

Advances in Care of Children with Hemophilia

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ABSTRACT

Care for children with severe hemophilia has moved from pediatric hospital wards and rehabilitation services to the home, school, and community. Advances in hemophilia are due largely to the development of specialized hemophilia treatment centers, which created a system of comprehensive care and focused healthcare efforts on prevention and education. Parallel advances in coagulation resulted in identification of clotting factors VIII and IX, elucidation of the protein molecular and biochemical structures and functions, sequencing of their respective genes and transfer of the human genes for production of proteins by recombinant technology, and development of gene therapy. The tragedy of the human immunodeficiency virus and hepatitis C raised awareness in patients as well as healthcare providers of the vulnerability of blood products to viral contamination and spurred progress in science leading to viral inactivation of purified proteins. Concomitantly, physicians treating bleeding episodes in the clinic investigated pharmacokinetics and pharmacoeconomics of various strategies of clotting factor replacement. The observation that trough factor levels as low as 1 to 2% were adequate to prevent most bleeding episodes led to current prophylactic regimens that allow boys to participate fully in school and community activities while factor concentrate is infused at home on a regular schedule. Currently, children with hemophilia look forward to a normal life expectancy and excellent health-related quality of life. Physician and community partnerships through research and advocacy societies have accelerated clinical advancements as well as extension of treatment to developing countries. The future of hemophilia promises a cure with gene therapy. Given the past accomplishments in hemophilia, a long-term solution to replacement of the genetically deficient protein lies on the horizon.

KEYWORDS: Hemophilia, treatment, factor concentrates, blood products, bleeding

Objectives: On completion of this article, the reader should be able to (1) list the main contributions that led to improved life expectancy of patients with hemophilia and (2) state which accomplishments led to a reduction of joint bleedings in hemophiliacs.

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The care of children with hemophilia has improved immensely over the last 40 years, from an era in which children with hemophilia rarely were expected to survive beyond the first decade to the present state in which babies currently born with severe hemophilia can be expected to have a normal life span, participate fully in school and the workplace, and receive treatment in the home with minimal disruption to personal and family life. Hope for a significant modification of hemophilia through gene therapy still looms as a promise, although lasting gene transfer has yet to be demonstrated in humans with hemophilia. The tremendous evolution in prognosis of severe hemophilia from a chronic crippling and often fatal condition to one for which parents can anticipate a fairly normal quality of life occurred through parallel improvements in several aspects of hemophilia care over the last four decades. A few advances originated in dramatic scientific discoveries, but the majority resulted from basic and practical incremental improvements in care contributed by a large number of dedicated hemophilia treaters world-wide. This paper reviews the major achievements.

ELUCIDATION OF BASIC MECHANISMS OF COAGULATION

The hemophilias are X-linked genetic bleeding disorders caused by deficiencies of coagulation factor VIII (FVIII) and factor IX (FIX). The history of early medical progress in understanding and treating hemophilia was published in a classic review by Rosemary Biggs in 1967.¹ In 1937, Carroll Birch² chronicled the clinical course in 98 living patients with hemophilia and reviewed records of other family members. Table 1 lists the cause of death in 113 persons with hemophilia reported by Birch² and serves as a stark testimony to the fatal nature of trivial lacerations, epistaxis, circumcision, and tooth extraction prior to factor replacement therapy. Macfarlane realized in the 1930s that treatment of hemophilia would not be achieved until the physiology of normal clotting and hemostasis were determined. In 1934, Macfarlane and Barnett reported that only transfusion of whole blood, and not any local therapies, showed efficacy in cessation of hemophilic bleeding.³ Macfarlane⁴ hypothesized in his seminal 1938 article that a clotting factor necessary to activate prothrombin was missing in persons with hemophilia, and identification of this factor would be necessary to understand and ultimately treat hemorrhage in persons with hemophilia. Until 1952, it was believed that tissue-derived thromboplastin directly activated prothrombin. In 1953, this group discovered a "plasma thromboplastin" activity formed in normal blood and defective in the plasma of persons with hemophilia.^{5,6} They went on to develop coagulation assays that differentiated plasmas deficient in FVIII from those deficient in FIX, and the stage was set for the development of specific therapies.⁷ The subsequent discovery of

