and Commonwealth countries are moving together towards a safer blood programme; thus, this may be an appropriate time to provide impetus to haemophilia care there. In the People's Republic of China, the Institute of Haematology at the Chinese Academy of Medical Sciences in Tianjin has expressed great interest in the development of a haemophilia programme. A National Haemophilia Co-operative Group for China was established in Nanjing in 1984. Blood transfusions services exist in Tianjin, Beijing and Shanghai. China is highly qualified and a high priority target for primary haemophilia care development²⁸.

A transfusion service exists in Indonesia and an interested physician has been identified, whilst in Vietnam, active steps are being taken to rehabilitate their medical services and the Institute of Haematology in Hanoi has a strong interest in haemophilia care.

In the vast subcontinent of India, transfusion services exist in several cities and WFH has recently staged workshops in Calcutta, Trivandrum and New Delhi. Progress in establishing haemophilia care, however, is slow.

In the Philippines, a transfusion service and considerable medical expertise exist but haemophilia care is lacking in many parts of the country.

Attention to eastern Europe may be appropriate. Much can be done for haemophilia care in such countries as Poland, Romania, Hungary and Czechoslovakia. In the USSR the current situation augers well for new approaches to haemophilia care.

In South America, WFH workshops recently have been staged in Bogota and Medellin in Colombia and one soon will take place in Santiago, Chile.

At the secondary level, several opportunities exist. In the Malay peninsula, transfusion programmes exist in Kuala Lumpur, Malaysia and also in Singapore, but the outreach to haemophilia care is limited. An excellent transfusion service exists in Bangkok with considerable modern technology and sophistication, thanks, in part, to the France's Cultural and Scientific Exchange Programme. Haemophilia care is good in Thailand, but this country now has a vast potential for expansion of haemophilia care as well as the potential ability to provide help to neighbouring lands such as Vietnam, Indonesia, Sri Lanka and perhaps even Pakistan and India.

Costa Rica is an exemplary model for haemophilia care and one of the triumphs of WFH. This country now wants to develop more sophisticated diagnostic methods including carrier detection and prenatal diagnosis by genomic analysis, and also wants to develop new therapeutic products. If assisted to achieve these goals, Costa Rica can then help expand haemophilia care in Central America, northern South America and the Caribbean. Argentina has standards of haemophilia care similar to those of Costa Rica and also has the potential to help expand haemophilia care in neighbouring lands such as Uruguay, Paragúay, Bolivia, Peru and parts of Brazil.

The International Haemophilia Training Centres Committee of WFH is concerned with introducing and expanding the knowledge of medical care of people with haemophilia in the developing world²⁹. Attempts to achieve this objective are made by two methods. The first involves the award of Fellowships to medical or paramedical persons with a proven interest in haemophilia in their own countries who are assured of being able to continue working in haemophilia care on return home after a Training Fellowship in a centre of excellence. The second method is the utilization of workshops, in which a short but intense

teaching exercise is conducted in a third world country by persons selected by the Training Centre Committee. These workshops may consist of open consultative clinics, "wet" laboratory teaching and lectures by the visiting team.

The International Haemophilia Training Centres (IHTCs) are a group of 22 strategically located haemophilia centres throughout the world (Table 6). Each of these centres has comprehensive facilities for the treatment of persons with haemophilia and operates under the leadership of a Director who is a member of the Training Centre Committee. (For geographic and linguistic reasons, a few centres were included which provide excellent primary care but may not have the advanced technology of the most industrialized countries, thus, they may qualify for secondary development). Most of these centres are located in university affiliated teaching hospital environments. Centres may be called upon to accept Fellows for short training periods or to staff relevant workshops. The Directors' policy on awarding Fellowships is to locate the trainee in an IHTC where geographic, cultural and ethnic conditions approximate those in the trainee's homeland. Languages spoken by the trainee obviously is a major factor in placement. Since its inception in 1970, over 80 Fellows have been trained in IHTCs.

In WFH Workshops, formal instruction is not of itself sufficient to improve haemophilia care. WFH executive members must conduct formal consultations with local or national health department officials to encourage support of future haemophilia care. Indeed, a commitment by health authorities to develop haemophilia care is advisable. Parallel commitment to improvement of blood transfusion services and instruction on blood transfusion principles and organization is an essential part of workshop programmes. To date, more than 22 workshops have been held under WFH auspices. Local costs usually are met by the host country but travel costs for a faculty of five or six persons, and the cost of minimal educational materials, usually are borne by WFH. The cost of providing workshops and establishing diagnostic laboratories for haemophilia (assuming the existence of a clinical laboratory to which they may be appended) and more sophisticated laboratories for genomic analysis are given in Table 7.

