Memoranda/Mémorandums

Prevention and control of haemophilia: Memorandum from a joint WHO/WFH meeting*

Haemophilia, the commonest hereditary bleeding disorder, arises because of the absence of, decrease in, or deficient functioning of plasma coagulation factor VIII or factor IX. With rare exceptions, exclusively males are affected. This Memorandum summarizes the discussions and recommendations for the prevention and control of haemophilia made by participants at a joint WHO/World Federation of Haemophilia Meeting, held in Geneva on 26–28 March 1990.

Introduction

Haemophilia is the commonest hereditary bleeding disorder that poses a heavy social and economic burden. The incidence of haemophilia is 15–20 per 100 000 males born, an estimate found in surveys in several parts of the world, indicating that the disease is fully recognized and equally frequent in all ethnic groups and geographical areas (Table 1). In developed and some developing countries the prevalence is approximately 7 per 100 000 inhabitants. The pattern of inheritance is X-linked recessive; thus, with rare exceptions, males are affected and females are carriers of the trait. Approximately one-third of cases are caused by recent genetic mutations. The underlying molecular defect is the absence of, decrease in, or deficient functioning of plasma coagulation factor VIII or factor IX, which cause haemophilia A (classic haemophilia) or haemophilia B (Christmas disease), respectively, with an incidence ratio of 5:1. Haemophilia A and B are clinically indistinguishable, and are characterized by delayed, prolonged, and repeated bleeding episodes. Haemorrhages into joints and muscles, unless properly treated by administration of the deficient factor, cause painful as well as progressive arthropathy and muscle atrophy, resulting in severe handicaps. These, in turn, cause poor adjustment to school, and create vocational problems as well as social and psychological sequelae (*1–3*).

Until recently, the foremost cause of death among haemophiliacs has been haemorrhage, especially intracranial haemorrhage. In developed countries, therapy with plasma derivatives has changed

Table 1: **Global demography of haemophilia**

Continent	Population ($\times 10^6$)	No. of births per annum ($\times 10^6$)	Expected number 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

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this pattern. As a result, the side-effects of treatment, such as transmission of the human immunodeficiency virus (HIV) and hepatitis viruses, leading to acquired immunodeficiency syndrome (AIDS) and liver cirrhosis, respectively, have become the predominant causes of death during the past decade. The recent excess mortality among haemophiliacs should be temporary because current plasma derivatives are subjected to viral inactivation measures. If deaths from AIDS and liver cirrhosis are disregarded, the survival of haemophiliacs approaches that of the general male population. Thus, the prevalence of haemophilia is expected to increase after its current temporary reduction. An additional element that will lead to an increased incidence of the disorder is the increasing frequency of haemophiliacs who survive until they reach reproductive age, since all their daughters will be carriers.

Prevention and control of haemophilia also means identification of all patients, with adequate provision of the plasma derivatives and health care facilities necessary to prevent any physical and psychological handicaps. Whereas patients previously had to endure severe disability, developments in specific therapy and in the organization and quality of care can now make the haemophiliac a liberated, autonomous, and fully active person, able to profit from his opportunities and attain the position in society that his abilities entitle him. Haemophilia care is one of the most gratifying examples of successful secondary prevention (*4, 5*).

Identification and diagnosis of haemophilia

A diagnosis of haemophilia is considered if a symptomatic person has a family history of the disorder or, in the absence of a family history, if the clinical history is suggestive. The patient or family should be questioned closely about any tendency to increased bruising, large haematomas or haemarthrosis after minimal trauma, and about prolonged bleeding after deep lacerations or after surgery such as dental extractions, circumcision, or tonsillectomy. If there is a family history of the condition, circumcision of male infants should be delayed until haemophilia can be ruled out by specific laboratory tests. Females also should be tested for the presence of the carrier state and for the level of the relevant clotting factor, because some carriers have clinically significant subnormal factor levels.