Table 1 Cause of Death for 113 Patients with Hemophilia²

Cause of Death	Number
Operations	25
Circumcision	15
Tooth extraction	6
Vaccination	1
Lanced hematomas	2
Tonsillectomy	1
Trivial injuries	23
(cut lip, bitten tongue, injuries to forehead, finger, scalp, etc.)	
Internal bleeding	21
Central nervous system bleeding	7
Birth trauma and umbilical bleeding	7
Epistaxis	6
Lung hemorrhage	5
Haematuria	4
Throat bleeding	3
Intestinal bleeding	3
Gastric bleeding	3
Cutting first tooth	1
Fracture of leg	1
Miscellaneous	4

Data from Birch.²

AQ10

a large number of proteins involved in coagulation led to development of the International Committee for the Nomenclature of Blood Clotting Factors, which was later renamed The International Committee for Haemostasis and Thrombosis, now The International Society for Thrombosis and Haemostasis (ISTH), including the Scientific Standardization Committees.

Rapid advances in the field of coagulation progressed from the identification, isolation, and biochemical characterization of factors VIII and IX^{8,9} to identification and sequencing of their respective genes^{10,11}; understanding coagulation protein structure, function, and interactions at the molecular level^{12,13}; and development of dynamic integrated theoretic models of thrombin generation and regulation.¹³ Functional assays of factors VIII and IX allowed prediction of bleeding risk and provided the rationale for structured treatment protocols to manage acute bleeding events and prevent surgical bleeding. New laboratory techniques to assess global thrombin generation potential helped to explain clinical differences among hemophilia patients and allow for therapies tailored to individual hemostatic potential.¹³

DEVELOPMENT OF SPECIALIZED CENTERS FOR HEMOPHILIA COMPREHENSIVE CARE

In 1958, in an attempt to organize experience and services for persons with hemophilia, Biggs and Macfarlane¹⁴ reviewed records of 187 hemophilia patients who received

specialized services at Oxford. Observations of these 187 patients led to several sentinel findings regarding the natural history of hemophilia, including the classification of hemophilia severity based on levels, with mild symptoms observed in most patients with more than 5% of FVIII and very mild disease noted in many hemophilia B patients with 1% or more FIX. In addition, it was noted that hemophilia A patients with 1 or 2% FVIII activity exhibited far fewer bleeding episodes in comparison with patients who had no detectable FVIII. Macfarlane and Biggs¹⁴ noted that it required far higher levels of factor activity to prevent surgical bleeding than to prevent spontaneous hemorrhages, an observation that laid the groundwork for rational design of factor replacement recommendations and suggested a role for prophylaxis. With experience, the Oxford group developed standardized approaches to various types of bleeding in hemophilia patients. At this time local hospitals often cared for hemophilia patients with routine hemorrhages and referred only the most difficult cases to Oxford. Biggs and Macfarlane¹⁴ described the case of a young man with protracted complications following surgery for trauma whose care consumed the time of 9 physicians, 5 of whom spent most of their time with him during a 3-month hospitalization, in addition to constant services of nurses, physiotherapists, and laboratory personnel. Biggs and Macfarlane¹⁵ suggested that treatment of this patient in a specialized center such as Oxford would have consumed a small part of one hematologist's time with fewer complications and a better outcome. In addition, they stressed collaboration among hematologists, surgeons, physiotherapists, and laboratory personnel was key to improved clinical outcomes. Thus, the rationale was presented for the development of specialized centers to deliver hemophilia comprehensive care. The same year Carol Kasper et al¹⁶ reported the first US multidisciplinary center serving more than 500 patients with hemophilia. The concept of hemophilia comprehensive care spread and 10 years later, reports were published on the benefits of organized comprehensive care clinics for hemophilia from Italy, the United Kingdom, France, the United States, and Asia.¹⁷⁻²¹

