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GUIDELINES FOR THE DEVELOPMENT OF A NATIONAL PROGRAMME FOR HAEMOPHILIA

WORLD HEALTH ORGANIZATION
HUMAN GENETICS PROGRAMME

WORLD FEDERATION OF HEMOPHILIA

GUIDELINES FOR THE DEVELOPMENT OF A NATIONAL PROGRAMME FOR HAEMOPHILIA

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On behalf of the

World Federation of Hemophilia

in cooperation with the World Health Organization

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FOREWORD

As the responsible officer for the Human Genetics Programme of the World Health Organization (WHO), I am honoured to have this opportunity to inform you of WHO's interest in the activities of the World Federation of Hemophilia (WFH).

Within the past decade WHO has initiated a series of activities to collect and quantify information on the application of genetic knowledge at the community level. Programmes on common hereditary conditions, such as thalassaemias, cystic fibrosis, haemophilia and neurofibromatosis, have been initiated in order to develop approaches suitable for incorporation into health services. Our experience has shown that any modern control programme on hereditary diseases has to be based on a comprehensive approach combining diagnosis, counselling, possible treatment and preventive measures. In this context, haemophilia is considered to be one of the genetic disorders which can be most successfully managed.

In the knowledge that haemophilia is a genetic disorder with a world wide distribution, the WHO Human Genetics Programme is paying close attention to the problems it presents. It is clear that the successful development of any programme of care can only be achieved with the close cooperation of all interested institutions, international organizations and governmental bodies. In order to increase public and professional awareness of haemophilia, and to promote it at the international level, WHO has been cooperating with WFH, and supporting activities on haemophilia control in different countries. I am sure that this joint collaboration will help to identify and implement possible strategies for haemophilia control. Information is regularly updated and revised at our joint meetings in the light of research development, experience available, and family needs. The present guidelines are no exception, and reflect the culmination of joint efforts of both WHO and WFH. I especially congratulate the author for his tremendous effort in compiling these guidelines.

I should like to encourage all of you involved in haemophilia management, whether as patients or their families, or as members of the health care professions, or as those involved in the planning and implementation of health services, to work together to alleviate the problems presented by haemophilia and related bleeding disorders.

Dr Victor Boulyjenkov, WHO

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1. INTRODUCTION

The inherited disorders of blood coagulation present providers of health and social care with formidable problems. The disorders are eminently treatable, even in their severest form. Untreated, they result in chronic incapacity and handicap by early adult life, and in premature death. So whilst proper treatment is expensive, inadequate treatment is even more so, both to individuals and their families and to the community.

The commonest of these disorders is haemophilia A, or clotting factor VIII deficiency. Haemophilia B, or clotting factor IX deficiency (sometimes known as Christmas disease after the name of the first patient described) is one fifth less common than haemophilia A. Both these disorders are inherited as sex-linked recessives; that is the inheritance of an abnormal gene on an X chromosome. Isolated deficiencies of the other clotting factors are much less common because they are usually inherited in autosomal recessive manner, and this requires both parents to carry the abnormal gene. The disorder called von Willebrand disease, in which the factor VIII molecule is abnormal, is usually inherited in a dominant fashion and is therefore probably the most common, but overall the least severe, of the inherited clotting disorders.

The incidence of haemophilia A is 1 case per 10,000 population. In its severe form (factor VIII clotting activity $< 1\%$) the incidence is 1 in 16,000 population. No geographical, ethnic or racial variations in the incidence of either haemophilia A or haemophilia B are known. It has been calculated that there are around 350,000 people with severe or

moderately severe haemophilia A worldwide, and 70,000 people with severe or moderately severe haemophilia B.

Given this rarity of haemophilia it is easy to appreciate how it can be overlooked or disregarded in countries faced with major problems of malnutrition and infection, and by those grappling with health care prioritization. However, both on an individual and on a community basis haemophilia therapy deserves recognition:

- individually, because of the suffering and loss of earning capability that must be endured without treatment,

- within the community, because the provision of haemophilia care can provide a template for the management of many other chronic disorders.

These guidelines have been written in conjunction with programmes developed by the World Federation of Hemophilia (WFH) to help affected families throughout the world, and following discussions held at joint WHO/WFH meetings. The WFH acknowledges the fact that treatment is only presently available to around 20% of those with severe haemophilia, mostly in developed countries. The task is therefore to do everything possible to help colleagues and families in developing countries arrange for the provision of safe and effective therapy. The guidelines are intended to provide ideas and to help in the organization and implementation of this support.

The guidelines are not intended to supersede previous WHO publications on haemophilia. In particular, those requiring guidance on the clinical management of patients are referred to the report of the Joint WHO/WFH Meeting on the Control of Haemophilia: Modern Treatment of Haemophilia (1994)", referenced on page 65.

2. BASIS OF MODERN TREATMENT

The haemophilias are inherited disorders of blood coagulation. Their severity is dependent on the level of clotting activity of factor VIII or factor IX in the bloodstream. This activity is the expression of small amounts of proteins manufactured in the liver and circulating in the blood stream. People with severe haemophilia have less than 1% activity[1], and are exposed to major bleeding episodes. People with 1 to 5% activity are moderately affected, whilst those with over 5% activity have mild haemophilia. The normal ranges of factors VIII and IX lie between 50 and 200% (5-20 iu/dl), with a mean of 100% clotting activity.

Haemophilia carriers frequently have factor VIII or IX levels below the normal range. These females may be at risk from abnormal haemostasis if challenged by surgery or dental extractions without appropriate treatment, and may occasionally have menorrhagia.

The level of clotting factor activity in an individual usually determines the clinical severity of haemophilia. Severely affected people bleed spontaneously into their major joints and musculature. Moderately affected people usually only bleed after trauma, whilst mildly affected people may only present after surgical challenge or major injury. However, it is important to note that severity is not always a reliable guide to abnormal bleeding and its treatment. Once haemorrhage has started the mildly

[1] also measured as 1 international unit per decilitre (iu/dl).

affected person requires the same attention to securing haemostasis as a more severely affected person.

Haemophilic bleeding can occur at any time of the day or night. The amount of blood lost initially is in keeping with the degree of trauma, but without treatment bleeding is prolonged. Untreated open bleeding (for instance from open wounds, or from the bowel) may eventually lead to exsanguination. Haemophilic bleeding into confined spaces (skull, synovial joints, major muscle masses) will only stop when the tension of the surrounding tissues equals or exceeds the pressure of escaping blood. Bleeding into joints or muscles is recurrent. Typically, a severely affected person with either haemophilia A or B bleeds 35 times a year on average, but some people with haemophilia bleed daily. Bleeding frequency is likely to be higher in tissues previously damaged by uncontrolled haemorrhage. Some people, usually those with haemophilia B, bleed less than this.

Acute pain is an immediate result of untreated bleeding into joints or musculature. The best pain control is treatment of the bleeding episode. Medicines containing aspirin are contraindicated because they cause an increased tendency to bleed as a result of their effect on blood platelet function. Similarly, the non steroidal anti-inflammatory agents (NSAIAs) may provoke bleeding, especially from the gastrointestinal tract. Repeated bleeds into the same joint eventually result in a breakdown of joint integrity and the development of a chronic, painful and incapacitating arthritis. This arthritis is irreversible, functional abnormality or pain only being relieved by major reconstructive surgery.

It follows that the basic needs of the person with severe haemophilia are:

- accurate diagnosis, which identifies the abnormal clotting factor and its level of activity, and
- immediate access to treatment at all times.

Treatment

Treatment of haemophilic bleeding is straightforward. Adequate replacement of the deficient clotting factor converts the patient's haemostatic response to normal, and bleeds stop in the usual way. If treatment is given early bleeds are less likely to progress. If treatment is late the bleeding will extend, causing more tissue disruption and increasing the likelihood of further haemorrhage. Thus early therapy results in less incapacity for the patient, and less need for repeated treatment with a consequent saving in cost.

Neither factor VIII nor factor IX can be given orally or by subcutaneous administration. Treatment must be given into a vein (intravenously; IV). The clotting factors are present in normal blood plasma from which they are harvested following donation. Preparation of therapeutic material demands:

- safe donation from healthy blood donors
- individual testing of each donation for known pathogens (especially hepatitis and the human immunodeficiency viruses 1 and 2)
- rapid and skilled processing which conserves the amounts of active clotting factor present, and improves final yield, and

- antiviral technology, ensuring end products are safe from transmittable viral disease.

Discovery of the molecular structure of both factor VIII and factor IX has recently allowed the development of genetically engineered products, prepared using recombinant DNA technology. In the long term preparations presently prepared from human plasma may eventually be superseded by recombinant clotting factor concentrates.

Home Therapy and Prophylaxis

Optimum haemophilia treatment is best administered by the patient or a suitably trained relative. This ensures early treatment and a reduction in the costs otherwise required to provide hospital based therapy. In general terms, a teenager weighing 50 kg with severe haemophilia A requires 35,000 units of factor VIII per year in order to control his bleeds (35 bleeds treated early with 1000 units of factor VIII). This figure will increase if he already has chronic arthritis (see also page 29).

The alternative to treating bleeds, which is called on demand or 'crisis' therapy, is to prevent them by maintaining a constant level of clotting factor in the patient's bloodstream. This is called prophylaxis. Definitions used to describe various forms of haemophilia treatment are shown in Table 1 overleaf.