Simple screening coagulation tests that are available in most hospitals can aid in making the diagnosis of a hereditary coagulation deficiency. However, specific quantitative factor assays are carried out only in specialized laboratories. If a diagnosis of haemophilia is suspected on the basis of an abnormal screening test, the patient should be referred to a centre that specializes in haemophilia.

The activated partial thromboplastin time (APTT) is the primary laboratory screening test for the diagnosis of haemophilia since it is sensitive to deficiencies or abnormalities in factor VIII or factor IX. Numerous commercially developed kits are available for determining the APTT. All detect factor deficiencies of $< 15–20\%$ of normal plasma levels, which are the most significant clinically. However, milder degrees of factor deficiency (20–30% of normal) may be missed with the APTT, especially if less sensitive reagents are used. For individuals with a definite history of bleeding, specific factor assays should be carried out even if the APTT is within normal limits.

Assays of factors VIII and IX

Factor VIII and factor IX assays are performed only in specialized centres, using one- or two-stage assays. The simpler one-stage assays are based on the correction of the APTT of haemophilic plasma (deficient in factor VIII or factor IX) by appropriate dilutions of the test plasma. Specialized centres can also perform tests to distinguish classic haemophilia from von Willebrand's disease, since factor VIII deficiency is common to both disorders.

Since the methods for carrying out factor assays are not standardized, the results may vary depending on the test centre. Some of this variation can be reduced by the use of uniform reagents. Most commercial manufacturers of factor VIII concentrates currently calibrate their own concentrate reference materials against the WHO International Standard for Blood Coagulation Factor VIII Concentrate. To reduce variation in factor assays in specialized clinical coagulation laboratories, external quality assurance programmes, such as those offered by WHO, should be used. Working plasma standards can be calibrated against the International Standard for Factor VIII and von Willebrand Factor in Plasma. Other international and national schemes for proficiency testing of coagulation laboratories should be encouraged.

If a patient does not respond adequately to factor replacement or the increase in the factor level is less than expected, the presence of an inhibitor antibody should be suspected. Screening for an inhibitor is carried out by adding a sample of the patient's plasma to a known concentration of factor VIII or factor IX. The mixture is incubated for a fixed period and the residual factor activity measured. If this is lower than expected, an inhibitor antibody is suspected. The potency of the inhibitor can then be measured using a standardized quanti-

tative assay. As with factor assays, determination of inhibitor levels can vary from laboratory to laboratory because of different reagents and variations in technique. Such inter-laboratory inconsistencies are problematic and have not yet been solved.

Haemophilia treatment

The role of blood transfusion services

Haemophilia care can be developed only if there is a well-structured and efficient blood transfusion organization, providing on a continuous basis the means for adequate, safe, and equitable treatment. Cryoprecipitate and fresh-frozen plasma, the simplest blood products used to treat haemophilia, can be prepared easily as by-products from whole blood donations using basic technology within the reach of all countries. Some developing countries need help from WHO, the League of Red Cross and Red Crescent Societies (LRCS), and the International Society of Blood Transfusion (ISBT) in shaping their blood transfusion capabilities.

Problems in the provision of adequate transfusion services have increased because of the AIDS epidemic and the resulting financial burden of ensuring safety in the supply of blood and blood components. The most visible and promising programme in this respect is the Global Blood Safety Initiative (GBSI), an endeavour initiated by WHO (Global Programme on AIDS) in close collaboration with LRCS and ISBT, which includes also strong and active involvement by the World Federation of Haemophilia. GBSI has published its first recommendations on the structuring of safe and effective blood transfusion organizations, the equipping and supplying 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 currently being formulated.

Some principles of self-sufficiency. 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 while the medical profession is the principal protector of the resource. National health authorities should accept their fundamental responsibility to promote the physical and moral interests of the blood donor and to protect the patient by instituting standards of practice and a mechanism for inspection, control, and registration. To achieve self-sufficiency, countries need to motivate all appropriate segments of the population to donate blood voluntarily.