Given the inherent interest in haemophilia displayed, the personnel present and existing transfusion programmes, it may be advisable to develop combined WFH-WHO workshops in two or three specific countries over the next two or three years. The establishment of early haemophilia programmes in these countries following the workshops would be compatible with WHO and WFH ideals. Subsequent objective follow-up assessments of achievements in these countries will guide implementation of similar proposals in other countries.

At the same time, it may be advantageous to mount a WFH/WHO effort at attaining a more sophisticated level of development in two countries with already established haemophilia care programmes. Such developments might concentrate on the control of haemophilia at the genetic level by emphasis on carrier detection and counselling. Other areas of concern might include improved diagnostic methods and improved management of musculoskeletal complications of haemophilia. Countries receiving such training should be encouraged to support and instruct the efforts of neighbouring lands towards haemophilia care. The development of teaching, ambassadorial and diplomatic skills would be involved.

5.4 The example and advice of Thailand

Developing countries contain three-quarters of the world's population. They differ markedly in many ways, and implementation of haemophilia programmes should be adjusted to suit each country and region. Thailand has been

exceptionally successful in establishing an excellent haemophilia care network, beginning in 1978-80 with conferences on bleeding disorders to interest and motivate health authorities. Those responsible for the triumph emphasize the importance of support from government health authorities. Now that infectious diseases are well-controlled in many countries, non-communicable diseases have gained recognition as important health problems. At the beginning, programmes should not be limited to haemophilia care but should include medical care for all bleeding disorders. Although the prevalence of haemophilia is low, patients bleed frequently and have many problems with economic impact. The impact of bleeding problems is not limited to haemophilia. In addition, a larger number of people are affected by bleeding disorders for other reasons such as infections, liver disease, malignancies, snake bites, and surgical and obstetric complications. Plans for haemophilia care should include improvement of blood banks, blood products, haematology and coagulation laboratories and other medical facilities, thus benefitting not only haemophiliacs but other patients as well, while raising the standards of medical care in general and arousing the interest of a wider spectrum of health care providers. Haemophilia programmes will be successfully implemented in the health system when government authorities recognize the significance of effective management of bleeding disorders, improve the blood bank standard and include them in their national health development plans and national health care system.

A national centre for blood diseases is recommended for supporting a haemophilia programme. Linking it to the Red Cross, haematology societies, haemophilia societies, public and private granting agencies, and other institutes and organizations will strengthen its support. Such a centre can integrate the haemophilia programme at different levels of the national medical care system, inform the government about improvement of medical care for its patients, and provide public relations and educational material for physicians and patients.

A national haemophilia registry should be established as a basis for planning national health policy for the management of haemophilia. Such a registry should include not only the numbers and locations of haemophiliacs but also a tally of disabled or handicapped persons and should track blood-transmitted infections such as HIV.

In developing countries, transportation of haemophiliacs to major haemophilia centres is very difficult, and health care resources including manpower and money are limited. Thus, promotion of home care is essential. Treatment can be provided with blood products prepared in the country, such as lyophilized cryoprecipitate or fresh dried plasma, stored in home or village communal refrigerators, which also may be constructed within the country at less expense than with importation³⁰. Village health personnel can assume the responsibility of home care therapy by storing the blood product and performing the infusion. Home care in developing countries has reduced hospital admissions very markedly and, because care is given promptly, has reduced the severity and sequelae of haemorrhages and the total consumption of plasma products. Another impressive benefit is the patient's psychological independence, well-being and improved quality of life.

The smallest local hospitals can provide care for simple problems. Larger hospitals can provide secondary medical care for such problems as major haemorrhages, dental extractions and minor surgery, whereas a tertiary-care facility might house the haemophilia centre and be responsible for such complicated problems as major surgery and management of patients with inhibitors. Management of patients with HIV infection should be undertaken by the haemophilia care system in collaboration with the national centre for blood

diseases and national AIDS programme. Patient education and genetic counselling can be provided at every health care level described, using publications provided by the national centre for blood diseases. Prevention of the disease is aided by carrier detection, which should be available in at least one centre in each country. In populous countries, prenatal diagnosis of haemophilia should be made available, whereas smaller countries may use the services of a neighbouring nation.