Table 1: Definitions

Home therapy	The intravenous injection of clotting factor outside the hospital setting, without direct medical supervision.
On-demand/crisis therapy	The injection of clotting factor, given usually as home therapy, on the first evidence of a bleed.
Prophylaxis	The intravenous injection of clotting factor in anticipation of, and in order to prevent, bleeding.
Single-dose prophylaxis	An injection given to prevent the disruption that would be caused by a bleed that might otherwise occur during a special event.
Limited period prophylaxis	Regular injections given over a limited period of time in order to reduce the frequency of bleeding.
Long-term (permanent) prophylaxis	Regular injections given in order to prevent bleeding and arthropathy.

In general, long term prophylaxis is more expensive than on demand therapy in the short term. However, the overall savings it provides in terms of health and prevention of disability in adult life often outweigh the short term but cheaper advantages of on demand treatment. This is especially so in the management of people with haemophilia B. They may only require weekly or twice weekly injections of factor IX in order to prevent spontaneous bleeding. This is because factor IX has a longer survival time (half life) in the bloodstream than factor VIII. People with haemophilia A on prophylaxis usually need to inject factor VIII three times a week to prevent bleeds, typically on Mondays, Wednesdays and Fridays; the days are easier to remember than, say, an alternate day prescription.

The establishment of a structured approach to haemophilia care helps provide for the needs of a wide group of patients with other conditions. It also helps focus scarce resources, both in terms of manpower and in terms of finance, on specific areas of health care. Thus, the establishment of a safe and efficient blood banking system serves the general community as well as the minority with haemophilia. Similarly the setting up of a laboratory capable of performing coagulation tests serves those with acquired disorders of haemostasis for instance after surgery, major trauma or childbirth, as well as the haemophilic population.

Focus of expertise, too, is wide-ranging. A physiotherapist skilled in the management of chronic musculoskeletal disorders, or a scientist with an interest in genetic analysis are examples. In addition most day-to-day care of someone with haemophilia is provided by nursing, physiotherapy or other paramedical staff, or by the family themselves, rather than a doctor, thus further conserving financial resource.

Precautions in Haemophilia

Aspirin (ASA) is strictly contraindicated in anyone with a bleeding disorder. Aspirin has an adverse effect on platelet function, and an inflammatory effect on gastric mucosa which may result in haematemesis.

Non-steroidal anti-inflammatory drugs (as used in arthritic conditions) should be prescribed with caution in haemophilia because of their aspirin-like effects. They should only be taken after food, and stopped in the event of indigestion.

Intramuscular injections are contraindicated because they may provoke severe intramuscular bleeding with subsequent cyst formation or fibrotic scarring. Oral, rectal, subcutaneous or intravenous medication are alternatives.

Whilst immunization routinely given by intramuscular injection is safe provided digital pressure is applied to the injection site for 5 minutes, it is probably safer to give all immunizations subcutaneously. In the rare event of haematoma formation following immunization, replacement therapy may be needed.

Activities and sports are positively encouraged in haemophilia because it is recognized that a healthy musculoskeletal system helps prevent bleeding. Only those sports likely to result in head injury (boxing and rugby football are the main examples) should be actively discouraged.

3. RECOGNITION OF CASES

About one third of cases of haemophilia occur with no preceding family history. It is assumed that these cases result from new genetic mutations.

When there is a family history of haemophilia, especially when this is severe, every effort should be made to identify female carriers. Identification depends on family history measurement of the relevant clotting parameters and, increasingly, on DNA analysis. It is essential that material for DNA analysis is obtained from key members within a family before death, and stored deep frozen in order to help in diagnosis later. Guidelines on DNA storage are given in Annex 2.

When a woman is aware that she is (or may be) a carrier of severe haemophilia certain options may be available to her. These may include preimplantation diagnosis of an embryo following in vitro fertilization, fetal diagnosis by chorionic villus sampling (CVS) using DNA technology, fetoscopy using clotting factor assay, or amniocentesis in order to obtain information on fetal status.

One third of carriers have factor levels below the normal range, and may therefore be in danger of abnormal bleeding following injury, surgery or dental extraction. Most haemophilia A carriers with low VIIIC levels will not need replacement therapy because they will respond to desmopressin (DDAVP). In pregnancy factor VIII levels rise naturally. Haemophilia B carriers with lower factor IXC levels will require replacement therapy with a virally safe factor IX preparation.

Presentation of Haemophilia

Severe haemophilia usually presents in the first year of life with raised unsightly bruises, or prolonged bleeding, often from minor lesions in the mouth. The manner of presentation may cause confusion with non-accidental injury and laboratory diagnosis is needed to establish the true diagnosis. Sometimes presentation follows circumcision which can result in the death of a severely affected infant.

Moderate or mild haemophilia may present first following surgery or dental extractions when prolonged or secondary haemorrhage occurs. Differential diagnosis in these cases may include aspirin induced thrombopathy.

It is essential that haemophilia A and haemophilia B are distinguished immediately so that the appropriate treatment can be given.

4. THE DIAGNOSTIC CONSULTATION

The first stage in diagnosis is the routine clinical history. People with severe or moderately severe haemophilia will usually have an unequivocal history of abnormal bruising and prolonged bleeding after trauma. Those with milder haemophilia may only complain of abnormal bleeding after surgical challenge.

There follows a guide to obtaining the haemostatic history from a patient or his/her parent. The alternatives (1, 2 etc.) may be entered for later computer analysis, or the options simply ticked.

DIAGNOSTIC HISTORY

The following history may be readily amended for computer analysis

Name:

Sex:

Date of Birth:

Date of Examination:

Reason(s) for Referral:

HISTORY OF

GUIDE TO QUESTIONING

1. Bruising

1.1 Excessive 1 Not excessive 2 *Do you bruise easily?*

1.2 Always associated with trauma 1 *Do you find bruises and not know what caused them?*
Sometimes spontaneous 2

1.3 Superficial bruising large (> 5cm diam) 1
small (< 5cm diam) 2 *Compare with coin size*

1.4 Bruises flat 1 or raised 2 *Is bruising in soft tissue lumpy?*

1.5 Deep haematoma experienced 1
not experienced 2

1.6 Principal sites of bruising:

2. Purpura

2.1 Experienced 1 Not experienced 2 *Have you ever had a pin-prick like rash that has faded away like a bruise?*

2.2 Sites:

2.3 Associated diagnosis:

3. Epistaxes

3.1 Excessive 1 Occasional 2 Never 3 *Nose bleeds may normally be associated with colds.*

3.2 Duration:

3.3 Associated diagnosis:

4. Gastrointestinal Bleeding

4.1 Haematemesis 1 No haematemesis 2 *Have you ever vomited blood*

4.2 Melaena 1 No melaena 2 *or had blood in your stool?*

4.3 Associated diagnosis:

5. Haematuria/Haemospermia

5.1 Experienced 1 Not experienced 2

5.2 Associated diagnosis:

6. Joints (especially knees, ankles, elbows) *People with lax joints may*

6.1 Swelling experienced 1 Not experienced 2 *describe themselves as 'double*

6.2 Joint laxity 1 Normal 2 *jointed' and have an inherited condition of abnormal collagen called Ehlers Danlos syndrome. They may bruise easily.*

RESPONSE TO HAEMOSTATIC CHALLENGE

7.1 Lacerations Experienced 1 Not experienced 2

7.2 Prolonged or secondary haemorrhage 1

No prolonged or secondary haemorrhage 2

7.3 Wound healing abnormal 1 normal 2

8.1 Dental Extractions Experienced 1 Not experienced 2

8.2 Bleeding following extractions:

Prolonged or secondary haemorrhage 1

Normal 2

8.3 If abnormal, does this apply to each extraction?

Yes 1 No 2

8.4 Details of any haemostatic treatment:

9.1 Surgery Experienced 1 Not experienced 2 *Ask specifically about*

9.2 Details of surgery: *circumcision and tonsillectomy.*

9.3 Prolonged or secondary haemorrhage 1

Normal 2

9.4 Wound haematoma or disruption 1

Normal healing 2

10.1 Medication With aspirin 1 No aspirin 2

10.2 Other medication, including non-steroidal anti-inflammatory agents:

GYNAECOLOGICAL/OBSTETRIC

11.1 Applicable 1 Not applicable 2

11.2 Periods Heavy 1 Light/normal 2

11.3 Post menopausal bleeding 1 None 2

11.4 Pregnant now 1 Not pregnant 2

If pregnant, last menstrual period (LMP):

11.5 Number of previous pregnancies:

11.6 Post partum haemorrhage 1 Normal 2

11.7 Contraceptive method:

TRANSFUSION HISTORY

12.1 Ever transfused 1 No transfusion 2

12.2 Details of previous therapy, including year of transfusion. If transfused, consider check for related viral disease.