The provision of safe blood and its components is a challenge to the blood bank organization at the national, regional, and local level. A national blood transfusion policy should be instituted and extended to regional and local levels. The policy should cover donor recruitment, medical selection, collection of the blood, component production and preservation, plasma fractionation, creation of reserves, and education on the appropriate use of blood and blood components. A well-organized network of regional blood transfusion services must be supported, since such services have primary responsibility for quality assurance.

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

Delivery of haemophilia treatment

Optimum delivery of haemophilia care is based on a comprehensive interdisciplinary approach (distributed from specialized centres) using supervised self-treatment. Comprehensive centralized care enables the patients to receive care from knowledgeable experts in an efficient manner, and allows new therapies to be instituted quickly.

Staff for comprehensive care ideally includes the services of the following persons or those with equivalent qualifications: a haematologist, a nurse adept at giving intravenous infusions, an orthopaedic surgeon, a physiotherapist, a dentist, a genetic counsellor, a social worker, and others as needed. A physician, typically a haematologist with an interest in blood coagulation, usually directs the team and plans the overall medical care. The main coordinator of patient care in many countries is a specially trained nurse, who has frequent contact with the patients, receives incoming telephone calls, and determines whether a patient needs to be seen at the centre or whether the problem can be handled in the home setting. The physiotherapist and orthopaedic surgeon work closely together, assessing joint mobility, teaching exercises, advising on the use of braces or other treatment, and planning surgical intervention if necessary. The social worker advises the patient and his family about education, employment, and financial matters, and also helps them to cope with the burdens of haemophilia and its complications, including HIV infection.

Ideally, the comprehensive care centre should be located within a general hospital, but effective

centres have also been established in other types of medical facilities. A fundamental requirement is a designated area, however modest, where haemophiliacs can expect a sympathetic and knowledgeable reception. In the optimum arrangement, all staff are based in or near this area, so that the haemophiliac can visit all needed personnel at one place as often as required during one visit. The responsibilities and decisions for the management of each patient are shared by all members of the team in joint meetings. Arrangements for the prompt, appropriate treatment of acute bleeding episodes at any hour of the day or night are essential.

Highly specialized services (such as surgery, genetic testing, and antenatal diagnosis) are typically provided at one major haemophilia centre in a given region. For patients living at some distance from such a centre, simple basic services, such as infusion therapy, can be provided by either several smaller cooperating outlying centres or knowledgeable clinicians who treat acute problems and refer complex ones to the comprehensive case centre. Communication and collaboration between local care-givers and the comprehensive centre must be nurtured diligently. Appropriate use of supervised home therapy may diminish the need for outlying haemophilia centres.

The frequency of routine, scheduled visits to comprehensive centres is determined by local circumstances and the condition of individual patients. Newly diagnosed patients with little understanding of haemophilia and patients with HIV infection and other serious complications should be seen at frequent intervals, whereas most uncomplicated HIV-negative haemophiliacs, especially those with mild-to-moderate haemophilia, can be seen annually. A routine visit may include a general physical examination and laboratory tests such as blood counts, liver function tests, and, in patients not known previously to be infected, tests for HIV and hepatitis. If a patient is HIV-positive, intermittent determination of CD4 lymphocyte levels can help the physician decide when to begin antiretroviral therapy and prophylaxis against opportunistic infections, and to monitor such interventions. Annual examination by a dentist and by an orthopaedic specialist is also customary, as is an interview with a social worker.

Care of HIV infection has been integrated into comprehensive haemophilia care: this demands greatly increased effort from staff, especially in countries severely affected by the AIDS epidemic. Continuity of care is best maintained if the haematologist remains the patient's primary physician, and consultation is obtained as needed from specialists in infectious diseases or other fields. Additional funds are needed to cope with these new demands, to increase the number of staff, and to provide the appropriate additional laboratory tests. The availability and cost of medications of proven usefulness in managing HIV infection, such as zidovudine and pentamidine, remain a major problem in many parts of the world.