Improvement of blood banking and provision of an adequate supply of HIV-safe plasma products are vital to betterment of haemophilia care in developing countries. Collection of blood in plastic bags facilitates its separation into components, including plasma and cryoprecipitate, that can be lyophilized and supplied to local and regional hospitals. Plastic bags, however, are expensive. The manufacture of such bags might be set up in the developing country itself. Indeed, each country or region should be encouraged to produce or manufacture its own equipment, reagents and therapeutic materials to the greatest extent possible in order to control costs. In large countries, plasma fractionation facilities can be developed locally. Smaller neighbouring countries can share such facilities using their own raw plasma. Such a strategy would lower the cost of plasma products dramatically³⁰⁻³¹. Ongoing training of medical personnel is important, and attention should be paid to career development of young staff members who will carry on the work initiated by their more senior colleagues. The assistance of WFH in providing training is very useful. The knowledge gained can be passed on to colleagues in neighbouring countries.

6. CONCLUSIONS AND RECOMMENDATIONS

Improvement of haemophilia care around the world by the end of the century depends on persistence in and support for proven methods of haemophilia care, on continued research into possible means of cure (gene therapy), and on expansion of haemophilia care to areas of the world where it is inadequate. In the latter pursuit, intense efforts expended by WFH on a few appropriate and receptive countries are deemed likely to have the most benefit.

Whenever possible, the mechanism for providing haemophilia care should be linked with that for other major health problems in the country and region, i.e., sickle cell disease or thalassaemia. This will not only strengthen the programme for controlling and preventing these disorders, but will also improve health services generally, public health, blood transfusion and laboratory services.

The following recommendations were adopted:

1. Supervised home treatment, the mainstay of haemophilia care, should be instituted in each country (including developing countries) as soon as possible.
2. The implementation of supervised home treatment is based on the availability of lyophilized and viral-inactivated concentrates of anti-haemophilic clotting factors. Although the availability of fresh-frozen plasma and cryoprecipitate is often the only reasonable short-term objective in developing countries, the ultimate goal of each country should be the availability of virus-inactivated lyophilized clotting factor concentrates.
3. Safe adequate supply of factor concentrate is achieved through the efficient national organization of a blood transfusion service based on an established programme of voluntary non-remunerated blood donation. Each country is recommended to foster such programmes and aim to provide enough blood products

to allow basic therapeutic management as a minimum target, to prevent major handicaps in all patients with haemophilia.

4. Countries that have no plasma fractionation facilities are recommended to collect plasma for processing by contract agreement with commercial or non-commercial fractionators.
5. Maintenance of a haemophiliac's good physical condition through normal activities plus a regular exercise programme is an effective and inexpensive way to help prevent musculoskeletal disability. Physiotherapists or other health care personnel should therefore be educated to implement such programmes.
6. Each country should set up and fund a network of specialized haemophilia centres where patients can be diagnosed and treated with an integrated multidisciplinary approach. Specialized haemophilia centres should also be used to provide diagnostic and therapeutic services to patients with acquired bleeding and thrombotic disorders.
7. Whenever possible, the mechanism for providing haemophilia care should be linked with that for other major health problems in the country and region, i.e., sickle cell disease or thalassaemia. This will not only strengthen the programme for controlling and preventing these disorders, but will improve health services generally, public health, blood transfusion and laboratory services.
8. WHO and WFH should undertake joint initiatives to foster haemophilia care in countries that have very limited or no programmes and to promote specific training of health professionals, e.g., haematologists, orthopaedists, physiotherapists and laboratory technicians.
9. WHO and WFH should ensure that the above-mentioned initiatives are fostered within the framework of the Global Blood Safety Initiative. WFH be consulted in the choice of target countries and that WFH International Haemophilia Training Centres be involved in WHO initiatives related to haemophilia.
10. WHO should identify, in consultation with WFH, and designate WHO Collaborative Centres in the field of haemophilia and allied disorders. Such centres should provide assistance to WHO Regional Offices both for training in the organization of comprehensive haemophilia care and also in development and standardization of laboratory methods.
11. WHO should organize, in collaboration with WFH, a meeting of experts to update the 1977 WHO/WFH Memorandum on Methods for the Detection of Haemophilia Carriers, in view of the recent explosive development of DNA techniques and their continued simplification.
12. WHO, in collaboration with WFH, should prepare and publish a simple education manual on haemophilia and distribute it to WHO Member States through WHO Regional Offices.