OTHER RELEVANT PERSONAL HEALTH HISTORY

13.1 Yes 1 No 2

13.2 Details

13.3 Vaccination against hepatitis A Yes 1 No 2

hepatitis B Yes 1 No 2

FAMILY HISTORY OF POSSIBLE BLEEDING DISORDER

14.1 Positive history 1 None 2

14.2 If positive draw family tree

Note details of affected relatives, and any consanguinity

PHYSICAL ABNORMALITIES

Yes 1 No 2

15.1 Telangiectasia

15.2 Abnormal bruising

15.3 Purpura

15.4 Haemarthrosis

15.5 Other evidence of bleeding disorder

5. LABORATORY DIAGNOSIS AND MONITORING

Many of the tests required to diagnose and manage the hereditary bleeding disorders are in general use for the day-to-day treatment of other patients presenting with abnormal bleeding or clotting. A few more sophisticated tests do require specialist methodologies only available in larger centres. An essential component of all coagulation testing is the use of national and local standards and quality control.

The World Federation of Hemophilia has developed suggestions designed to help laboratories involved with haemophilia diagnosis (Peake et al, 1995). They stress the importance of close collaboration and interdependence between laboratories, as well as the role of the laboratory in training and teaching.

In order to take account of the wide range of expertise and available resource three types of laboratory are suggested:

Coagulation Laboratory

A coagulation laboratory should be able to perform these essential basic tests:

* Bleeding time
* Platelet count
* Blood film for platelet clumping
* Clot retraction
* Prothrombin time (PT)
* Activated partial thromboplastin time (APTT)

* Correction tests using PT and APTT
* Thrombin time
* Factor VIII activity
* Factor IX activity
* Fibrinogen assay
* Screening tests for inhibitors

Note that the whole blood clotting time (WBCT) is not recommended as a reliable indicator of abnormal haemostasis. It may be normal even in severe haemophilia.

Comprehensive Coagulation Laboratory

A comprehensive coagulation laboratory should, in addition to these tests, be able to investigate von Willebrand disease and assay other clotting factors:

- von Willebrand antigen (vWF Ag)
- vWFAg qualitative test by two dimensional immunoelectrophoresis
- vWF activity
- Platelet aggregation test with adenosine diphosphate (ADP), collagen, epinephrine and ristocetin at a range of concentrations
- Factor II (prothrombin), V, VII, X, XI assays, and a qualitative XIII test
- Quantitative factor inhibitor assays

Reference Coagulation Laboratory

In addition the reference coagulation laboratory should have access to the following tests:

- vWF multimers
- Factor VIII binding to vWF
- Factor IX antigen (FIX Ag) assay
- Carrier detection of haemophilia by
  : phenotypic analysis
  : genetic analysis
- Prenatal diagnostic tests
- Factor XII assay
- Other contact factor (high molecular weight kininogen; prekallikrein) assays
- Alpha 2 antiplasmin

Whilst there will clearly be overlap between the tests available in these three categories, on a national level it is recommended that there should be at least one laboratory capable of acting as a reference point for the referral of cases, including those requiring carrier detection. This laboratory should be a part of a haemophilia comprehensive care centre.

Other laboratory tests frequently required for the management of haemophilia include examination for markers of transfusion related disease especially hepatitis A, B and C, and human immunodeficiency viruses (HIV 1 and 2). Patients infected with a hepatitis virus will require monitoring of liver function. Those with HIV infection will require monitoring of their immune function.

Samples for Genetic Analysis

Blood samples suitable for DNA analysis are often needed in order to advise patients requesting carrier detection or prenatal diagnosis. The lack of a specimen from a relative with haemophilia can make this impossible. It is recommended that blood samples suitable for DNA analysis, or DNA itself, be stored from all those with haemophilia. Storage should be at -20°C (see Annex 2).

Safety

All those working with specimens from multi-transfused patients should practice universal precautions to protect them from possible cross infection. Staff should be trained in safety measures and encouraged to adopt all relevant national guidelines. Each member of staff should be tested for the presence of antibodies to hepatitis A and hepatitis B and, if negative, offered the appropriate vaccine. Antibody testing prevents the unnecessary and expensive use of vaccines in those who have already acquired natural immunity.

6. RATIONALE OF TREATMENT IN HAEMOPHILIA

Untoward bleeding ceases once sufficient circulating clotting factor reaches the site of injury. Once bleeding has stopped conditions around the wound must predispose to normal consolidation of the blood clot and subsequent healing.

In severe and most cases of moderately severe haemophilia the relevant clotting factor must be injected into the patient's bloodstream in order to raise the concentration to the necessary level. In mild haemophilia A, and many cases of a related abnormality of the factor VIII molecule called von Willebrand disease, the patient's body is capable of releasing sufficient factor VIII if stimulated by the synthetic hormone desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP; see references also). Desmopressin can be given intravenously or by subcutaneous injection, or by intranasal spray. Administration of desmopressin does not release factor IX, so the drug is of no benefit to people with haemophilia B.

Clot consolidation and wound healing may be aided by the concomitant administration of an antifibrinolytic agent like tranexamic acid, which delays normal clot breakdown. Antifibrinolytic drugs should not be used when treating people with factor IX preparations, which may be thrombogenic. They should be used with caution in patients with haematuria because of the dangers of clot retention and renal damage.

Severe bleeds or major tissue disruption, for instance a result of surgery, require either continuous or intermittent replacement therapy in order to

maintain haemostatic levels of the relevant clotting factor. When this is in short supply or unavailable, wound immobilization will help normal healing to occur.

Wound infection predisposes to further bleeding, and early antibiotic treatment is advocated. This should be given orally or intravenously, and not by intramuscular injection.

7. THERAPEUTIC MATERIALS

Treatment of severe and moderately severe haemophilia and related disorders is dependent on the availability of preparations containing factor VIII or factor IX.

Factor VIII is present in:

fresh whole blood*

freshly separated plasma*

fresh frozen plasma *

dry (lyophilized) fresh plasma *

cryoprecipitate *

factor VIII concentrates (human)*

factor VIII concentrates (porcine) [1]

factor VIII concentrates (r DNA) [2]

* also contain the von Willebrand factor part of the factor VIII molecule. Note that this does not apply to high purity factor VIII concentrates.

Factor IX is present in:

fresh whole blood †

freshly separated plasma †

fresh frozen plasma †

cryoprecipitate removed plasma †

dry (lyophilized) fresh plasma †

dry (lyophilized) cryoprecipitate removed plasma †

factor IX concentrates (human) [3]

factor IX concentrates (r DNA) [4]

† availability of sufficient factor IX to have a therapeutic effect in these products is low, and circulatory overload, and renal impairment from protein overload, may have to be taken into account in treating patients with them.

Further Notes

1 Porcine factor VIII (Hyate C) is of especial use in the management of patients with factor VIII inhibitors.

2 At the time of publication 4 recombinant factor VIII concentrates were licensed for use in some countries. They were stabilized with human albumin. A product containing a modified factor VIII molecule but not requiring albumin stabilization was under trial.

3 Factor IX concentrates exist in two forms

: prothrombin complex concentrates (PCCs) which contain factors II, VII, IX and X in varying proportions

: high purity concentrates containing only factor IX

PCCs have been linked with thromboembolic incidents and are not recommended for the treatment of haemophilia B in patients undergoing prolonged immobilization, for instance following surgery.

4 Under development at time of publication.

Source of Therapeutic Material

At present the recombinant, genetically engineered products are in relatively short supply and are more expensive than plasma derived products. As a result the majority of people with haemophilia remain dependent on a human plasma supply. Whilst it is the policy of many national and international bodies including the World Health Organization to recommend that blood and its products only be obtained from altruistic unremunerated (unpaid) voluntary donors, in practice most of the world's present supply of factor VIII and IX *concentrates* are fractionated by commercial companies from the plasma of paid donors. In contrast most people with haemophilia in developing countries are reliant on local transfusion sources which produce fresh frozen plasma and cryoprecipitate from volunteer sources. Whatever the source it is essential that safety be considered at each step required for the preparation of the final therapeutic product.

It is the policy of the World Federation of Hemophilia, having mind of the overwhelming needs of people with haemophilia for therapeutic material, to support all initiatives aimed at increasing blood product supply. However, intrinsic to all collection, manufacture and distribution of products is the need for safety of both donors and recipients.

Safety of Therapeutic Materials

Until comparatively recently it was generally considered that the risk of transmission of transfusion related infection in haemophilia was outweighed by the risk of death or crippling as a result of untreated bleeding. In the early 1980's the advent of the AIDS pandemic and evidence of transfusion

related HIV infection resulted in the introduction of measures designed to eliminate viral contamination of blood products. These measures are:

- testing of individual donations for known pathogens or surrogate markers
- quarantine periods between collection and distribution, allowing for an additional check on donor health
- withdrawal of all material made from batches of source plasma containing donation(s) from someone subsequently shown to be infected with a transmittable disease
- exclusion of high risk donors with a history of possible transmittable disease contact, and
- encouragement to develop donation services using only the plasma from unpaid donors

In addition, the use of smaller plasma pools from fewer donors than presently included in commercial manufacture has been advocated. At the time of publication this appears to be the only option presently available (apart from withdrawal of all suspect source plasma) if transmission of slow viruses or other agents (for instance Creutzfeldt-Jakob disease) are shown to be a transfusion hazard.

In considering the safety of products for the treatment of haemophilia attention should be given to the incidence of infection in the population from which donors are chosen. For instance, donors of cryoprecipitate from areas of low prevalence of HIV or hepatitis C will provide a safer product than donors in areas of high prevalence.