Supervised self-treatment (home treatment) is most feasible if lyophilized clotting factor concentrate is widely available. With home infusion, an episode of bleeding can be treated very quickly after its onset, thus avoiding the large haemorrhages that often lead to chronic problems and increased use of factor concentrate. Training for self-infusion starts with education of the family about the disorder as soon as a child is diagnosed. They are taught about signs and symptoms of bleeding episodes, what constitutes an emergency, and the natural history of the disease. As soon as the child is aged 3–5 years, the nurse teaches the parents how to calculate factor doses, mix concentrate using a sterile technique, perform the venepuncture, and infuse the concentrate into the child. The training can take many hours over several days. When the child is 9–10-years-old, this process is repeated and he is taught how to self-infuse.

Home care is monitored and supervised by the centre nurse and physician through telephone communications and review of infusion records. The centre makes sure that appropriate doses are used and that haemorrhages are treated properly. Very serious haemorrhages must be reported to the centre immediately, so that hospital treatment can be arranged as needed.

Musculoskeletal disorders, the sequelae of haemarthrosis and muscle haemorrhages, can cause long-lasting disability. In developed countries, severe chronic disability occurs in about 2% and moderate disability in about 20% of patients with severe haemophilia, while in developing countries severe disability occurs in 20% or more of such patients.

Musculoskeletal problems can be prevented by patients maintaining excellent physical fitness and by appropriate orthopaedic management of acute bleeding episodes and rapid rehabilitation. Maintaining patients' fitness through normal physical activities, sports, and exercises is an effective and inexpensive way of preventing joint problems. The physiotherapist or similar specialist explains to patients how to undertake such activities as safely as possible. Boys do not want to be different from their peers, and often engage in popular but rough sports (Table 2), deriving physical, psychological, and social benefits from doing so. The risks of injury can be reduced if the haemophiliac has proper training,

Table 2: **Sports for haemophiliacs according to the risk of injury**

Minimal risk	Moderate risk	
Badminton	Archery	Jogging
Ballroom dancing	Baseball	Roller-skating
Fishing	Basketball	Running
Golf	Body building	Sailing
Rowing	Canoeing	Skiing
Swimming	Cricket	Softball
Table tennis	Curling	Tennis
Walking	Cycling	Volleyball
	Field and track	Wheelchair basketball
	Horse-riding	Windsurfing
	Ice-skating	

protective clothing, and reliable equipment.

Acute joint or muscle haemorrhages often require temporary immobilization of the limb, and, as soon as a haemostasis is achieved, exercises to mobilize, stretch, and strengthen the muscles are recommended to regain previous functional ability.

Chronic musculoskeletal disabilities, such as contractures around joints, degenerative arthritis, and malalignment of long bones, can be treated using conservative measures such as nonsteroidal anti-inflammatory drugs, traction, splints, or braces. When such measures fail to restore adequate function or relieve serious pain, the orthopaedic surgeon may consider operative intervention. For such surgical operations, haematological care (including laboratory facilities and adequate clotting factor concentrate), operating theatres, and hospital postoperative care should meet high standards. Only a centre familiar with operative treatment of haemophilia patients should undertake such intervention.

Current developments in haematological care

Elimination of blood-borne infections has become possible through the use of physical or chemical viral inactivation processes, such as heat or solvent–detergent treatment, respectively, on clotting factor concentrates. Furthermore, various chromatographic processes are being used to produce factor VIII or factor IX concentrates of extremely high purity. Highly purified factor IX concentrate is specific replacement therapy for haemophilia B, which avoids the excess thrombogenicity, e.g., deep vein thrombosis, sometimes associated with the use of 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. Their efficacy has been demonstrated, but long-term safety studies and advances in production techniques will determine whether recombinant coagulation factors will replace treatment with plasma derivatives to a large extent. Recombinant DNA techniques also permit the development of new mutants of the native proteins, which, it is hoped, might exhibit improved pharmacokinetic characteristics and lower immunogenicity.