In 1975, the US Congress appropriated money for the creation of a national network of Hemophilia Diagnostic and Treatment Centers by Section 1131 of the Public Health Service Act.²² The first centers were established the next year. The system was expanded gradually to the current 135 federally funded hemophilia treatment centers. Similar national programs were developed in Canada and several European countries. The initial charge to the treatment centers was to establish and maintain high-quality reference coagulation laboratories with validated assays to identify accurately persons with the hemophilias and other congenital bleeding disorders. Comprehensive clinic programs staffed by a team of specialists were developed to provide comprehensive evaluation and generate an integrated treatment plan.²⁰ The

central figure in the hemophilia treatment center was the nurse coordinator, who was responsible to provide education about hemophilia to the patient, the family, teachers, employers, and healthcare providers in the community.²³ In addition to nurse coordinators, the original multidisciplinary hemophilia center teams included hematologists, pediatricians, internists, geneticists, dentists, physical therapists, orthopedic surgeons, social workers, and psychiatrists to deal with the protean issues surrounding hemophilia.^{1,16,20} Hemophilia care advanced significantly when all patient calls were funneled to one nurse specialist who expedited clinic visits for bleed assessment, facilitated prompt outpatient factor replacement therapy, and ultimately taught and monitored home infusion therapy. The majority of persons with severe hemophilia rapidly enrolled in the US federal hemophilia system and within 5 years of their inception, Smith, Levine, and others were able to document that comprehensive hemophilia treatment centers dramatically reduced cost, hospitalizations, and absenteeism from work and school.^{24,25} By 1984, the World Federation of Hemophilia determined international standards for hemophilia centers.²⁶ More recently, the US Centers for Disease Control and Prevention (CDC) funded a surveillance project and confirmed reduced mortality and morbidity for persons with hemophilia who access federally funded hemophilia treatment centers.²⁷ The role played by the hemophilia comprehensive care centers in the improvement in hemophilia outcome cannot be overstated.

PARENTAL AND SELF-INFUSION OF FACTOR CONCENTRATE IN THE HOME

Early observations linked prompt treatment with faster, more effective control of hemorrhage. Shortly after cryoprecipitate became available, families requested support to institute replacement therapy in the home. A home program including 14 patients with FVIII deficiency was reported from Michael Reese Hospital in Chicago in 1970.²⁸ Home therapy was quickly adopted in countries with access to replacement therapies.²⁹⁻³¹ Of interest, hemophilia patients using self-treatment at home were noted to use a higher FVIII dose, based on perceived efficacy.³¹ International recommendations endorsing home therapy were published in 1979.³² Home therapy avoids time delay and expense associated with emergency room visits, allows treatment in a comfortable environment, and continues as a keystone in hemophilia therapy. In 2001, the US CDC Surveillance Project reported that home therapy and hemophilia comprehensive care centers were each independently associated with a reduced rate of hospitalization for bleeding episodes.³³

The goal of home therapy for young children with hemophilia is to facilitate prevention or early treatment of bleeding events in hopes of preventing target joint disease. Venous access is often problematic in chil-

dren below the age of 4 or 5 years. Placement of indwelling central venous access devices (CVADs) has made primary prophylaxis available to many children who live far away from treatment centers. CVADs carry potential morbidities of infection, mechanical malfunction, and large vessel thrombosis. Short-term observations of single centers (median, 30 months) yielded low infection rates of 0.14 and 0.19 per 1000 catheter days in contrast to a national US nursing survey that found infection in 45% of 568 CVADs.³⁴⁻³⁶ Infection within the port is more common than systemic bacteremia.³⁷ All studies have found a higher rate of infection in CVADs used to induce immune tolerance of inhibitors.³⁸ Symptomatic thromboses appear to be rare.³⁹ Despite complications, CVADs have greatly increased therapeutic options for very young children with hemophilia while decreasing cost and stress.

DEVELOPMENT OF SAFE, EFFECTIVE REPLACEMENT PROTEINS

The development of safe, effective coagulation proteins for replacement therapy has been paramount in the advancement of hemophilia care. The history of plasma product safety has been reviewed recently.⁴⁰ The transmission of viral pathogens to children with hemophilia through blood products caused untold pain and suffering in the hemophilia community and substantially delayed implementation of preventive strategies including prophylaxis and immune tolerance (see the following sections). However, remarkable advances came even from the tragedy of human immunodeficiency virus (HIV) in the form of basic scientific discoveries in virology and immunology as well as application of the hemophilia comprehensive care system to creation of comprehensive pediatric HIV programs. Emerging knowledge regarding hepatitis transmission through blood products stimulated the development of rational approaches to prospective safety studies of new products through the ISTH Subcommittee for factors VIII and IX.⁴¹