Safety Measures Available During Manufacture

Given proper donor selection, individual testing of each donation and a high standard of quality control during fractionation, therapeutic safety of each product depends on the elimination of any virus present. Methods available and currently in use include exposure to:

- heat/pasteurization
- solvent detergent
- monoclonal antibody separation
- ion exchange chromatography, and
- ultra filtration

The ultimate safety of any product depends on strict quality control at all stages of collection and manufacture. With the exception of heating, all methods of virus exclusion to date are based on steps incorporated into the fractionation process. Heating at 80^0C for 72 hours in the final, sealed vial of lyophilized concentrate has been shown to eliminate major pathogens like HIV and hepatitis C. In contrast solvent detergent technology is being developed to remove viral contamination of source plasma. This step should be applicable to fresh frozen or lyophilized fresh plasma as well as to cryoprecipitate, whilst providing an early safety barrier in the production of more concentrated products. However to date none of the methods presently available render concentrates free of all viral contamination. For example human parvovirus, which has a protein coat, is known to be resistant. It is also possible that some slow viruses may prove to be transmittable despite all known virucidal methods, including pasteurization (60^0C for 10 hours) as used routinely in the production of albumin.

Supply of Therapeutic Material

The demand for safe blood products consistently exceeds supply, especially in developing countries. Whilst it is axiomatic to good health care that every effort be made to ensure that all patients receive proper treatment, those responsible for planning services often have little or no choice but to prioritize according to need. The figure of 35,000 units of factor VIII per patient per year suggested on page 7 of these guidelines is a generalization. Individual needs at different ages vary widely, and some patients, especially those with inhibitors (page 30), or on high dose prophylaxis require substantially more than 100,000 units of factor VIII annually.

Before setting targets planners need to know the numbers of patients likely to require treatment within their country. It is strongly recommended that a national epidemiological survey of the prevalence of bleeding disorders be carried out early in the development of the service to patients and their families, and that this survey be the responsibility of government.

Once prevalence and location of affected people are known much haemophilia care can be provided using local resources (page 49). In any programme with limited resource it is suggested that priority be given to the care of affected children, and especially to the prevention of disability which would otherwise increase dependency in adult life.

8. INHIBITORS TO FACTOR VIII OR IX

Inhibitors are antibodies which reduce the efficacy of factor VIII or IX replacement therapy. Inhibitor development is not predictable and can present at any time. It is less likely once a patient has received 100 treatments with the relevant clotting factor. The frequency of inhibitors in haemophilia B is much lower than the frequency in haemophilia A.

In haemophilia A estimates of frequency suggest that up to 50% of patients receiving factor VIII develop an inhibitor at some stage. Uncommonly, inhibitors to factor VIII may be acquired by people without haemophilia, and have been associated with childbirth, autoimmune disease, penicillin therapy and old age. These patients present with a bleeding disorder as a result of inhibitor development.

The effect of an inhibitor depends upon its strength or titre. Low titre inhibitors are easily overcome either by increasing the dose of factor VIII or by giving regular replacement therapy in order to induce immune tolerance. The majority of inhibitor patients are in this category. Responses to, and in vivo survival of, transfused factor VIII usually return to normal.

The most generally accepted measurement of inhibitor titre expresses the result in Bethesda units (B.U.). People with < 10 B.U. are classed as low responders. Some 10 to 20% of patients develop inhibitor titres of > 10 B.U., and are called high responders. In them factor VIII replacement therapy induces an anamnestic response with increasing inhibition of

circulating clotting factor. High titre inhibitors negate factor VIII therapy completely, even at very large doses.

Detection of Inhibitors

Inhibitors are detected in three ways:

- on the routine laboratory screening which should be part of the regular follow-up of all patients with haemophilia
- during the measurement of response to factor VIII therapy, typically before and after surgery, and
- as a result of a reduced clinical response to treatment noticed by the patient or his parents.

Laboratory confirmation of inhibitor development is based on mixing studies using the patient's plasma and normal plasma. Inhibition is time dependent, and increases with incubation at 37°C. Quantitative results from the Bethesda assay (Kasper et al 1975) demand a 2 hour incubation period.

Management of Inhibitors

A review of available therapy will be found in the WHO publication (1994) and as a supplement to the journal Haemophilia (1995). Many low responders lose their inhibitors spontaneously or after a period of treatment with slightly increased therapeutic doses of factor VIII, or daily infusion of about 25-50 units/kg. High responders are more problematic and their management may be very expensive. Most will eventually become

responsive to factor VIII therapy again if given daily infusions of factor VIII in very high doses, such as 200 units/kg for over a year ('immune tolerance induction').

Options for treatment of acute haemorrhages include:

- intermittent or continuous infusion of human VIII concentrate
- porcine VIII concentrate ('Hyate C', Speywood Laboratories, UK)
- prothrombin complex concentrate
- activated prothrombin complex concentrate (FEIBA, Immuno, Austria; Autoplex, Baxter, USA), or
- recombinant activated factor VII (Novo Nordisk, Denmark)

Choice of treatment and result is dependent on the inhibitor titre and prior pattern of response. Inhibitors to human factor VIII usually have much less ability to neutralize porcine factor VIII, thus, porcine factor VIII may raise plasma VIII levels more easily than human VIII. Prothrombin complex concentrate, whether inactivated or activated, or activated factor VII may encourage hemostasis without regard to the inhibitor titre. Efficacy of these two agents is judged by clinical response; in general, laboratory tests are not helpful.

For dental extraction or an open wound, local therapy with a factor VIII concentrate is sometimes effective. Strict immobilization of the bleeding site is indicated.

Invasive procedures entail high risk. Planned procedures are best performed when the inhibitor titre is low. A window of opportunity exists for effective treatment in the few days before an anamnestic response makes management increasingly difficult. Plasmapheresis may buy additional time by temporarily reducing the inhibitor titre.

Financial Implications

Contractors for health care should be aware that inhibitors may develop spontaneously at any time. If they do and are of high titre it is probable that early attempts at inducing immune tolerance are most likely to be successful. For this reason it is suggested that a strategy for the treatment of high titre inhibitors, whether in congenital or acquired haemophilia, be developed for each country, in consultation with directors of haemophilia comprehensive care centres. Lack of local guidelines and expertise from comprehensive care centres may result in considerable unnecessary expenditure.

9. SOCIAL AND PSYCHOLOGICAL SUPPORT

A diagnosis of haemophilia colours every aspect of a person's life and that of his family.

A. Haemophilia is rare. In its severe form, the incidence of haemophilia A is 1 in 16,000 of the population. The majority of people, including doctors and paramedical workers, will never knowingly meet someone with haemophilia.

B. Haemophilia is inherited. The sex linked recessive nature of this inheritance means that carrier mothers sometimes think they are the "cause" of their child's disorder. This knowledge can be especially hurtful when major bleeds disrupt the child's development, or when decisions about pregnancy and the possibilities for antenatal fetal testing have to be taken.

C. Haemophilia is associated with bleeding. This association is frequently misinterpreted by the lay public who are not aware that the majority of the bleeds of severe haemophilia are internal, into muscles and joints, rather than external. The myth that those with haemophilia can collapse and exsanguinate following trivial injury is common, and perpetuated by the media for dramatic effect.

D. Haemophilia is associated with transfusion transmitted disease. Infection with the human immunodeficiency virus (HIV) and AIDS are associated in the public mind with haemophilia. More recently

hepatitis C and worries about slow virus transmission have added to public unease.

E. For all these reasons families with haemophilia easily become isolated. Normal family growth and development suffers. There is a tendency to hide the diagnosis from others, including the caring professions.

F. Boys with haemophilia should attend normal schools and compete with their peers. Uninformed teachers may be reluctant to allow this. Parents may be frightened to let their haemophilic sons attend playgroups or nursery school. Normal formal education may be denied the haemophilic child in favour of special schooling designed for the handicapped or home tuition.

G. People with haemophilia may be denied access to everyday leisure activities and sports despite the fact that there is no reason why they cannot compete in the usual way without risk. The only sports universally banned for someone with severe haemophilia are boxing and rugby football because of the dangers of head and neck injury.

H. Unenlightened prospective employers may be reluctant to offer the man with haemophilia a job, especially if manual work is involved. Unfounded fears of bleeding, effects on other employees, problems with insurance and pensions, and loss of work through illness mitigate in favour of the non haemophilic applicant. In fact people with haemophilia make good employees, especially if they are trained in self treatment. However, the perception of what an employer might

think when considering someone with haemophilia for employment, results in the man hiding his diagnosis. He may then delay treatment during working hours in order not to draw attention to his condition. In physical terms the long term result may be severe arthropathy, chronic pain, and handicap.

The only jobs not suitable for someone with haemophilia are those that involve obvious risk, whether to the person or to those working with him. These include military service and law enforcement agencies.

I. Misinformation and isolation predispose people with haemophilia to a sedentary life with few social contacts. Prospects for marriage and the normal rearing of families are lower than those in the general community.

J. Longevity is normal, or near normal if haemophilia is treated properly. If it is not the man with severe haemophilia can expect the development of severe, painful and crippling arthritis and premature death from bleeding.