Blood-borne infections can also be avoided in patients with mild haemophilia 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 in the body. Initially the drug was given intravenously, but recently, more convenient means of administration, including subcutaneous injections and nasal sprays, have proved to be effective.

Inhibitor antibody against the deficient factor can be suppressed in the majority of patients through the use of regimens to induce immune tolerance; such regimens involve the regular administration of the factor concentrate, sometimes together with immunosuppressive drugs. Special products for the management of bleeding episodes in patients with inhibitors include porcine factor VIII concentrate (human inhibitors inactivate non-human factor VIII much less than human factor VIII), activated prothrombin complex concentrates (which may contain activated factors or complexes of factors that bypass the need for factor VIII), and factor VIIa (an experimental agent now made by recombinant technology, which also bypasses the need for factor VIII).

Clinical cure of haemophilia A or B has been achieved with a few patients who underwent liver transplantation, but since the mortality rate is considerable and life-long immunosuppression mandatory, such a procedure is only justifiable for selected patients with end-stage liver disease. A more general cure for haemophilia may become available through gene insertion therapy. It is already technically feasible to introduce the gene for factor VIII or factor IX into human cell lines, which then synthesize functional coagulation factors; however, many technical as well as ethical problems remain to be solved.

Genetic services

Genetic counselling

Haemophilia centres are the most appropriate setting for genetic counselling. Haemophiliacs must understand that although their sons cannot inherit their condition, all their daughters are obligate carriers. Parents of a carrier or potential carrier can

be offered help in discussing with their daughter the inherited nature of the disorder and the girl's carrier status. The centre staff can assist with the early education and emotional support for potential and obligate carriers. At the appropriate time, carriers and their intended spouses can be counselled together so that decisions about having children are made jointly, avoiding subsequent guilt, blame, and resentment wherever possible.

Carrier detection and antenatal diagnosis

Obligate carriers can be identified readily from family information. Additionally, it is known that there are five–six potential carriers for every haemophiliac. Reliable diagnosis of carriers has the effect of not only eliminating normal females from further concern, but also reducing the number of antenatal diagnostic procedures, which then are performed only on definite carriers.

Phenotypic detection of carriers can sometimes be carried out. Known carriers of haemophilia A or B have, on average, 50% of the mean normal plasma level of factor VIII or factor IX, measured biologically. Immunological measurements (factor VIII or factor IX antigen) show concomitant reductions except in cases where normal plasma levels of biologically inactive coagulation factors occur in the haemophiliac concerned (cross-reacting material positive haemophilia: CRM+). In a potential carrier, a factor level clearly below the normal range confirms the carrier state. (Some carriers have levels similar to those of mild-to-moderate haemophiliacs and require appropriate haematological care). In women from families with CRM+ haemophilia, the carrier state is implied if a significantly higher level of the factor is found by immunological than by biological assay. In haemophilia A, determination of the ratio of factor VIII to von Willebrand factor (typically 1 : 1 in normal women, but 1 : 2 in carriers) significantly increases the number of women who can be diagnosed as carriers. Despite such analyses, about 5–10% of true carriers of haemophilia A exhibit factor level phenotypes within the normal range. Antenatal diagnosis by phenotypic measurement of factor VIII or factor IX levels in fetal blood obtained at fetoscopy can be performed at 18–20 weeks' gestation at the earliest; thus, an affected fetus is at a gestational age that many find unacceptable for abortion.

Genotypic analysis, by identifying the affected gene itself, is the ideal way to analyse potential carriers and fetuses at risk. This can be performed in two ways. First, the identification of normal polymorphic DNA variations within or close to a particular gene can provide markers for that gene. These variations generally are detected as restriction fragment length polymorphisms (RFLPs), following restriction enzyme digestion of DNA and use of specific DNA probes (Southern blotting techniques). The overall usefulness of a single RFLP depends on its frequency within a specific population and, for a series of RFLPs, the level of linkage disequilibrium between them. Cross-overs may occur between the locus of an extragenic-linked RFLP and the gene locus, limiting the reliability of such an RFLP. The second method of genotypic analysis is detection of the specific defect within the gene ("direct defect detection"). In the past, this process was laborious. However, by using the polymerase chain reaction (a recently introduced technique that amplifies DNA) it is more practical, especially for the factor IX gene, which is much smaller than the factor VIII gene. Direct defect detection is at an early stage of development for haemophilia A, whereas for haemophilia B several laboratories with high levels of expertise are able to determine, within a few days, the gene defect in every patient.