Early attempts to develop concentrates of "antihemophilic globulin" from animal and human plasmas were initiated in the United Kingdom, France, and Sweden. However, the 1965 description by Judith Graham Pool et al^{42,43} of a FVIII concentrate made using cryoprecipitation in a procedure easily adaptable to most blood banks led to immediate large-scale clinical application of FVIII replacement therapy to hemophilia A. Concentration of FIX in prothrombin complex concentrates was described the same year.⁴⁴ Routine treatment of joint and muscle bleeds became widespread shortly thereafter. However, the emergence of viral transmission through blood products, in the form of hepatitis B as well as non-A, non-B hepatitis was recognized soon after widespread application of human plasma products for infusion.^{45,46} It was observed that the risk of hepatitis was greater with the use of pooled in comparison to single-

donor products.⁴⁶ The US National Institutes of Health convened a consensus conference to discuss the prevalence and potential consequences of non-A, non-B hepatitis in 1975.⁴⁷ Hepatitis C was later identified as the offending viral agent in most transfusion-associated hepatitis, and most hemophilia patients who had been exposed to blood products manifested positive serologic evidence of hepatitis C infection.⁴⁸ Heat treatment of factor concentrates was the first effective viral attenuation procedure, inactivating several logs of lipid-encapsulated viruses, including human immunodeficiency virus (HIV) and hepatitis B and C.⁴⁹ Isolation of FVIII by affinity chromatography employing monoclonal antibodies provided the next significant advancement in blood product purity and safety in 1989.⁵⁰ Hepatitis A and Parvovirus B19, lacking a lipid capsule, were more difficult to inactivate using heat and solvent detergent.^{51,52} The application of several procedures including donor screening and donor unit testing for viral antibody, antigen, and nucleic acids, in addition to improved viral inactivation, have increased the safety of products derived from human blood.^{53,54} Still, fears of emerging infections such as West Nile virus (which has been determined to be transmissible through blood transfusions) and variant Creutzfeldt-Jacob disease (which has not been determined to be transmissible through blood transfusions) continue to exert pressure for the development of alternative treatment products to human blood-derived proteins.^{55,56}

The FVIII gene was first sequenced in 1984.⁸ Factor VIII produced in cell culture by recombinant technology was first applied to human trials in 1989.⁵⁷ Two full-length recombinant FVIII molecules are available commercially with excellent performance for clinical efficacy and safety.⁵⁷ More recently, a β -domain-deleted FVIII (BDD FVIII) has allowed more efficient yield from tissue culture systems and has contributed to an increased availability of FVIII.⁵⁸ BDD FVIII is clinically comparable to the full-length recombinant molecule.^{58,59} However, assay of BDD FVIII by clotting activity yields results approximately 50% compared with the full-length molecule; this phenomenon is related to the phospholipids in the assay.⁶⁰ Using a chromogenic assay, function of BDD FVIII and the native molecule are comparable. There is one recombinant FIX molecule.⁶¹ Recombinant FIX lacks phosphorylation at serine 158, has decreased tyrosine sulfation, and has a variably decreased peak plasma concentration following injection (known as plasma recovery) as compared with plasma-derived FIX.⁶¹ Still, the hazards of emerging infectious risks, such as prions, that could contaminate plasma or recombinant clotting proteins has driven a demand for recombinant proteins completely devoid of human proteins.⁶² Currently, third-generation recombinant FVIII molecules are being developed with no human proteins either in the cell culture or in final stabilization of the lyophilized recombinant protein. To date, tens of million units of recombinant FVIII and IX have been in-

fused worldwide with no evidence of HIV or hepatitis C transmission.^{53,57} Recombinant clotting factor concentrates have increased the world supply of hemophilia treatment products and, owing to their excellent safety profile, have fostered more liberal application of preventive treatment protocols for young children and reconstructive surgeries for adults. To date, however, recombinant FVIII molecules have not fulfilled physician and patient expectations of unlimited factor quantity at a price affordable for widespread use in many countries.