Services that should be Available

Two aspects of haemophilia comprehensive care are especially relevant for psychosocial support:

- ease of access to experienced nurses, social workers and psychologists.

- continuing education of both families and health care workers, allowing those with haemophilia to participate fully in all aspects of their care.

Underpinning the work of the haemophilia centre should be access to voluntary support groups, the most important of which is the local or national haemophilia society. These societies are often affiliated to the World Federation of Hemophilia, and are able to provide up-to-date factual information to their members, as well as practical help and friendship.

In collaboration with their medical and nursing colleagues, the professional and voluntary psychosocial services should be able to provide:

- general information on haemophilia and its treatment,
  growing up with haemophilia,
  haemophilia and sport,
  activities,
  travel and holidays;

- specific information on:
  sexual relationships, marriage and parenthood,
  access to genetic counselling,
  access to confidential counselling on all aspects of haemophilia care,
  education and employment,
  availability of state or local benefits or other practical help for people with chronic disorders,

referrals to agencies that may be able to provide help for specific problems.

Whilst both the social and psychological elements of comprehensive care are usually hospital based, much is to be gained by visiting families at home, seeing teachers, career advice personnel or prospective employers at their places of work, and encouraging contacts with other affected families outside the hospital setting.

Some Additional Practical Aspects of Haemophilia Care

Living with haemophilia in the family can be eased considerably by ensuring:

- the provision of a telephone in the home. Secure communication with the haemophilia centre at any time of the day or night is essential;

- the provision of a radio pager or mobile telephone, especially to the parent of a young son with haemophilia. Ease of communication provides security for both the family and those supervising the boy (baby sitters, teachers, coaches);

- help with transport. People with haemophilia, especially when they are not on self treatment, must be able to reach help (and get home again) at any time;

- a safe environment. Children with severe haemophilia should be given every advantage normally available to the general population to avoid injury. Aspects include:
  good housing with easy access to a secure garden or play area,
  stairs guarded by gates,
  car seat belts and restraints suitable for the age of the child,
  cycle helmets, and
  normal protective sports gear.

10. FOLLOW-UP

Regular follow-up is an essential component of haemophilia comprehensive care. Every severely affected child should be seen at six monthly intervals by a doctor with haemophilia experience. Every severely affected adult should be seen at least once a year.

People with moderate or mild haemophilia or an associated disorder may be seen less frequently, unless they have received blood products (or recombinant products).

Those people known to have health or social problems in addition to their bleeding disorder may need more frequent consultations.

Comprehensive care follow up is a function of the haemophilia team. Patients should be consulted and assessed by the nurse, physiotherapist and social worker, and referred for specialist opinion as required. Regular dental follow up is also advocated.

The following parameters should be known and discussed with the patient or his parent at follow up:

- bleeds since last consultation
- treatments since last consultation
  - type of product used
  - amounts in units
  - batch numbers
  - efficacy of treatment

- attendance at school or work
- inhibitor screen
- musculo skeletal assessment of joint ranges and muscle power
- radiology or scan results of joints subject to recurrent bleeding or pain
- dental care
- results of screening for hepatitis A, B or C and HIV 1 and 2 when relevant
- immunology screening when relevant

Patients and their families should be given the opportunity of discussing their health and answering questions in privacy.

Follow up is aided if easily understandable visual aids are used to explain treatment and recommended changes in treatment to families. Transfer of treatment episodes to a calendar chart is recommended. Patients can then not only see their own progress but have a direct comparison with others with an equivalent severity of haemophilia. These charts are especially valuable when monitoring target joints or prophylaxis[2].

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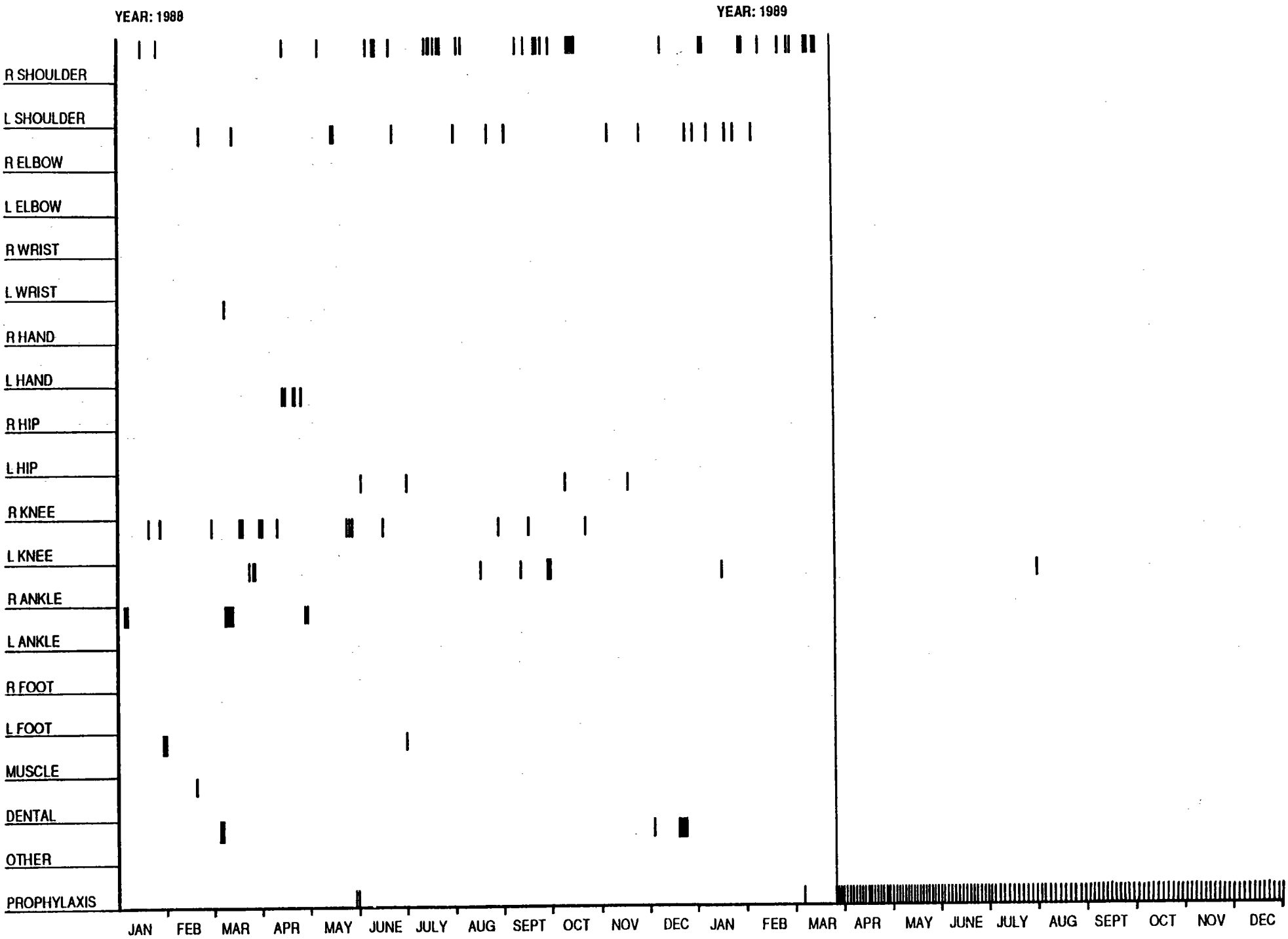
[2] Caption to chart: The Newcastle calendar chart records individual treatments in haemophilia A or B. Each vertical line is a single treatment. Failure of a particular bleed to respond to treatment is easily identified by looking for blocks of lines, for instance in the March 1988 record of a bleed into the left ankle. Recurrent bleeding signifies a target joint, which needs to be looked at with a view to change in management. Thus recurrent bleeds into the right shoulder in particular, but also into the right elbow and ankle, and both knees, suggested that in this patient regular prophylaxis would help. This was started in March 1989 and only one bleed into the right ankle, which responded to a single treatment, occurred in the next nine months. Prior to this regular prophylaxis the patient had given himself injections which anticipated events which he thought might result in bleeding (May 1988 and March 1989). All the rest of his therapy prior to prophylaxis was on demand, in response to his recognition of bleeding. The chart illustrates both the common pattern of bleeding in severe haemophilia A and the response to prophylaxis. *Reproduced from Living with Haemophilia, 4th edition, Jones P, 1995, Oxford University Press.*


YEAR: 1988
YEAR: 1989
R SHOULDER
L SHOULDER
R ELBOW
L ELBOW
R WRIST
L WRIST
R HAND
L HAND
R HIP
L HIP
R KNEE
L KNEE
R ANKLE
L ANKLE
R FOOT
L FOOT
MUSCLE
DENTAL
OTHER
PROPHYLAXIS
JAN FEB MAR APR MAY JUNE JULY AUG SEPT OCT NOV DEC JAN FEB MAR APR MAY JUNE JULY AUG SEPT OCT NOV DEC

11. THE PREVENTION OF HAEMOPHILIA: CARRIER DETECTION AND PRENATAL DIAGNOSIS

Modern techniques, including the application of DNA technology, have extended the choices open to couples planning their families. When there is a family history of haemophilia it is now possible to identify accurately most females who carry the haemophilia gene. Women who know they are carriers, or might be carriers, may have options for prenatal diagnosis to obtain information on fetal status.