The advantages and disadvanages of genetic diagnostic methods should be understood. Phenotypic analysis is widely available, but DNA analysis offers a considerable advantage since it generally provides an absolute diagnosis. Carrier detection by intragenic RFLP analysis is highly accurate (99.8%) as, of course, is direct defect detection. With the polymerase chain reaction, only very small samples of blood or other tissue are required. Very importantly, the technique permits antenatal diagnosis to be performed in the first trimester at between 10 and 12 weeks' gestation by analysis of DNA obtained from samples of chorionic villi.

RFLP analysis, because it does not detect the gene defect but only a polymorphic marker close to it, has 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, 70–80% of females of European descent are heterozygous for the known intragenic RFLPs for haemophilia A and up to 90% for haemophilia B (these proportions are lower for certain other ethnic groups). Extragenic linked RFLPs significantly increase these proportions but also introduce a cross-over error rate of up to 5%. Mistaken paternity can also occasionally cause errors of interpretation. RFLP analysis is of limited use for families with sporadic haemophilia, i.e., no prior history of the condition, where it can diagnose the noncarrier 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, through polymerase chain reaction technology, it is becoming a relatively simple, inexpensive, and quick procedure. In contrast to direct defect detection, RFLP analysis may be informative when no kindred haemophiliacs are alive or available.

Samples for DNA extraction as well as DNA itself are extremely stable and can be stored for many years. Since genotypic analysis by direct defect detection invariably requires samples of DNA from a haemophiliac, it is very important to obtain and store such samples, particularly in view of the current high mortality rate from AIDS among haemophiliacs.

Educational aids and training

Improvement in education and training about haemophilia can be approached at several levels. At the international level, WHO can disseminate written information in several languages and can promote conferences. WFH identifies expert centres (International Haemophilia Training Centres) that are capable of hosting and instructing health-care providers from other countries; provides scholarships for haemophilia care trainees; identifies physicians, cities, and countries suitable for setting up haemophilia centres and assists those who request advice or help; distributes newsletters; and holds workshops and scientific congresses in various countries.

National governments can provide funding for new or expert centres and often concomitantly set standards for centre care. Governments can fund haemophilia-related training of individual health care professionals, and can sponsor focused symposia and publications.

National and local haemophilia societies traditionally have assumed a major educational role. Centre staff, patients, and families attend joint meetings where all parties express their priorities and concerns. Haemophilia societies also disseminate publications such as treatment manuals and newsletters to patients, families and health care providers, and usually take a leading role in educating the community and government about the problems facing haemophiliacs.

Haemophilia treatment centres educate individual patients and families, answer questions from medical personnel in outlying areas, and provide guidance to local schools, employers, etc.

One learned society, the International Society on Thrombosis and Hemostasis, focuses attention on problems relevant to haemophilia through the Factor VIII and Factor IX Subcommittee of its Scientific and Standardization Committee.

Developing and maintaining haemophilia programmes

The development of a haemophilia programme requires recognition of the need, and the knowledge and enthusiasm necessary to secure and develop resources. Typically, the initiator of a programme is a specialist physician whose major interest is haematology and/or blood banks. As the principles of haemophilia care have become more widely disseminated, a lay organization may sometimes be the driving force. Whichever the case, successful programmes are difficult or impossible to establish and maintain without the support of government authorities. International precedent is not always the most persuasive argument in attempting to gain such support. Often, it is more effective to focus arguments within the context of the prevailing local situation. In developing countries, programmes should not be limited to haemophilia care, but should include and support medical care for all blood disorders and for transfusion services, thus broadening the base of support and drawing attention to the interrelated nature of these needs. A national centre for blood disorders can be linked to various supportive organizations. The requirements of many other groups of patients will be satisfied in the process of meeting the needs of haemophiliacs. The expertise of the haemophilia staff must be fully exploited to treat all blood coagulation disorders, some of which are more common than haemophilia (such as acquired bleeding problems in renal and liver disease and thrombotic disorders).