DEVELOPMENT OF OTHER THERAPIES

In addition to specific factor concentrates, the development of a small number of other therapies has contributed enormous benefit for prevention or treatment of bleeding episodes in persons with hemophilia. The efficacy of the fibrinolytic inhibitor epsilon-aminocaproic acid in dental extractions was first reported from the Cardeza Foundation in Philadelphia in 1964.⁶³ Epsilon-aminocaproic acid is still a mainstay for adjuvant therapy of mucus membrane bleeding including mouth and gum bleeding and menorrhagia. A controlled trial of the fibrinolytic inhibitor tranexamic acid was reported in 1973.⁶⁴ Tranexamic acid causes less gastrointestinal distress as compared with epsilon-aminocaproic acid and is equally effective. 1-Deamino-8-D-arginine vasopressin (DDAVP), a synthetic vasopressin, was found to increase plasma levels of FVIII and von Willebrand factor in patients with mild hemophilia A and von Willebrand disease.⁶⁵ This nonblood-product therapy can be used for either prevention or treatment of bleeding in individuals with an adequate response. Seizures secondary to hyponatremia have been reported, especially in infants; accordingly, DDAVP is not recommended for children younger than the age of 2 years.⁶⁶ Activated recombinant FVII (rFVIIa) was first successfully employed to control hemostasis in a hemophilia patient with inhibitory antibodies in 1991.⁶⁷ rFVIIa has been demonstrated to bypass factors VIII and IX in the activation of FX on the platelet surface in the absence of tissue factor, and in addition, may aid tissue factor-mediated generation of activated FX.⁶⁸ rFVIIa has become a first-line therapy for bleeding in children with inhibitors.⁶⁹ Finally, a local hemostatic agent concocted from a combination of proteins including fibrinogen, thrombin, FXIII, and aprotinin was developed in Israel as a topical agent to promote hemostasis.⁷⁰ Fibrin glue is particularly useful in oral bleeding.

PROPHYLAXIS

The most costly and prevalent complication in persons with severe hemophilia is progressive degenerative arthritis following recurrent episodes of hemorrhage into joints. Hemophilic arthropathy results in debilitating chronic pain, decreased range of motion of joints, and functional

impairment. Prophylaxis in hemophilia refers to a treatment strategy of infusing factor concentrate preventively, prior to the onset of bleeding. Prophylaxis using lyophilized plasma was first given to halt intractable bleeding events by John Johnson at Howard University in 1942.⁷¹ Limitations in the quantity and safety of factor concentrate limited preventive therapy for at least two decades. During the 1960s, early reports of prophylaxis were published from Sweden, Canada, the United States, and The Netherlands.⁷²⁻⁷⁵ Clinical trials to determine optimal dose and dose frequency were conducted in the late 1960s and early 1970s primarily in patients with a long history of joint hemorrhage.⁷³⁻⁷⁹ A single case study of Shanbrom and Thelin⁷⁴ reported the response of 100% FVIII correction given daily, five times a week, three times a week, and weekly, and showed a minimal effective dose of 50 U/kg given weekly. The US National Institutes of Health published pharmacokinetic data on FVIII prophylaxis and related clinical cessation of bleeding events to a trough FVIII level of 2%, achieved giving 60% correction every 36 hours.⁷⁶ Incremental effects of increasing prophylactic dosing were shown by Kasper et al⁷⁷ and demonstrated optimal efficacy using daily dosing with 50% reduction of bleed frequency using 250 U of FVIII per day and 75% reduction with 500 U/day. The effect of higher doses was limited to 3 or 4 days. A double-blind, placebo-controlled crossover trial performed by Aronstam et al⁷⁸ in children with hemophilia given 25% FVIII correction once weekly showed reduced frequency of bleeding by 15% overall, with most of the effect in the first 3 days. The same authors showed that 30% correction twice a week was superior to 15%, with most of the effect in the first 48 hours.⁷⁹ Although availability and safety of factor concentrates limited broad application of prophylaxis to children, Inga Marie Nilsson⁸⁰ continued to pioneer regular infusions of FVIII to prevent joint bleeding in young Swedish children with hemophilia. In observational studies, Nilsson et al⁸¹ were able to demonstrate physical and radiologic evidence of improved joint outcome in children treated with early prophylactic regimens. Initiation of prophylaxis after the onset of joint changes was determined to improve physical functioning and pain, but did not reverse or halt progressive arthritic changes.⁸² However, the cost and effort of factor infusion three to four times weekly is enormous and long-term compliance is a significant issue.⁸³ Less intensive preventive strategies had not been well-studied in young children with healthy joints.