Both haemophilia A and haemophilia B are inherited as sex linked recessive disorders. The genetic instructions for the production of normal factor VIII and factor IX are located on the X chromosome. A genetic abnormality of one of these genes therefore results in haemophilia A or B in the male (XY), but not in the female (XX) because she has a duplicate set of normal instructions on her other X chromosome.

The inheritance of haemophilia A and B

Mother	Father		Possible children			
XX +	XY	=	XX or	XX	or XY or	XY
1 2	3 4		1 3	2 3	1 4	2 4
Normal	Haemophilic		Carrier daughters		Normal sons	

X = the sex chromosome with the haemophilia gene. Daughters of a haemophilic father must be carriers because they inherit his X chromosome. Sons are normal and cannot pass haemophilia on to their progeny.

Mother	Father		Possible children					
XX +	XY	=	XX	or	XX	or	XY	or	XY
1 2	3 4		1 3		2 3		1 4		2 4
Carrier	Normal		Carrier		Normal		Haemophilic		Normal

Each daughter of a carrier mother has a 50:50 (1 in 2) chance of being a carrier. Each son has a 50:50 chance of having haemophilia. Rarely, a female may inherit haemophilia if her mother is a carrier and her father has haemophilia. In this case both her X chromosomes carry the haemophilia gene.

Carriers

Females with a haemophilia gene are called carriers. They are usually, but not always, symptom free.

Obligatory Carriers

An obligate carrier is a female who:

- has a father with haemophilia
- has more than one haemophilic son (identical twins excluded)
- has a haemophilic son and a carrier daughter, or
- has a haemophilic son and a relative with haemophilia on the maternal side of the family

Very rarely haemophilia occurs because the parent is a mosaic in which two or more genetically different cell lines develop from a single zygote. For instance, fertilization of an ovum from a nest of genetically distinct

cells in the maternal ovary may result in a haemophilic son of a mother who herself tests as normal on DNA analysis.

Possible Carriers

Females are possible carriers if they:

- have one haemophilic son
- have a carrier mother, or
- have affected relatives on the female side of the family

Full details on how to determine probability of haemophilia carriership, and on the tests available for carrier detection and prenatal diagnosis up to the time of publication in 1992 may be found in the report of a joint WHO/WFH meeting (see references). Since this report further advances in DNA technology have increased substantially the ability to detect carriership, especially in the case of haemophilia A (Lakich et al, 1993) and von Willebrand disease (Eikenboom, Reitsma and Briet, 1995). The discovery of an inversion involving intrachromosomal rearrangements in the sequence of intron 22 at the tip of the X chromosome now provides immediate genetic diagnosis in 50% of haemophilia A carriers, and has become the first test of choice in DNA analysis of severe haemophilia A kindreds. In haemophilia B, if DNA from a haemophilia relative is available, the ability to confirm or eliminate carriership by identification of a factor IX mutation is very high.

Carrier Testing

Women who carry the haemophilia gene need careful counselling and support, especially if the haemostatic disorder in their family is severe. Desire for testing, and perhaps acting on the test results, varies from family to family and from country to country. Whatever the circumstances carrier detection should never be attempted without sensitive counselling and the means to follow up those identified as carriers.

It is standard practice in some countries not to perform DNA analysis for the purpose of carrier detection until a girl is old enough to give her own informed consent (i.e., in her teens). However, in the case of haemophilia A and B it is important to know the girl's phenotype in childhood. This is because her factor VIII or IX clotting activity may be low enough to cause problems with haemostasis following injury or surgical challenge. The reason for this is that a disproportionate number of her cells expressing factor VIII or IX may contain the X chromosome with the haemophilia gene. It follows that the consistent demonstration of abnormal factor VIII or IX activity signals carriership. These girls will require treatment to cover surgery or dental extraction, either with desmopressin (DDAVP) for factor VIII deficiency, or a product containing factor IX in the case of haemophilia B.

Choices for Prenatal Diagnosis

Ultrasonography

All pregnant women should be offered an ultrasound scan to confirm gestational age, identify multiple pregnancy, and exclude major fetal

abnormality. Ultrasonography between 16-20 weeks may be used to determine fetal sex. If the fetus is female, the invasive techniques used to diagnose haemophilia can be avoided.

Parents who choose further prenatal testing should do so in the knowledge that it is only indicated if they wish to consider the termination of an affected fetus. This is because all the tests carry a risk, albeit small (< 3% overall). However, parents should of course have the option of changing their minds at any stage in the light of test results. Due attention should be paid to the clinical severity of the haemostatic disorder within a family. It is usually inappropriate to consider prenatal testing if the disorder is mild.

The tests available are:

First trimester

- chorionic villus sampling (CVS)
  Biopsy of chorionic tissue early in pregnancy provides material for DNA analysis. Both fetal sex and haemophilia genotype may be determined.
- amniocentesis also provides material for both fetal sex and haemophilia genotyping.

Second trimester

- fetal blood sampling under direct vision using the technique of fetoscopy provides the phenotype by assay of factor VIII or IX.

All these techniques, especially fetal blood sampling, demand meticulous attention to detail. Requirements are set out in the joint WHO/WFH document on prenatal diagnosis.

Umbilical cord sampling

Phenotypic diagnosis may be made on a fresh sample of cord blood taken into sodium citrate. Factor VIII or IX assays at birth should always be checked later, when a peripheral vein becomes available for atraumatic venepuncture. This check allows for variations in gestational age which may affect VIII or IX levels, especially the latter, as well as artefact caused by difficulty in sampling or delay in processing the cord blood specimen.

Venepuncture using external jugular or femoral veins in infants with suspected haemophilia is strictly contraindicated. This is because major bleeding and haematoma formation into neck or thigh may result from the procedure.

12. HAEMOPHILIA CENTRES

The wide ranging needs of people with haemophilia and their families are best provided through centres of expertise rather than by individual doctors. Centres able to meet these needs have become known as Haemophilia Comprehensive Care Centres (HCCCs). In general each HCCC should be responsible for the overall management of at least 40 severely affected people with haemophilia.

Clearly, it is not appropriate to expect every patient to travel to an HCCC whenever he or she needs treatment. Of practical importance is the need to assure that someone with haemophilia needing help will receive it from a health care worker with, or at least in touch with, knowledge of the underlying bleeding disorder. This requirement is provided by the establishment of Haemophilia Centres (HCs) linked to each HCCC. Services available at HCs will vary according to the expertise and interest of health care workers in post, but in general they will be able to diagnose haemophilia and give first aid and appropriate clotting factor therapy on demand. The integration of a universally accessible haemophilia care system into the existing health care system of a particular country is both sensible and cost effective.

Within some countries the exact requirements expected of both HCCCs and the smaller HCs have been defined by Health Departments. Those in use in the United Kingdom, updated in 1993, provide a guide to those planning

equivalent services in other countries. They have been amended for this publication.

Background

The haemophilic population comprises a group of patients whose medical management is both complex and costly. Some of the complexity arises because of the rarity of the condition, its lifelong nature, its variable severity, and the fact that patients do not appear "ill" in the accepted sense of that term. It may not always be understood that the lack of prompt, appropriate treatment may lead to prolonged hospitalization and the misuse or even on occasion the wastage of expensive blood products.

People with haemophilia may have built up relationships with a chosen centre for various reasons, and this centre may not be within their administrative or geographical health area. Haemophilic patients tend to refer themselves direct to a particular haemophilia treatment centre, and may bypass customary consultation with their family doctor because of the specialized knowledge required for their treatment.

In planning the provision of services for people with haemophilia health authorities will need to take into account a number of particular considerations needed if the aim of access to comprehensive care is to be achieved:

- variability and severity of the haemophilic condition;

- complexity of the condition which may require a diverse and complex range of services. Given the nature of the condition, the amount of treatment required by individual patients will be ***unpredictable***;

- expertise in treatment of haemophilia patients will not be uniformly available across the country;

- the need for ease of access to supplies of blood products to support home treatment programmes;

- the prevalence of side effects of therapy including infection with hepatitis C and HIV, which are significant problems in this group of patients, and the need for treatment and counselling;

- mildly affected individuals may need little more than review and access to treatment in the event of bleeding, but more sophisticated treatment will be required in many cases.

Haemophilia Treatment Centres

For simplicity of organization it is suggested that the haemophilia centres available to respond to patient needs within a country are of two types:

- The Haemophilia Comprehensive Care Centre
- The Haemophilia Centre

In addition, coagulation laboratories set up as part of general haematology services in district hospitals will act as referral points for patients diagnosed as having a hereditary bleeding disorder.