Health authorities require evidence of need. An initial task is to register patients with haemophilia and related coagulation disorders, identifying their demography and severity of illness. Since haemophilia care is an impossible financial burden for the affected individual and his family, public funding is needed. In this connection, it is worth pointing out that appropriate haemophilia care prevents severe handicaps. In terms of outcome, therefore, the treatment of haemophilia can be considered a highly effective use of resources. When costs are considered it is important to assess the costs of nontreatment or undertreatment, e.g., the dependency of the patients and their parents, which result in long-term economic burdens that fall directly or indirectly on government authorities.

Funding for 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 that require patients to contribute towards the cost of medications and medical care must exempt those

with expensive, life-long disorders such as haemophilia. Infusion of blood products at home is forbidden by law in some countries; legislation is therefore needed to exempt haemophiliacs. Also in some countries without national health systems, only employed persons have health insurance, which therefore excludes most haemophiliacs. The governments in such countries can be asked to categorize haemophilia as a disease that causes exceptional social and financial burdens, thereby entitling patients to free medical care. Funding for haemophilia care must be the responsibility of governments, which must create an integrated and coordinated system.

The concept of the "haemophilia centre" is now well-established as a core element of any successful haemophilia control programme, but the specifications and functions of centres may differ considerably according to local circumstances. The organizational framework may shift towards fewer but larger centres with expanded functions, but with less involvement in the day-to-day aspects of primary care. Self-treatment programmes may bring other problems in their wake; in particular, a shift of control and responsibility away from the physician towards the patient himself. The former may be unhappy to lose control and the latter may not be prepared to accept the responsibility entailed.

However organized, the delivery of comprehensive care requires input from and active collaboration with a variety of health care professionals. Ways must therefore be found to interest 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. Usually, they are more 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 by opportunities for academic studies.

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, are sometimes still used but are not ideal). Assurance of concentrate availability entails an adequate supply of plasma (which can be obtained by separation of blood components or plasmapheresis) and the necessary technology to fractionate it. A country may choose to develop and use its own fractionation facilities. Alternatively, arrangements and contracts with countries that have developed fractionation facilities may be acceptable, and indeed often are the best means of avoiding unnecessary duplication of effort and expense. The type of concentrate to be produced should be decided by each country, taking into consideration the scientific evidence of benefits, the advice of local haematologists, and the amount of plasma as well as the fractionation technologies available. The goal should be to produce enough concentrate to prevent most physical and psychological handicaps in all haemophiliacs living in the country.

Developing countries can present exceptional challenges for haemophilia programmes. Transportation of haemophiliacs to major centres may be very difficult, and home care is therefore highly appropriate for all but the most serious haemorrhages. Plasma fractions can be infused by village health personnel and stored in a communal refrigerator. Equipment (e.g., refrigerators and orthopaedic braces), reagents, and supplies can often be made within the country at affordable costs. The training of medical personnel in haemophilia care is often undertaken in other countries at experienced haemophilia centres. Trainees can then pass on their knowledge to prospective haemophilia staff in their own and neighbouring countries.

Pilot programmes in developing countries

Countries targeted for development of haemophilia care should meet the following prerequisites: they must have a functioning blood transfusion programme with component separation or the potential for this, and possess an interested key leader, preferably in a medical setting, who is willing to provide and maintain the care.