Currently, there is an ongoing US prospective, randomized clinical trial of every other day prophylaxis versus an intensified episode-based therapy in 65 young children < 2.5 years of age with FVIII \leq 2% that will compare joint outcome using very sensitive magnetic resonance imaging (MRI) and a physical evaluation tool specifically developed for young children.⁸⁴ The US prophylaxis study will be completed in 2005. A recently

completed single-arm trial of escalating prophylaxis in young children has been conducted in Canada and will be analyzed shortly.⁸⁴ The rationale of dose-escalation in prophylaxis is to decrease the cost of factor and limit the need for CVADs by treating children with less frequent infusions of factor replacement based on clinically evident bleeding rate. There is no doubt that prevention of bleeding episodes, overall, conveys a better outcome for hemophilic arthropathy as well as life-threatening bleeding events, such as intracranial hemorrhage. Likewise, the widespread use of CVADs has fostered earlier home therapy and more effective treatment of acute bleeding events in addition to prophylactic infusions. Clinical trials such as the US and Canadian studies described will refine prophylaxis and determine optimal dose, dose frequency, and age of initiation to achieve the best outcome with the least morbidity and cost.

IMMUNETOLERANCE

One of the most significant morbidities of hemophilia therapy is the development of inhibitors.⁸⁵ Inhibitors are immunoglobulin G (IgG) antibodies (most frequently subclass IgG₄) that bind to specific FVIII epitopes, primarily active sites in the A2 and C2 regions of the molecule.^{86,87} Inhibitory antibodies cause irreversible inactivation of FVIII, limiting the usefulness of replacement factor therapy. Inhibitor titer is determined in the Bethesda assay in which serial dilutions of patient plasma are incubated with an equal volume of pooled normal plasma for 2 hours at 37°C.⁸⁸ The titer is defined as the plasma dilution that inactivates 50% of the FVIII in normal plasma and expressed in Bethesda units (BU). High-titer inhibitors are variously defined as those higher than 5 or 10 BU. Inhibitor formation always follows exposure to exogenous FVIII. In prospective studies of young children given recombinant FVIII, the incidence of inhibitors was approximately 30%, with half being high titer; the median time to development of an inhibitor was 9 exposure days to recombinant FVIII, with most inhibitors presenting within 50 exposure days.⁵⁷

The predisposition to inhibitor formation is determined partly by the nature of the gene mutation and partly by the immune constitution of the patient.⁸⁹⁻⁹³ The risk of inhibitor development is increased in patients with large deletions, the intron 22 inversion, and nonsense mutations, and decreased in patients with missense mutations and small deletions. In addition, the immune response elicited by FVIII is a mixed Th1 and Th2 response. Inhibitor formation may be modulated by blockade of costimulatory molecules important in optimal T-cell activation.⁹³

Persons with inhibitors cannot be treated optimally for bleeding events. As a consequence, they suffer more severe and extensive hemophilic arthropathies, recurrent intracranial hemorrhages, and other bleeding complications. The cost of care is significantly increased and

quality of life is markedly diminished.⁹⁴ Nilsson^{95,96} reported regimens using a combination of factor and cytoxan to suppress the inhibitory response to FIX and FVIII in 1973 and 1974, respectively. After many modifications of the original therapy, Nilsson et al⁹⁷ published the Malmö regimen for immune tolerance induction employing FVIII exposure (100 U/kg/day) with monthly courses of cytoxan and intravenous immune globulin (IVIG) in 1988. A German immune tolerance regimen dubbed the Bonn protocol, first reported in 1976, employed higher doses of FVIII (100 U/kg bid) without immunosuppressive therapy and showed similar efficacy.⁹⁸ A Dutch adaptation was shown to achieve tolerance with as little FVIII as 50 U/kg three times weekly.⁹⁹ A recent retrospective review of immune tolerance suggests that up to 90% of young children with high-titer inhibitors can achieve tolerance.¹⁰⁰ Doses of 100 U/kg/day or higher, and initiation within a year of inhibitor onset, predicted successful tolerance induction. However, there are many unanswered questions including the optimal dose schedule, treatment product, and window of therapeutic efficacy following diagnosis of an inhibitor. Currently, an international study is ongoing to determine relative benefits and costs of high-dose versus low-dose immune tolerance.¹⁰¹