A. Services Provided by a Comprehensive Care Centre

i. a clinical service provided by experienced staff for the treatment of patients with haemostatic disorders and their families at short notice at any time of the day or night.

ii. a laboratory service capable of carrying out all tests necessary for the definitive diagnosis of haemophilia and all common inherited haemorrhagic disorders, including the identification and assay of the relevant specific haemostatic factors. Further, capable of monitoring therapy and carrying out preliminary testing for inhibitors.

iii. where appropriate and indicated, to conduct in collaboration with other haemophilia treatment centres the further investigation of relatives of patients with haemophilia or other haemostatic disorders.

iv. an advisory service to patients and close relatives on matters specific to haemophilia. Advice should also be given to family doctors as appropriate.

v. maintenance of satisfactory quality control and assurance for all laboratory tests offered in relation to clinical services, both by establishing appropriate internal procedures and by participation at the appropriate level in a quality assessment scheme in blood coagulation.

vi. maintenance of medical records; records must be maintained of all treatment administered and all adverse reactions reported. Special medical cards with details relevant to future treatment are to be issued and a register kept of all patients attending the centre.

vii. counselling in privacy of patients and their relatives.

viii. participation in appropriate clinical audit.

ix. where appropriate, to provide advice on and organization of home therapy programmes either individually or in collaboration with other haemophilia treatment centres.

x. the provision of prophylactic treatment programmes for patients with haemophilia and other haemostatic disorders.

xi. 24-hour advisory service to Haemophilia Centres and support to such Centres as appropriate.

xii. a specialist consultant service for all surgery including orthopaedic and dental, for infectious diseases (such as HIV and hepatitis) and paediatric care, and for genetic, HIV, and social care and any other counselling services.

xiii. a reference laboratory service for Haemophilia Centres. The services should also include the diagnosis of atypical cases, genotypic analysis, the assay of inhibitors and other haemostatic factors, the diagnosis of hereditary platelet disorders, the supply of assay standards and reagents and, when requested, advice and recommendations concerning analytical procedures.

xiv. educational facilities for medical staff, nurses, laboratory staff, counsellors and other personnel as required in order to promote optimal comprehensive care of patients.

xv. co-ordination of meetings and undertaking research programmes, including the conduct of clinical trials and to establish and participate in suitable national programmes of clinical audit.

B. Services Provided by a Haemophilia Centre

It would normally be expected that a Haemophilia Centre would provide services (i) to (ix) above.

13. CLINICAL AUDIT

The ultimate purpose of audit is to improve patient care. Effective audit addresses both patient expectations and measures the standard of health care in terms of available resources. These include medical and paramedical staffing, facilities for treatment, therapeutic products, and cost.

Within a country much comparative audit between centres, including patient demography and use of therapeutic materials, can be performed by the regular (annual) collection of data by post or fax, rather than by personal visit.

However, personal visit audit provides the opportunity for a friendly, objective and entirely confidential appraisal of a centre. It also affords time for patients' views on their care.

Haemophilia audit of a centre should be carried out by a haemophilia specialist from a geographical area not served by that centre. Someone knowledgeable in haemophilia care is essential because of the very specialized nature of comprehensive haemophilia care.

Key features of any audit are:

i. Annual data collection for national audit †

(† based on returns to the Oxford Haemophilia Centre, UK)

a) Primary Information:

Notification of
- name
- date of birth
- diagnosis
- factor level
- Centre attended
- date of death

This information provides the basic demography of inherited bleeding disorders. Knowledge of the number of people with a severe or moderately severe disorder in a country allows for accurate assessment of clotting factor demand. Knowledge of age at death provides an immediate objective comparison with the non-haemophilic male population.

Names of patients are required by the co-ordinating centre in order to avoid duplication.

b) Secondary Information:

From Centre

- Total annual use of clotting factor products for the treatment of haemophilia and related disorders,
- Total number of patients treated in the year for haemophilia A, B, von Willebrand disease, or other inherited disorders of haemostasis.

This information provides the number of units of factor VIII or IX used per patient per year for each Centre, together with the cumulative total for the country as a whole. Such figures are comparable internationally.

- Individuals developing inhibitors and, when available, a measure of whether these are of low or high titre (usually expressed as Bethesda units),
- Treatment used for inhibitor patients.

In addition, and dependent on local circumstances, data relating to other complications of treatment, causes of death, and haemophilia carriership might be collected.

c) From Personal Visit

- inspection of coagulation laboratory
  - ability to perform tests
  - quality control measures in force
  - out of hours availability of assays

- inspection of clinical service
  - staff experienced in haemophilia care
  - times of cover provided
  - facilities available:
    access to centre
    out-patient treatment

in-patient treatment
counselling in private
referral to specialist services.

- Inspection of record keeping system in use
  - diagnosis
  - family trees
  - genetic counselling
  - recording of bleeds and their treatment
  - follow-up (periodic review) records
  - screening for inhibitors
  - screening for side effects
  - vaccination
  - in-patient notes.

d) From Patient Questionnaire

This questionnaire may be mailed to a sample number (< 20) of patients attending the centre to be audited, together with a reply-paid envelope and an explanatory letter. Alternatively, the auditor can go through the questionnaire with individual patients and their families in private during his or her visit. Because the completed questionnaire bears no names or identifying features the former method is probably more likely to produce objective replies.

All patients invited to answer the questionnaire should have severe or moderately severe haemophilia or von Willebrand disease.

PATIENT QUESTIONNAIRE

1. Do you attend this haemophilia centre regularly?

2. Which type of product is normally used for your treatment:
   Whole blood
   Fresh plasma
   Fresh frozen plasma
   Cryoprecipitate
   Factor concentrate prepared from human plasma
   Recombinant factor concentrate?

3. Are you on:
   Home therapy (self injection)
   Prophylaxis (regular injections to prevent bleeds)?

4. If you need their help at any time do you have easy access to the following people who are skilled in haemophilia care?
   a) Haematologist
   b) Paediatrician, internist or general practitioner
   c) Orthopaedic surgeon

d) Nurse

e) Physiotherapist (physical therapist)

f) Dentist

g) Genetic counsellor

h) Social worker

i) Psychologist

5. Please say how satisfied you are with the care given by your centre with:

a) The treatment of bleeds:

b) The treatment of arthritis or other problems:

c) Answering your questions about haemophilia and its treatment:

d) The follow-up (review clinics):

e) The care of any side effects of treatment:

6. What improvements in your care would you like to see at your centre?

14. OVERALL RECOMMENDATIONS

1. Haemophilia is eminently treatable. The costs of treatment are more than balanced by gains in health and productivity. Untreated haemophilia may result in premature death, but may also result in chronic handicap and lifelong economic and social dependency on families and the State.

2. Education about haemophilia is a primary requirement for affected families and their doctors. Morbidity and mortality are reduced by refraining from unnecessary intervention, as well as by treating bleeds appropriately.

3. Replacement therapy in haemophilia does not necessarily require high cost imported products. It does require safety, which is one of the essential parts of a blood transfusion service. The establishment of a local blood transfusion service is a primary requirement in meeting the overall health needs of any population.

4. Day-to-day haemophilia care does not require expensive resources. With proper training most care may be provided by family members and paramedical staff, including nurses and physiotherapists.

5. Regular follow-up which should include clinical audit is an essential component of haemophilia comprehensive care.

6. Haemophilia is preventable in some families. Prevention depends on carrier detection and counselling. DNA from family members with haemophilia should be stored for later analysis and use in carrier detection and prenatal diagnosis.

7. Access to expertise about haemophilia is readily available via the World Federation of Hemophilia, 1310 Greene Avenue, Suite 500, Montreal, Quebec, Canada H3Z 2B2. Tel: (514) 933 7944, Fax: (514) 933 8916, e-mail: wfh@wfh.org., Internet Web Site: http//www.wfh.org.

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1992 Educational Materials on Haemophilia for Families (WHO/HDP/HAEM/EMT/92.1).

1992 Educational Materials on Haemophilia for Health Care Professionals (WHO/HDP/HAEM/EMT/92.2).

1992 Report of a Joint WHO/WFH Meeting on the Control of Haemophilia: Carrier Detection and Prenatal Diagnosis (WHO/HDP/WFH/92.4).

1994 Report of a Joint WHO/WFH Meeting on the Control of Haemophilia: Modern Treatment of Haemophilia (WHO/HDP/WFH/94.6).

17. GLOSSARY OF TERMS

Concentrate	Concentrates are fractionated, freeze dried preparations of individual clotting factors or groups of factors. They provide convenient high dose to volume material for the rapid treatment of bleeds. Reconstitution is with sterile water, and administration (as with all blood products) is into a vein.
Cryoprecipitate	A fraction of human blood prepared by slowly thawing fresh frozen plasma. Cryoprecipitate is rich in factor VIII, von Willebrand factor and fibrinogen. It does not contain factor IX.
Factor VIII	One of a series of clotting proteins (factors) manufactured in the liver, and released into the bloodstream. A deficiency or absence of factor VIII clotting activity results in haemophilia A.
Factor IX	One of the blood clotting ingredients manufactured in the liver. Deficiency or absence results in haemophilia B. Factors II (prothrombin), VII, IX, and X are referred to as the 'prothrombin complex', and are dependent on vitamin K for their manufacture.
Fresh frozen plasma (FFP)	Human plasma separated from blood cells soon after donation and deep frozen at -40^{0}C. FFP contains all the clotting factors, but at low concentration to volume. FFP may be freeze dried (fresh dry plasma) obviating the need for freezer storage.