Pilot programmes can be formed at two levels: at a primary level in a country with minimal or no previous haemophilia care services; and at a secondary level in a country with an existing haemophilia programme that is ready to increase its level of sophistication. Selection of potential target countries depends on the strategies that WHO and WFH wish to pursue. At the primary level, prerequisite conditions appear to exist in China, Indonesia, and Zambia. In India and the Philippines, despite considerable medical expertise and efforts, progress has been limited. In view of the current political climate in eastern Europe, we might expect much to be accomplished there. In South America, workshops have recently been staged in Colombia and will soon be held in Chile and in Mexico. At the secondary level, transfusion programmes exist in Kuala Lumpur (Malaysia) and in Singapore, but haemophilia care is limited. Transfusion services are excellent in Bangkok, and Thailand now has a vast potential to expand its existing haemophilia programme and to help neighbouring countries develop

similar programmes. Costa Rica has a good haemophilia programme and now plans to introduce more sophisticated diagnostic tests, including carrier detection and antenatal diagnosis. This should help expand haemophilia care in Central America, northern South America, and the Caribbean. Argentina has similar standards of haemophilia care to those in Costa Rica and also has the potential to help other South American countries.

The WFH International Haemophilia Training Centre Committee is concerned with introducing and expanding knowledge about haemophilia care in developing countries. For this purpose, travelling fellowships are awarded to medical or paramedical persons who have demonstrated an interest in haemophilia in their own countries and who will return there after training in a centre of excellence. Secondly, visiting teams hold workshops in developing countries, with lectures, open consultative clinics, and initiation of new tests in working laboratories. Formal instruction itself is not sufficient to improve haemophilia care, and WFH executive members therefore consult with local and national health authorities to support a future model and commitment for haemophilia care.

Recommendations

The recommendations made by participants at the meeting are outlined below.

- Supervised home treatment, the mainstay of haemophilia care, should be instituted in each country (including developing countries) as soon as possible.
- The implementation of supervised home treatment is based on the availability of lyophilized and viral-inactivated concentrates of antihaemophilic 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.
- 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 nonremunerated blood donations. 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.
- Countries that have no plasma fractionation facilities are recommended to collect enough plasma for processing by contract agreement with commercial or noncommercial fractionators.
- 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.
- 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.
- 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, orthopaedic specialists, physiotherapists, and laboratory technicians.
- WHO and WFH should ensure that the abovementioned initiatives are fostered within the framework of the Global Blood Safety Initiative. WFH should be consulted in the choice of target countries and WFH International Haemophilia Training Centres should be involved in WHO initiatives related to haemophilia.
- WHO should identify, in consultation with WFH, and designate collaborating centres for haemophilia and allied disorders. Such centres should assist WHO Regional Offices to provide training in the organization of comprehensive haemophilia care as well as in the development and standardization of laboratory methods.
- 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 (*1*), in view of the recent explosive development of DNA techniques and their continued simplification.
- WHO, in collaboration with WFH, should prepare and publish a simple education manual of haemophilia and distribute it to WHO Member States through WHO Regional Offices.

References

1. **Bloom, A.L.** Inherited disorders of blood coagulation. In: Bloom, A.L. & Thomas, D.P., ed. *Haemostasis and thrombosis.* Edinburgh, Churchill Livingstone, 1987, pp. 393–436.
2. **Levine, P.H.** The clinical manifestations and therapy of haemophilias A and B. In: Colman, R. W. et al., ed.

Hemostasis and thrombosis: basic principles and clinical practice. Philadelphia, J. B. Lippincott, 1982, pp. 75–90.

3. WHO Technical Report Series No. 668, 1981 (*Report of the WHO Expert Committee on Disability Prevention and Rehabilitation*).
4. Methods for the detection of haemophilia carriers: a Memorandum. *Bulletin of the World Health Organization*, **55**: 675–702 (1977).
5. **Ala, F.A.** Comprehensive haemotherapy programme for developing countries. In: Das, P. C. et al., ed. *Supportive therapy in haematology*. Boston, Martinus Nijhoff, 1985, pp. 379–388.