ORTHOPEDIC INTERVENTIONS FOR JOINT DISEASE

Despite the greater availability of safe, effective factor concentrate for treatment and prevention of acute bleeding episodes, persons with severe hemophilia continue to develop synovitis and arthropathy.¹⁰² Local therapies targeted to the affected joint are indicated for children with mild hemophilia, children in whom most bleeding events are localized to one joint, and in areas of the world where prophylaxis is not available or affordable. Intra-articular injections of P32, termed radiosynoviorthesis, were first applied to persons with rheumatoid arthritis.¹⁰³ P32 radiosynoviorthesis has been applied to children and adolescents with hemophilia. Radiosynoviorthesis in children, particularly with early synovitis, is effective in long-term reduction in bleeding rate.¹⁰⁴ The procedure is effective, well tolerated even by children as young as 4 or 5 years, inexpensive, and appears to be safe.^{104,105} Radiosynoviorthesis should not be considered an equal alternative to prophylaxis in children with recurrent hemorrhages into multiple joints. However, radiosynoviorthesis has been so successful that it is being recommended as a first approach to local therapy of hemophilic arthropathy in many hemophilia centers.

Synovitis has also been treated with surgical removal of synovium. Early synovectomies were performed in open joint procedures. Open surgical synovectomy is effective in decreasing the rate of joint hemorrhage,¹⁰⁶ but is expensive, requires protracted physical therapy and factor replacement, and is accompanied by a high

rate of decreased joint range of motion and functional gait abnormalities. Arthroscopic synovectomy appears to have less damaging effects on range of motion and gait.¹⁰⁷ Arthroscopic synovectomy is limited technically by the small size of the joint in young children, particularly the elbow and the ankle; results are dependent on the skill and experience of the surgeon.

EXPANDING HEMOPHILIA CARE TO DEVELOPING COUNTRIES

During the last decade extensive work has been performed by the World Federation of Hemophilia to develop hemophilia programs for children throughout the world.¹⁰⁸ Success has been achieved by twinning programs that link personnel from established hemophilia centers with interested physicians and other healthcare personnel in developing countries, in addition to linkages with national healthcare initiatives to organize basic healthcare elements required for comprehensive hemophilia care.¹⁰⁸ Despite the obstacle created by the high cost of safe replacement factor concentrates, remarkable progress has been made in several countries throughout the world in development of safer national blood supplies, and the extension of safe, manufactured factor concentrates to more countries.¹⁰⁹⁻¹¹¹ The greatest achievement may be that, through the efforts of the World Federation of Hemophilia, hemophilia healthcare personnel throughout the world have embraced the principle that we must work globally, and not just locally, for improvement in hemophilia care and outcomes.

FORMING COLLABORATIONS FOR RESEARCH AND THE ADVANCEMENT OF CARE

As demonstrated in this article, many if not most seminal observations regarding the nature and therapy of hemophilia were made long ago. However, the development of evidence-based medicine was hampered by small numbers of patients at any one treatment center. The last decade has seen progress in the development of clinical trials brought about by increased collaborations through newly developed organizations such as the Hemophilia and Thrombosis Research Society, an embrace of hemophilia research through established organizations such as the International Society for Thrombosis and Haemostasis, and economic support through government funding. Through these combined efforts national and multinational randomized clinical trials on prophylaxis, immune tolerance, and novel therapies have been developed.

GENETHERAPY FOR HEMOPHILIA

No discussion of advances in care of children with hemophilia could be complete without inclusion of milestones in the development of gene therapy. The five gene ther-

apy trials that have enrolled subjects with hemophilia have been reviewed recently.¹¹² Exciting progress has been made. Long-term expression of the transgene product has been demonstrated in dogs and safety of gene therapy has been demonstrated in human adults. To date, however, gene therapy is not a therapeutic option for children with hemophilia. Children with other disorders have experienced adverse outcomes following gene therapy. An adolescent with a metabolic liver disease developed liver failure following receipt of a hepatic-directed adenoviral vector and two children have developed leukemia following gene therapy for severe combined immunodeficiency. Despite these setbacks, enthusiasm for the cure of hemophilia persists and will ultimately be achieved.

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