Genotype	A person's genetic constitution; his or her hereditary information. For instance the structure of his or her factor VIII or IX gene(s).
Haemarthrosis	Bleeding into a joint.
Haemophilia A	Factor VIII deficiency.
Haemophilia B	Factor IX deficiency (also known as Christmas disease).
Haemophilia Comprehensive Care Centre	A tertiary care centre providing a full range of facilities for the diagnosis and management of the inherited bleeding disorders.
Haemophilia Centre	A secondary care centre providing basic diagnosis and treatment of the inherited bleeding disorders. Haemophilia Centres should be linked to Haemophilia Comprehensive Care Centres.
Haemophilic arthropathy	The painful, chronic arthritis which develops as a direct result of inadequately treated haemarthroses. This arthritis is especially evident in the major synovial joints (shoulders, elbows, hips, knees and ankles).
Haemostasis	The mechanism by which spontaneous haemorrhage and undue blood loss from injured vessels is prevented.
Home therapy	A generic term for the self intravenous injection (or injection by a relative) of clotting factor outside the hospital setting. Home therapy obviates day-to-day reliance on hospital services and provides rapid treatment for people with haemophilia.

Inhibitors	Antibodies against one of the clotting factors, usually factor VIII. Inhibitors may occur in non haemophilic patients (acquired inhibitors) and require clotting factor therapy.
Phenotype	A person's observable characteristics; the expression of his or her genotype. For instance the level of factor VIII or IX in his or her bloodstream.
Porcine factor VIII	A concentrate of factor VIII prepared from pig plasma. Used mainly for the treatment of haemophilia A patients with inhibitors.
Primary Haemophilia Care	The provision of first aid facilities for people with inherited bleeding disorders. All hospitals providing primary haemophilia care should be linked to a Haemophilia or Haemophilia Comprehensive Care centre.
Prophylaxis	Regular injections of clotting factors given in order to prevent spontaneous bleeding.
Recombinant products	Concentrates made by genetic engineering. Presently, commercial recombinant factor VIII concentrates are available. Factor IX and von Willebrand factor preparations are under development.
Spontaneous bleed	A bleed, usually internal, which occurs at any time without known cause. The hallmark of severe haemophilia A or B.
von Willebrand disease	An inherited bleeding disorder resulting from a defective von Willebrand factor. This factor is closely linked to factor VIII in the bloodstream.

Annex 1

The World Federation of Hemophilia

Founded in 1963, the World Federation of Hemophilia (WFH) is a federation of national member organizations representing over 84 individual countries.

The overall mission of WFH is to stimulate services and increase access to care worldwide for people with haemophilia and related disorders.

To achieve this mission WFH offers medical, psychosocial, scientific and technical support through its programmes and centres of expertise. 23 International Haemophilia Training Centres (IHTCs) educate people working with haemophilia. In addition, WFH supports programmes of twinning of both haemophilia centres and National Member Organizations between developed and developing countries, ensuring that whenever possible expertise and resources may be shared. Other programmes are being developed. They include support services for surgery and Operation Access, which has been designed to encourage government commitment to haemophilia care. Up-to-date information about these and other initiatives may be obtained from the

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Up-to-date details of WFH recognized International Haemophilia Training Centres may be obtained from the Secretariat. At the time of publication, IHTCs were established in the following cities:

Bangkok, Thailand
Basel, Switzerland
Buenos Aires, Argentina
Chapel Hill, North Carolina, USA
Groningen, Netherlands
Helsinki, Finland
Leuven, Belgium
London, UK
Los Angeles, USA
Malmö, Sweden
Milan, Italy
New York, USA
Oxford, UK
Paris, France
Philadelphia, USA
Rio de Janeiro, Brazil
Rochester, Minnesota, USA
Sheffield, UK
Sydney, Australia
Tel Aviv, Israel
Tokyo, Japan
Vienna, Austria
Worcester, Massachusetts, USA

At the time of publication the following National Member Organizations were recognized by WFH. Please contact the Secretariat for details of contact addresses within these countries:

Albania
Algeria
Argentina
Australia
Austria
Belgium
Bolivia
Brazil
Bulgaria
Canada
Chile
China
Colombia
Costa Rica
Croatia
Cuba
Cyprus
Czech Republic
Denmark
Dominican Republic
Egypt
El Salvador
Estonia
Finland
France
Georgia
Germany
Greece
Guatemala
Honduras
Hungary
Iceland
India
Indonesia
Islamic Republic of Iran
Ireland
Israel
Italy
Jamaica
Japan
Kenya
Kuwait
Latvia
Lebanon
Lithuania
Luxembourg
Malaysia
Malta
Mexico
Morocco
Nepal
Netherlands
New Zealand
Nicaragua
Nigeria
Norway
Pakistan
Panama
Paraguay
Peru
Philippines
Poland
Portugal
Republic of Korea
Romania
Russian Federation
Singapore
Slovakia
Slovenia
Somalia
South Africa
Spain
Sweden
Switzerland
Thailand
The former Yugoslave Republic of Macedonia
Trinidad and Tobago
Tunisia
Turkey
United Kingdom of Great Britain and Northern Ireland
United States of America
Uruguay
Venezuela
Zimbabwe

WFH Goals

There are 5 goals within the WFH strategic plan. WFH exists to:

1. Encourage and foster the highest possible levels of diagnosis, comprehensive care and support for people with haemophilia and related disorders, for all countries throughout the world.

2. Help initiate and assist programmes to address the local factors which restrict access to areas of comprehensive care for people with haemophilia and their families in the developing world.

3. Encourage the education and training of direct care givers as well as people with haemophilia, their families, concerned organizations and the general public, using the most appropriate means.

4. Promote research and development of the medical treatment of haemophilia and related disorders, and encourage the development of the technology base for this support.

5. Strive to accomplish its goals through appropriate organizations at global, regional and national levels.

Implementation

Strategic planning requires the continued commitment and enthusiasm of dedicated individuals if objectives are to be fulfilled. The World Federation's global challenge is to help provide comprehensive care to all

families with haemophilia. Fundamental to this challenge is education and WFH is committed to the provision of accurate, up-to-date information about haemophilia at every level. Eight initiatives provide examples of this commitment.

- A biennial International WFH Congress which invites the participation of all those concerned with the comprehensive care of haemophilia, including both scientists, doctors and paramedical workers and people with haemophilia and their families.

- A series of workshops specifically designed to help those in developing countries improve haemophilia care. These workshops are tailored to the individual needs of the country or countries concerned, and may include 'wet workshops' on laboratory technique.

- Haemophilia, the Official International Journal of the World Federation of Hemophilia (CODEN HAEMF4 ISSN 1351-8216) is published quarterly by Blackwell Science Ltd, Osney Mead, Oxford, OX2 0EL, UK.
  Tel: +44 1865 206206; Fax: +44 1865 71205.
  The journal contains review articles, original scientific papers and case reports related to haemophilia.

- The Manual of Haemophilia Care, to be published by Blackwell Science. The manual details the comprehensive care of

haemophilia, providing essential information on treatment for doctors and paramedical staff.

- An Illustrated Hemophilia Guide, including a section on HIV infection, designed to help when teaching people about haemophilia and its treatment.

- 'Passport', an international listing of haemophilia centres and haemophilia societies, and the services they provide.

- A Skills Manual for National Member Organizations, designed to help people develop national programmes of care.

- The Haemophilia Forum on the Internet is being developed in order to provide a concise summary of contemporary management, and the opportunity for people with haemophilia and those responsible for their treatment to access expert opinion.

Details of these and other educational initiatives are available from the WFH Secretariat.

Since 1969, the WFH has been recognized as a non-governmental organization in official relations with WHO. Collaboration has been aimed at the development of clinical and laboratory technology for health systems based on primary health care and the improvement of haemophilia management at the country level. Please refer to the chapter on references for a list of recent publications resulting from joint activities.

Annex 2

STORAGE OF DNA

The analysis of factor VIII and factor IX genes in patients with haemophilia A and B respectively is resulting in a greater understanding of the nature of these diseases, and in precise carrier detection and prenatal diagnosis within affected families.

In order to perform these studies, it is generally important that a sample of blood from which DNA can be extracted is obtained from the affected patient. Unfortunately because of the present position regarding HIV infection, situations have arisen when family studies to detect carriers and to enable prenatal diagnosis to be performed have been prevented because the affected family member has died and no blood sample from which DNA can be extracted is therefore available.

Blood for DNA extraction, and DNA itself, is extremely stable if stored under the right conditions and may be used for studies many years hence. The techniques of gene and DNA analysis are rapidly becoming simpler and DNA studies in haemophilia, particularly when performed to provide accurate carrier detection and prenatal diagnosis, will become more widespread. The World Federation of Hemophilia therefore recommends that samples of blood suitable for DNA extraction are obtained from all patients with haemophilia A and B and stored under suitable conditions (see below). This is, unfortunately, particularly important for those patients

who are HIV antibody positive. WFH recommends the following procedure.

1) Counsel the patient and his family regarding the need for a sample. Explain that the sample will only be analyzed with the expressed permission of the patient and/or his family.

2) Collect up to 20 mls of citrated or heparinized blood.

3) Divide the whole anticoagulated blood into 2 or 3 aliquots and store at minus 20°C (in separate deep freezers if possible).

4) Keep and maintain a record of samples stored.

5) If possible extract DNA from one of the aliquots (using standard methods) and store at minus 20°C. Storage of samples as extracted DNA is not essential but may be performed in laboratories where extraction procedures are established.

It is expected that samples stored in this way will provide valuable material for family studies in years to come.

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