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TABLE 1: GLOBAL DEMOGRAPHY OF HAEMOPHILIA

Continent	Population (x 10 ⁶)	No. of births per annum (x 10 ⁶)	Expected no. of haemophiliacs
Africa	645	29.7	1500-3000
Asia	3047	82.5	4100-8200
Australia/ New Zealand	20	0.6	30-60
Europe	499	7.0	350-700
North America	275	4.4	220-440
South America	299	9.3	465-930
USSR	291	5.5	225-550

TABLE 2

DEFINITION OF LEVELS OF MUSCULOSKELETAL PROBLEMS³²**Impairment:**

Any loss or abnormality of psychological, physiological or anatomical structure or function (in a haemophiliac, any sequela of a haemorrhage).

Disability:

Any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being.

Handicap:

A disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfillment of a role that is normal (depending on age, sex, social and cultural factors) for that individual.

TABLE 3

SPORTS FOR HAEMOPHILIACS ACCORDING TO RISK OF INJURY

MINIMAL RISK

Badminton
Ballroom dancing
Fishing
Golf
Rowing
Swimming
Table Tennis
Walking

MODERATE RISK

Archery
Athletics (field & track)
Baseball
Basketball
Body building
Bowling
Canoeing
Cricket
Cross-country ski-ing
Curling
Cycling
Horseback riding

Ice-skating
Jogging
Roller-skating
Running
Sailing
Ski-ing
Softball
Tennis
Volleyball
Weight-lifting
Wheelchair basketball
Windsurfing

TABLE 4

RFLPs AND HETEROZYGOSITY RATES FOR FACTOR VIII GENE

<u>Enzyme</u>	<u>RFLP</u>		<u>% OF HETEROZYGOSITY</u>				
	<u>Probe</u>	<u>Fragments Kb</u>	<u>White</u>	<u>Japanese</u>	<u>Chinese</u>	<u>Other Asian</u>	<u>USA Black</u>
BcII	p114.12	1.1/0.8	42	42	29	44	29
BgII	probe C	20/5	24	16	0	11	38
XbaI	p486.2	6.2/4.8 (1.4)	49	48	49	--	--
MspI	p625.3	7.5/4.3	43	--	--	--	--
HindIII	p114.12	2.7/2.6	42	--	--	--	--
BgIII	DX13*	5.8/2.8	50	27	--	--	--
TaqI/MspI	ST14*	Various	70	--	--	--	--

* Denotes linked extragenic sites.

TABLE 5

RFLP AND HETEROZYGOSITY RATES FOR FACTOR IX GENE

Enzyme	RFLP Probe	Fragments Kb	HETEROZYGOSITY RATE				
			White	Japanese	Chinese	Other Asian	USA Black
TaqI	VIII	1.8/1.3	43	0	6	2 - 32	27
XmnI	VIII	11.5/6.5	37	0	8	0 - 11	21
DdeI	XIII	1.75/1.7	36	0	--	--	45
MspI	cDNA	5.8/2.4	36	--	--	--	48
BamHI	VIII	25/23	4	--	--	--	46
SstI	DXs99*	8.8/5.9	49	--	--	--	50
MnII**	(Ala/Thr)		43	--	--	0	21
HhaI***	(PCR)		48	--	--	--	--

* Linked extragenic probe.

** Alanine-threonine 148 dimorphisms detected by oligonucleotide probes, MnII digestion or by specific monoclonal antibodies.

*** HhaI RFLP only detected in PCR amplified DNA.

TABLE 6

LOCATION OF INTERNATIONAL HAEMOPHILIA TRAINING CENTRES

Buenos Aires, Argentina	Malmö, Sweden
Sydney, Australia	Basel, Switzerland
Vienna, Austria	Bangkok, Thailand
Leuven, Belgium	Oxford, UK
Rio de Janeiro, Brazil	London, UK
San José, Costa Rica	Los Angeles, California, USA
Helsinki, Finland	Worcester, Massachusetts, USA
Paris, France	Rochester, Minnesota, USA
Milan, Italy	New York City, New York, USA
Tokyo, Japan	Chapel Hill, North Carolina, USA
	Philadelphia, Pennsylvania, USA

TABLE 7

COST OF WORKSHOP AND LABORATORY DEVELOPMENT IN TARGET COUNTRIES

	COST IN US\$
<u>Workshop over 2-3 years</u>	
Travel, 4-6 faculty	25,000
Educational materials	5,000
<u>Diagnostic laboratory</u>	
Development costs:	
Reagents and Equipment	80,000
Staff	40,000
<u>Genetics laboratory</u>	
Development costs:	
Reagents and Equipment	150,000
Annual Operating Costs	100,000

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